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Cubane: 50 Years Later

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1. INTRODUCTION

The fascination with elaborate molecular architectures that differ significantly from those ordinarily present in nature have motivated synthetic, physical organic, and theoretical chemists alike, to explore their distinct properties and to pursue novel applications.^{1–3}

In this respect the five regular convex polyhedra as defined by Euclidean geometry, and known as the Platonic solids, the tetrahedron (4 faces), the hexahedron, or cube (six faces), the octahedron (eight faces), the dodecahedron (12 faces), and the icosahedrons (20 faces) have attracted the most attention. Of these five polyhedra, only two have been translated to their corresponding hydrocarbons; the hexahedron (cube) and the dodecahedron. Specifically, the hydrocarbon equivalent of the hexahedron, is a molecule with molecular formula of C_8H_8 , where each of the eight equivalent vertices is comprised of a methine (CH) unit; this molecule is pentacyclo-[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane, or more conveniently, cubane (**1**), and is the first of the five regular complex polyhedra to succumb to a considered chemical synthesis in 1964.⁴ In the subsequent 50 years, the chemistry of this remarkable hydrocarbon and its many derivatives has been well developed and explored (Figure 1).

Cubane (**1**) boasts a combination of physical properties that is emulated by no other stable hydrocarbon (Table 1). Structurally, it features the arrangement of eight methine (CH) units in a

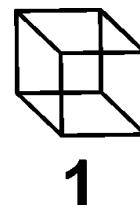


Figure 1. Structural formula of cubane.

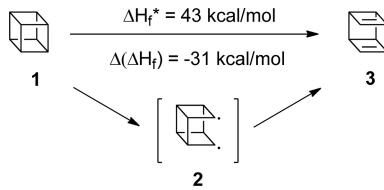
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Table 1. Some Physical Properties of Cubane

molecular formula:	C_8H_8
shape: ⁵	O_h point group; cubic symmetry; rhombic crystals
melting point: ²³	133.5 °C (phase transition 124.5 °C)
boiling point: ²³	161.6 °C
decomposition: ¹⁷	>220 °C
density: ¹⁰	1.29 g/cm ³
vapor pressure: ⁹	177 Pa at 25 °C (1.3 mmHg)
heat of formation (ΔH_f): ^{13,14}	144 kcal/mol
enthalpy of sublimation ($\Delta_{sub}H^\circ$): ^{24–26}	19 kcal/mol
strain energy (SE): ^{13,14}	161.5 kcal/mol
toxicity: ¹⁰	none

perfect cubic arrangement, resulting in a compact, spherical molecular entity that belongs to the octahedral point group O_h and possesses cubic symmetry.⁵ Interestingly, in its crystalline form, cubane (**1**) forms rhombic crystals.⁶ It possesses C–C and C–H bond lengths of 1.571 and 1.109 Å, respectively,⁷ and a C–C–H bond angle of ~125°.⁸ Consistent with its high symmetry and hydrocarbon nature, it has a significant vapor pressure of 177 Pa at 25 °C,⁹ and boasts an unusually high density for a hydrocarbon molecule of 1.29 g/cm³.¹⁰ Cubane (**1**) and methylcubane are both transparent to UV radiation down to near 200 nm.¹¹ Cubane also displays single resonances in its ¹H and ¹³C NMR spectra at 4.04 and 47.3 ppm, respectively.¹² This unique and distinctly unnatural geometry renders cubane (**1**) thermodynamically unstable ($\Delta H_f = 144$ kcal/mol), and highly strained (SE = 161.5 kcal/mol).^{13,14} As a comparison, cyclobutane has a ΔH_f of 6.8 kcal/mol¹⁵ and a strain energy of 26.3 kcal/mol.¹⁶ Despite these seemingly limiting physical properties, cubane (**1**) displays a remarkable kinetic stability capable of withstanding temperatures of up to 220 °C.^{17–21} Pyrolytic ring opening studies of cubane (**1**) at constant pressure, in the temperature range 230–260 °C, established an energy of activation for homolysis of a C–C bond (i.e., ring opening) of 43.1 kcal/mol.^{17,18} The origin of this large barrier to ring opening is due in part to the absence of symmetry-allowed pathways for concerted two-bond ring opening, and the limited relief in ring strain [~72 kcal/mol]²² provided by the conversion of **1** to *syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**3**) through intermediacy of the corresponding secocubane diradical **2** as a result of homolysis of a single carbon–carbon bond in **1** (Scheme 1).

Scheme 1. Thermal ring-opening of cubane (**1**)^{17,18}

Other reviews of cubane have been produced over the years, including one by Eaton in 1992.¹⁰ Additional reviews and book chapters which cover the chemistry of cubane, cyclobutanes, and other prismanes have also been written.^{3,27–30} This review is intended to be a reflection piece on the synthetic accomplishments of cubane which span the 50 years since its initial synthesis. The work included in this review will focus solely on cubane and its derivatives, yields are included where reported and relevant for discussion.

2. SYNTHESIS OF THE CUBANE RING SYSTEM

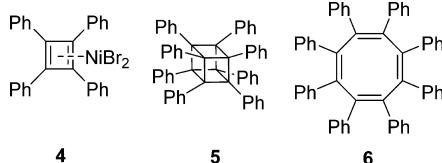
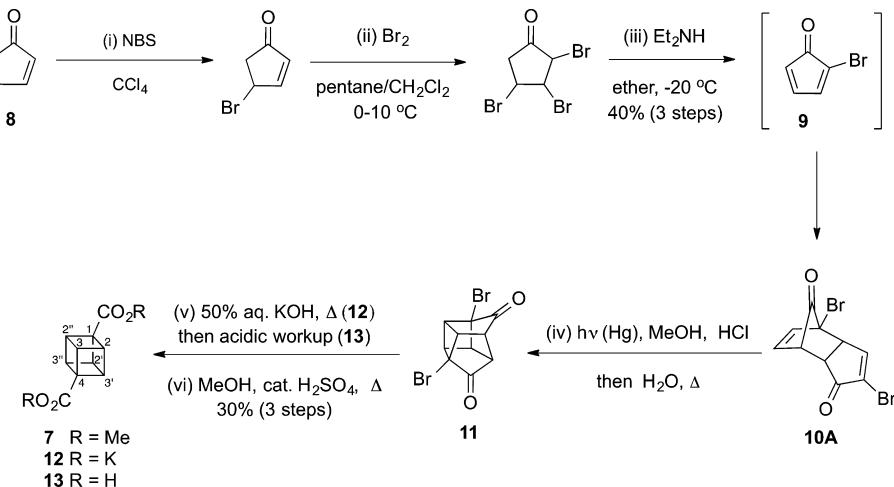
The final sentence in Weltner's 1953 publication on strained hydrocarbons stated: "Tricyclooctane (read cubane) is a more dubious case and may or may not be capable of synthesis". This conclusion was reached on the basis of a theoretical study that found that the heat of formation of cubane was about 84 kcal/mol higher than that of its unsaturated isomer, cyclooctatetraene.³¹ Several years later Freedman,^{32–34} while pursuing the generation of stabilized tetraphenylcyclobutadiene nickel bromide complex **4** (Scheme 2), reported the inadvertent synthesis of octaphenylcubane (**5**) as a sparingly soluble colorless hydrocarbon with a melting point of 425–27 °C. Thronsdæn and Zeiss³⁵ also claimed to have prepared **5** through their study of the thermal reaction of diphenylacetylene and phenylmagnesium bromide. Subsequent studies provided compelling evidence that the colorless hydrocarbon with a melting point of 425–27 °C was in fact octaphenylcyclooctatetraene (**6**; Figure 2).^{35,36}

2.1. Tactical Synthesis of the Cubane Ring System

The first tactical and practical synthesis of the cubane ring system was the subject of two communications in 1964 by Eaton and Cole; the first describing the synthesis of the dimethyl diester **7** (Scheme 2), and the second cubane (**1**) itself (Scheme 3).^{4,37} This sequence illustrated in Scheme 2 outlines the approach to **13**, in eight discrete steps from 2-cyclopentenone (**8**), in an overall yield of about 12%;³⁸ There are three key synthetic elements to Eaton's remarkably simple, but elegant, synthesis: (i) the highly *endo*-selective [4π+2π] Diels–Alder dimerization of the highly reactive, *in situ* generated, 2-bromocyclopentadienone (**9**), producing the *endo*-dimer **10**, almost exclusively (Figure 3); (ii) the [2π +2π] ene-enone photocyclization of **10**, producing **11**; and (iii) the double Favorskii ring contraction of the cage dione **11**, producing first the dipotassium dicarboxylate **12**, and then the corresponding diester **7** upon esterification of the dicarboxylic acid **13**. This sequence demonstrated beyond a doubt the intrinsic kinetic stability of the cubane nucleus, and provided a practical pathway for the accumulation of the diester **7** in multigram quantities.

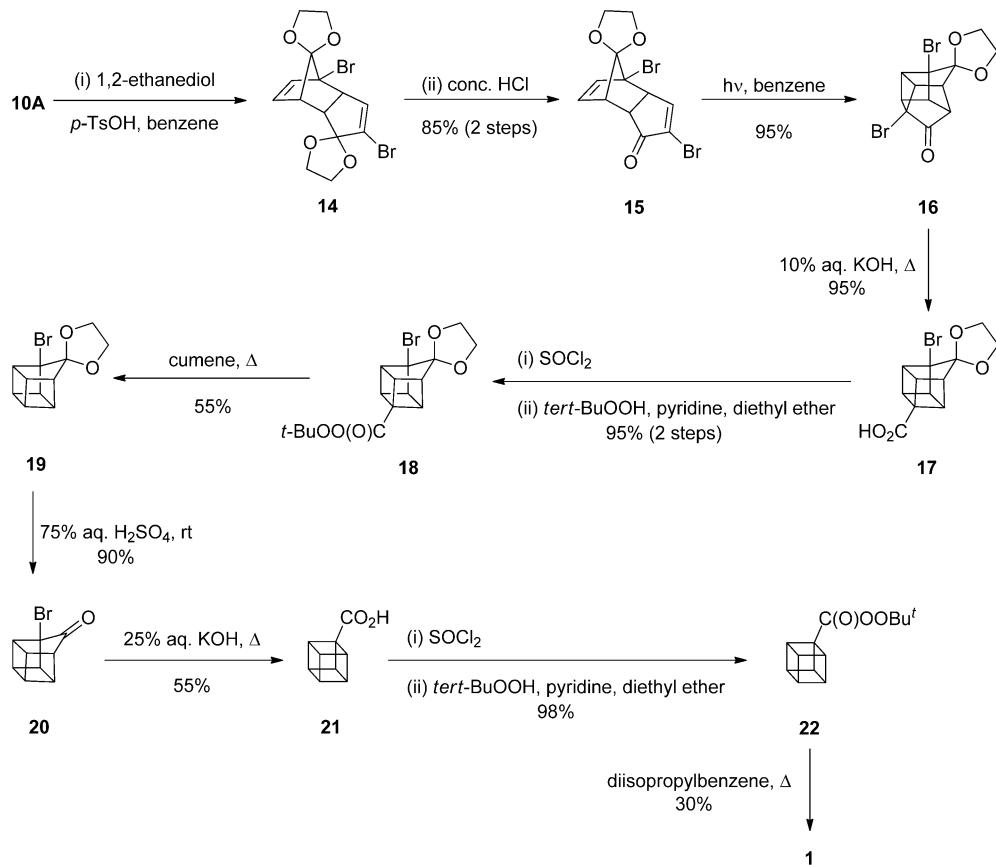
Eaton and Cole observed that in the conversion of diene **9** to its corresponding dimer **10A**, the reaction proceeded with complete stereoselectivity, of which they rationalize *a priori* with three supporting explanations. First, they argued that the dimerization should occur in accordance with the dimerization of cyclopentadienone, proceeding through an *endo* transition state. In addition, drawing analogy to what is observed for chlorobenzoquinone,^{4,37} they believed that the dienophilic reactivity of **9** would be lowest at the halogen-substituted double bond, meaning that one vinyl position should be attached to a bromine, rather than a hydrogen atom. Lastly, they argued that the interactions of like dipoles should be minimized in the geometry of the transition state for the Diels–Alder dimerization of **9**, so they believed that transition state A should be more favorable than transition state B, resulting in the formation of **10A** as product (Figure 3).

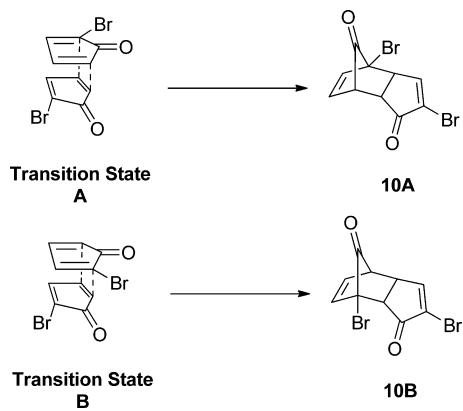
The authors were able to further verify the structure of **10A** in full. The evidence that they provided included that the *endo* configuration was essential to the subsequent light-induced ring closure, compound **10A** only contained three vinyl proton resonances in the ¹H NMR spectrum, confirming that there is substitution of a bromine vs a hydrogen in one of the positions. Lastly, they noted that the completion of the synthesis of methyl ester **7** leads to substituents on the diagonal vertices of the

Scheme 2. Eaton and Cole's Synthesis of the Cubane Ring System^{4,37}Figure 2. Structural formulas of tetraphenylcyclobutadiene nickel bromide complex (4), octaphenylcubane (5), and octaphenylcyclooctatetraene (6)^{32–36}

cubane core (positions 1 and 4), which is only possible if **10A** were an intermediate in the sequence.

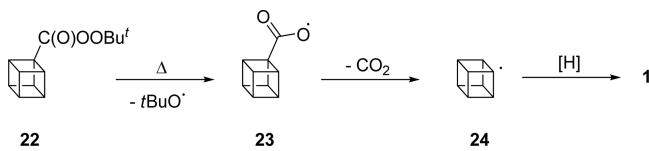
The first synthesis of cubane (**1**) itself involved the multistep sequence depicted in Scheme 3. Starting from the dione **10A** the bisethylene ketal **14** was first isolated and then selectively hydrolyzed to the enone **15**. This selective deketalisation occurs without complication under mild acidic conditions to expose the relatively unstrained conjugated α -bromoenoone moiety in **15** while leaving the bridged ketal intact. Irradiation of **15** with UV light in benzene generated the cage ketone **16**, which collapsed to the homocubyl carboxylic acid **17** through a Favorskii ring

Scheme 3. Eaton and Cole's Synthesis of Cubane (**1**)

Figure 3. Transition states leading to dimer **10**.⁴

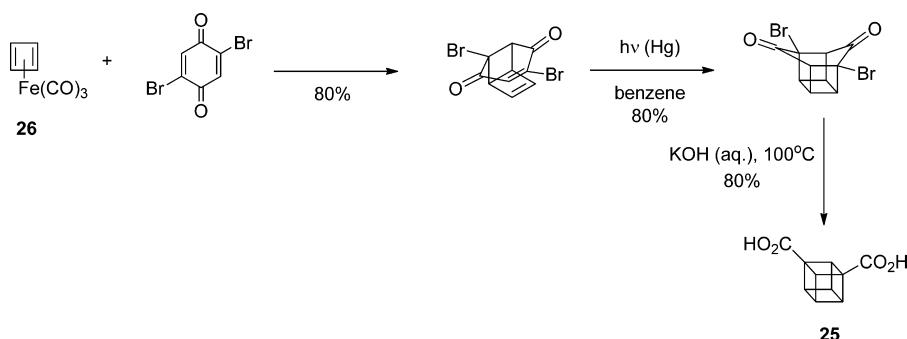
contraction. Reductive decarboxylation of **17** to give **19** proceeded through thermal decomposition of **18** in cumene. Conversion of the homocubyl ketal **19** to cubane (**1**) made use of a similar sequence (**17** → **19**); hydrolysis of **19**, ring contraction of **20**, and reductive decarboxylation of **21** via the perester **22**. A few points are worthy of highlighting in relation to this latter sequence: (i) deketalisation of **19** required more forceful conditions, consistent with the generation of a more highly strained bridged ketone; (ii) more concentrated basic conditions were required to effect ring contraction of the homocubyl to the cubyl system, again consistent with the concomitant increase in strain in progressing from **20** to **21**; and (iii) thermal decomposition of **22** to furnish **1** proceeded via the cubyl radical (**24**) obtained upon decarboxylation of the cubylcarboxy radical (**23**) (Scheme 4).³⁹

Scheme 4. Reductive Decarboxylation of Perester **22** in the Presence of Diisopropylbenzene



Shortly after the appearance of Eaton's work, Pettit and co-workers described an alternative 3-step sequence for accessing the cubane system as the 1,3-dicarboxylic acid **25** (Scheme 5). Again, the key synthetic elements in this process were as those described by Eaton. However, the need for cyclobutadiene iron tricarbonyl (**26**) has limited the expediency of this approach.

Scheme 5. Pettit's Synthesis of 1,3-Cubanedicarboxylic Acid (**25**)⁴⁰



2.2. Improved Synthesis

Several years later Chapman and co-workers described several modifications to Eaton and Cole's protocol (Scheme 6).⁴¹ Building on the work of DePuy,⁴² and of Eaton, which investigated the reactivity of cyclopentadienone ketals,⁴³ Chapman utilized 2-bromomycyclopentadienone ethylene ketal (**28**) instead of 2-bromocyclopentadienone (**9**) to access the dicyclopentadienone system. In this sequence, Chapman subjected cyclopentanone ethylene ketal (**27**) to bromination with three equivalents of molecular bromine in anhydrous 1,4-dioxane, to generate the tribromoketal **28**, which was then exposed to NaOMe in methanol to generate the reactive diene **29**, which in turn dimerized to produce the bisketal **14**. Selective hydrolysis of the less strained ketal in **14** with concentrated HCl in THF at room temperature furnished the monoketal **15**. Irradiation of a solution of **15** in deoxygenated benzene, through quartz, with UV light produced by a Hanovia 450W medium-pressure Hg lamp afforded the cage ketal **16**. Deketalisation of **16** with concentrated H₂SO₄ delivered the cage dione **11**, which was then converted to the dimethyl ester **7** using the familiar Favorskii/esterification sequence. The overall yield of **7** obtained by Chapman through this protocol was ~3% primarily due to difficulty with the double Favorskii ring contraction of **11**.

More recently, Tsanaktsidis and co-workers have described an improved and refined protocol that integrated the key elements of the Eaton and Chapman approaches to produce a robust and operationally simple pilot-scale process for the production of multigram quantities of dimethyl 1,4-cubanedicarboxylate (**7**; Scheme 7).^{23,44}

2.3. Other Approaches

Per-substituted cubanes, octamethylcubane (**29**),^{45,46} propellacubane (**20**),⁴⁷ octa(trifluoromethyl)cubane (**31**),⁴⁸ and octacyclopropylcubane (**32**; Figure 4).⁴⁹ While interesting molecules in their own right, these fascinating materials are not easily obtained in quantity and, hence, offer little opportunity for further elaboration.

While there have been several advancements in making cubanes with a number of different substitution patterns, there have been fewer that do it by means of constructing the cubane core in a unique way. One other approach to the construction of the cubane core came from the work of de Meijiere and co-workers. In an effort to construct an octacyclopropyl-substituted variant of cubane, they began with the treatment of dicyclopropylacetylene (**34**) with zirconocene dichloride and *n*-butyllithium (*n*BuLi). The reaction mixture was then treated with iodine and finally cuprous chloride to initiate a Diels–Alder type dimerization of the intermediate tetracyclopropylcyclobu-

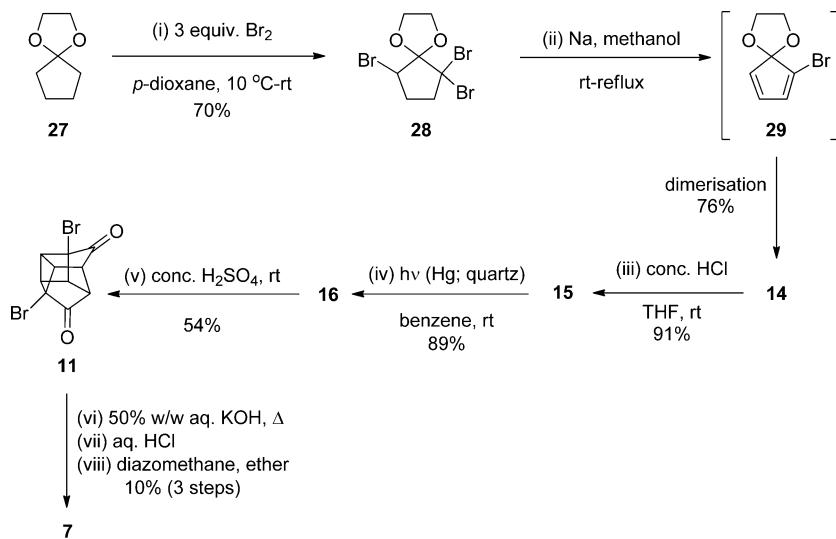
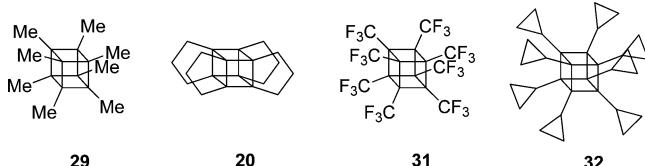
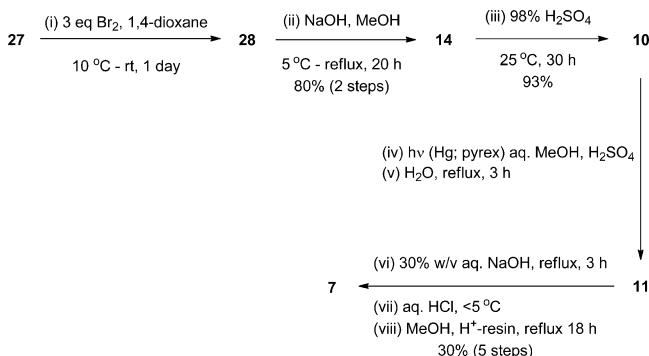
Scheme 6. Chapman Synthesis of Dimethyl 1,4-Cubanedicarboxylate (7)^{41,42}Scheme 7. Tsanaktsidis' Pilot-Scale Synthesis of Dimethyl 1,4-Cubanedicarboxylate (7)^{23,44}

Figure 4. Structures of per-substituted cubanes.

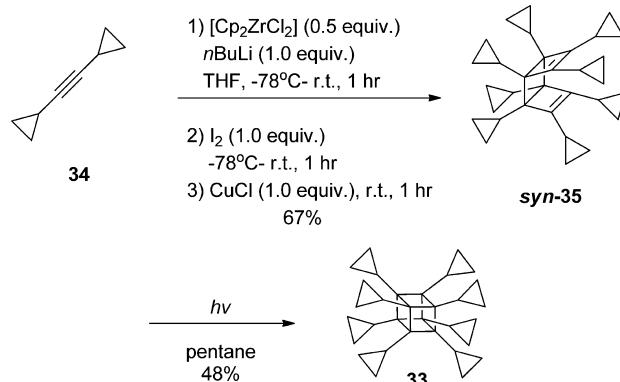
tadiene (*syn*-35) in 67% yield. They then dissolved *syn*-35 in pentane and it was irradiated with a medium-pressure mercury lamp in a quartz sleeve at ambient temperature to give the desired octacyclopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}], octacyclopropylcubane (33; Scheme 8), in 48% yield.⁴⁹

3. CHEMICAL REACTIVITY OF THE CUBANE NUCLEUS

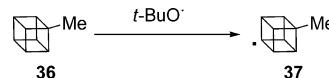
3.1. Cubyl Radical

The first proposal of the existence of the cubyl radical was during the original synthesis of cubane by Eaton and Cole. They proposed that there was a radical mechanism associated with the decarboxylation step of the perester to cubane.⁴ Since then, there have been a number of research efforts associated with confirming the existence of the cubyl radical in a variety of mechanistic pathways.

3.1.1. H Atom Abstraction. One mode by which the generation of a cubyl radical was envisioned to be generated

Scheme 8. Synthesis of Octacyclopropylcubane (33)⁴⁹

through direct H atom abstraction. It has been demonstrated that, through the use of *tert*-butoxy radicals, it is possible to generate a cubyl radical through a direct H atom abstraction. For example, treatment of methylcubane (36) with photochemically produced *tert*-butoxy radicals produced methylcubane radical (37), which was examined through use of electron paramagnetic resonance (EPR; Scheme 9).⁵⁰

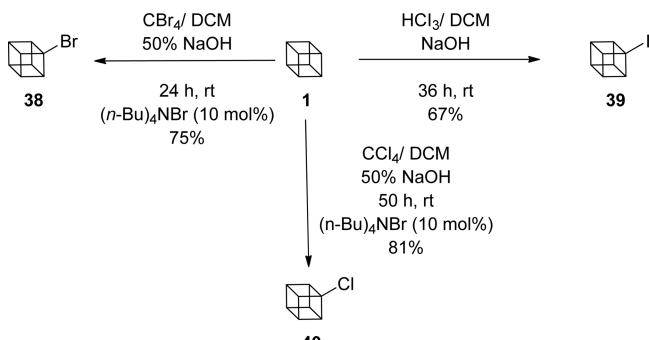
Scheme 9. Production of Cubyl Radical with *tert*-Butoxy Radicals⁵⁰

Surprisingly, it was found that H atom abstraction is more favored for any C–H bond on the cubane core than the hydrogen atoms on the methyl group of 36. This has been rationalized with the idea that this H atom abstraction is most likely occurring through a polarized transition state, so charge delocalization of radical formation would be greater for the formation of a radical on a tertiary vs a primary carbon center.^{50,51}

Another discovery of the intermediacy of an H atom abstraction came from the work of Schreiner and co-workers. They developed the first highly selective C–H bromination, iodination, and chlorination of cubane through use of phase-transfer conditions. Starting from cubane (1), the authors

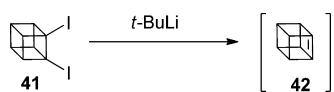
discovered that they could obtain brominated (**38**), iodinated (**39**), and chlorinated (**40**) cubanes in high yields through the employment of the respective halomethane (Scheme 10).⁵²

Scheme 10. Direct Halogenation of the Cubane Core⁵²



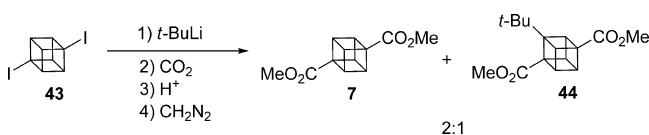
3.1.2. Halogen Abstraction. The cubyl radical has also been shown to be generated from the corresponding halogenated cubane through a halogen abstraction.⁵³ Eaton and Maggini observed that when 1,2-diiodocubane (**41**) was treated with *tert*-butyllithium that it produced reactive intermediate 1,2-dehydrocubane (**42**), also referred to as cubene (Scheme 11; for further discussion of reactivity and trapping of cubene see section 4.1. Cubene).⁵⁴

Scheme 11. Cubene (**42**) Generation from 1,2-Diiodocubane (**41**)⁵⁴



Two years later, Eaton and Tsanaktsidis showed that reactions of 1,4-diiodocubane (**43**) with alkylolithium reagents generated products that were similar to those produced by such reactions with 1,2-diiodocubanes.⁵⁵ For example, when 1,4-diiodocubane (**43**) was treated with excess *tert*-butyllithium, followed by carboxylation and esterification with diazomethane, the reaction gave primarily 1,4-dimethoxycarbonyl cubane (**7**) and additionally the trisubstituted cubane **44** in a 2:1 ratio (Scheme 12).

Scheme 12. Reaction of 1,4-Diiodocubane (**43**) with *tert*-Butyllithium⁵⁵



It had been proposed that the reaction could have been proceeding through a variety of reactive intermediates that represent a 1,4-dehydrocuban species including cubylane (**45**), a triply bridged [2.2.2]propellane, diene **46**, or diyl **47** (Figure 5). The authors argued that the structure **45** would have a weak

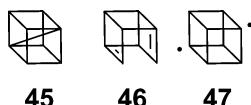
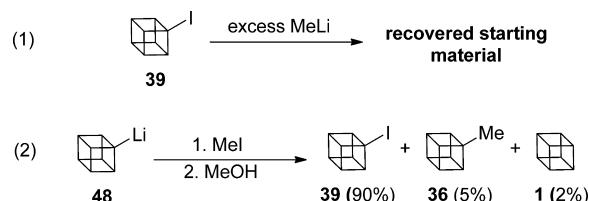


Figure 5. Potential intermediates for the conversion of **43–7** and **44**.⁵⁵

internal bond and the phases of the required orbitals to generate it are mismatched, making this an unlikely intermediate. To further support this, Borden et al. and Michl et al. have independently performed calculations that suggest that the formation of **45** is highly disfavored given the exceedingly high strain present in the intermediate.^{55–57} In the case of diene **46**, they expected that it would readily react with Diels–Alder dienes if it was produced during the reaction. However, exposure of the reaction mixture from **43** and *tert*-butyllithium to furan or 9,10-diphenylisobenzofuran did not effectively produce adducts corresponding to the formation of **46**. Thus, it was determined that the reaction proceeds through the intermediacy of diyl **47**, additionally the singlet state of this diyl was calculated to be 10 kcal/mol more stable than its triplet state.

Further evidence for cubyl radical generation by halogen abstraction came from Eaton et al. in 1995, demonstrating the synthesis of methylcubane (**36**) and cyclopropylcubane from 1,4-diiodocubane (**43**).⁵¹ In initial experiments, they found that treatment of iodocubane (**39**) with excess methylolithium produced only recovered starting material (Scheme 13, line 1).

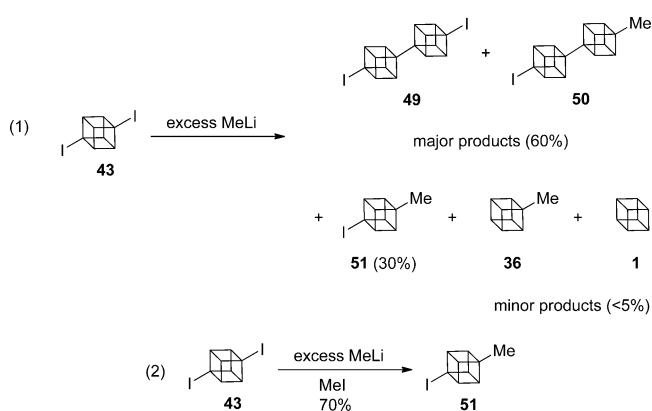
Scheme 13. Organometallic Reactions of Iodocubane (**39**)⁵¹



They subsequently found that the reverse reaction of cubyllithium (**48**) (produced by reaction with cubyl iodide and *tert*-butyllithium) with methyl iodide produced predominantly iodocubane (**39**) (Scheme 13, line 2).

The rationalization for this phenomenon is based primarily on the acidity of the respective hydrogens. They continued their experiments with reactions of 1,4-diiodocubane (**43**) in an effort to prepare methylcubane (**36**). They found that treatment of **43** with excess methylolithium gave predominately bicubyl products **49** and **50** (Scheme 14, line 1). The authors noted that these products would arise from cubyllithiums adding to the cubane 1,4-diyl (**47**). Interestingly, they found that addition of excess iodomethane to the reaction mixture suppressed radical recombination of the cubyl radicals and produced 4-methylcubyl

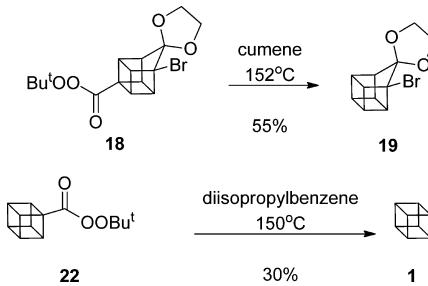
Scheme 14. Organometallic Reactions with 1,4-Diiodocubane (**43**)



iodide (**51**) almost exclusively in 70% yield (Scheme 14, line 2). It should be noted that they were also successful in generating the cyclopropyl variant in high yield using cyclopropyllithium.⁵¹

3.1.3. Decarboxylation. One of the primary ways in the literature to generate a radical on the cubane core is through decarboxylation methods. This was performed in the original synthesis of cubane in 1964 by Eaton et al. They found that thermal decomposition of peresters were an effective strategy for performing a decarboxylation on the cubane core (Scheme 15).^{4,37}

Scheme 15. Thermolysis of Peresters in Synthesis of Cubane^{4,37}



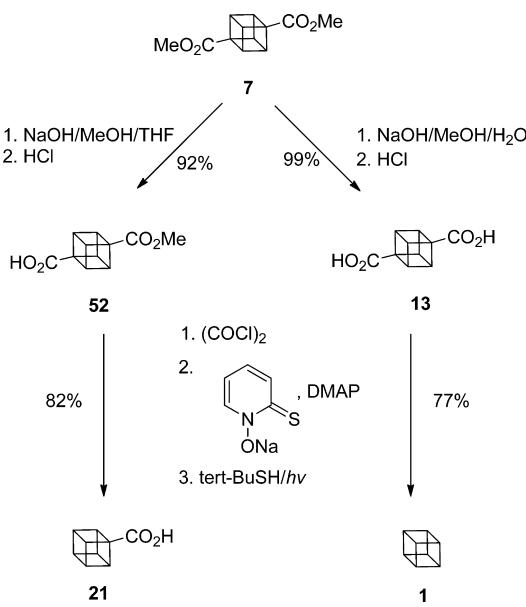
Since the original synthesis, a number of other methods have been reported by which one can perform a decarboxylation on the cubane core. With the recognition that the best route into the cubane family had been through the route of Chapman and Eaton, Tsanaktsidis intended to develop superior methods for the manipulation of the two resulting carboxylic acids from the aforementioned route.⁵⁸ They rationalized doing this because, in previous reports, the thermal decomposition of *tert*-butyl peresters **18** and **22** suffered from low yield due to in-cage recombination of connate radicals to produce cubyl *tert*-butyl ethers. Subsequently, Eaton and others^{44,58} adopted the Barton protocol⁵⁹ for decarboxylation, which involves facile homolytic cleavage of the corresponding thiohydroxamic ester, which is prepared by the reaction of the corresponding acid chloride with the sodium salt of *N*-hydroxypyridine-2-thione (Scheme 16). More recently, Tsanaktsidis and colleagues have demonstrated the Barton reductive decarboxylation reaction with cubane using CHCl₃ as the hydrogen atom donor.^{60,61}

A reaction that is particularly unique to cubane is the Moriarty reaction.^{57,62} This reaction uses a hypervalent iodine source, iodobenzene diacetate (IBDA), and molecular iodine to replace a carboxylic acid on the cubane core with an iodine (**21** → **39**). The mechanism of this is illustrated in Scheme 17.⁵⁴

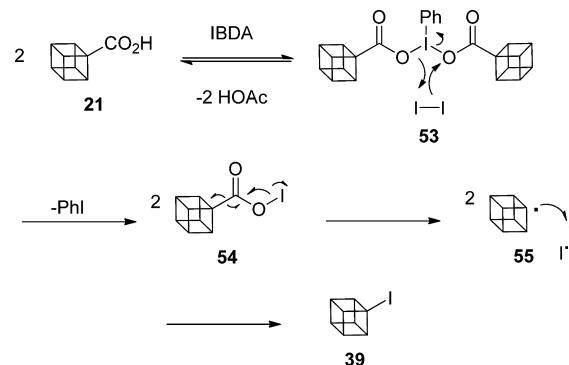
3.2. Cubyl Cation

From a conceptual standpoint, it was rather difficult for chemists to imagine the formation of a cubyl cation. There are a number of rationales for why a cubyl cation would be disfavored including: (1) the geometry that would result from forming such an intermediate would be far from flat, (2) the exocyclic orbitals in cubane are very rich in *s*-character, and finally (3) hyperconjugative stabilization would require a high-energy, cubene-type structure.¹⁰ Furthermore, ab initio calculations by Hrovat et al. demonstrated that less energy is required to form the cubyl cation over the 1-norbornyl cation.⁶³ Additional theoretical and experimental work evaluated carbocation stability of bromocubane and found that the standard Gibbs energy change for the exchange of bromine with 3-noradamanyl cation which was determined to be 0.5 kcal/mol toward 3-bromonoradamtanyl.⁶⁴

Scheme 16. Barton Decarboxylation for Manipulation of Monoacid **52 and Diacid **13** on the Cubane Core**



Scheme 17. Mechanism of the Moriarty Reaction⁵⁴

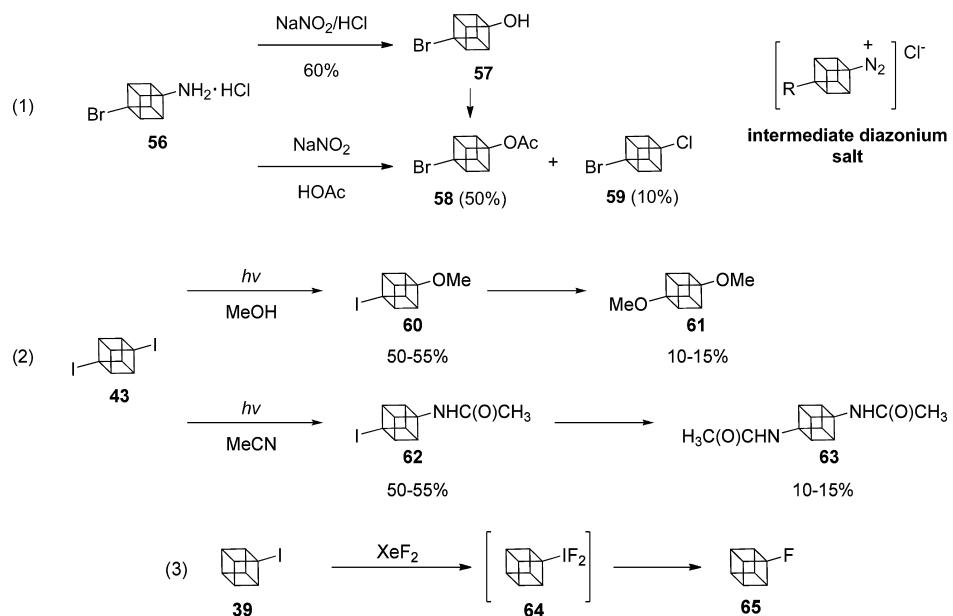
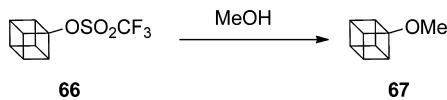


A large fraction of the synthetic community, especially those that specialized in the study of cubane, had a hard time imagining such an intermediate. There are a number of reactions that appear to have gone through a cubyl cation including the decomposition of diazonium salts generated from the corresponding cubylamine (**56** → **59**), photolytic etherification or amidation of 1,4-diiodocubane (**43** → **56** or **43** → **63** respectively), and halogen exchange reaction of iodocubane with XeF₂ (**39** → **64** → **65**; Scheme 18).^{10,65–69}

Due to the possibility for intramolecular rearrangements, front-side attacks, “hot intermediates,” etc., Eaton et al. set out to perform a series of solvolysis reactions with cubyl triflate **66**. This was performed by stirring **66** in anhydrous methanol for 30 min at 70 °C to furnish methyl ether **67** (Scheme 19). The reaction was reported to proceed smoothly and cleanly without skeletal rearrangement.⁶⁹

Eaton et al. subsequently compared experimental and calculated rates of solvolysis for a variety of tertiary tosylates in acetic acid. As summarized in Table 2, most of the pairs are exceptionally close, except for the cubyl tosylate which differed between calculated and experimental rates of solvolysis by over 15 orders of magnitude.⁷⁰

Eaton et al. offered an explanation for the surprisingly facile formation of the cubyl cation. They attributed it to a unique

Scheme 18. Substitution Reactions of Cubane That Are Proposed to Proceed through a Cubyl Cation Intermediate^{10,65,66}Scheme 19. Solvolysis of Cubyl Triflate (66) in Anhydrous Methanol⁶⁹Table 2. Experimental and Calculated Solvolysis Rates of Some Tertiary Tosylates in Acetic Acid at 70 °C⁷⁰

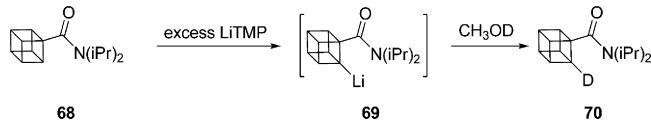
tosylate	experimental	calculated
tert-butyl	1	1
1-adamantyl	10^{-3}	10^{-4}
1-bicyclo[2.2.2]octyl	10^{-7}	10^{-8}
1-norbornyl	10^{-13}	10^{-14}
cubyl	10^{-10}	$<10^{-25}$

ability of the cubane skeleton to contribute electron density to the cationic center.⁷⁰ Given the high *p*-character of the C–C bonds, the newly generated positive charge would be delocalized throughout the surrounding α,β - and β,γ -carbon–carbon bonds, as was shown computationally by Borden et al.^{63,71} In addition, Eaton et al. as well as Moriarty et al. simultaneously reported that electron-withdrawing groups in the γ -position relative to the leaving group on the cubane skeleton significantly retard solvolysis while α -donors in the β -position increase the rate of solvolysis.^{63,72}

3.3. Cubyl Anion

3.3.1. Directed *ortho*-Metalation. Adopting a previously developed methodology for the directed *ortho*-metalation, specifically *ortho*-lithiation of tertiary arenecarboxamides with lithium tetramethylpiperide (LiTMP) on variety of arenes, in 1985 Eaton et al. demonstrated the possibility of directly attaching substituents to the cubane core with the assistance of an adjacent tertiary carboxamide functionality.^{73–75} In preliminary experiments, cubane-*N,N*-diisopropylcarboxamide (68) was treated with an excess of LiTMP in THF at 0 °C. After 10 min the reaction was quenched with CH₃OD and found roughly 3%

of monodeuterated cubane 70, most likely proceeding through intermediate lithiated cubane 69 (Scheme 20).

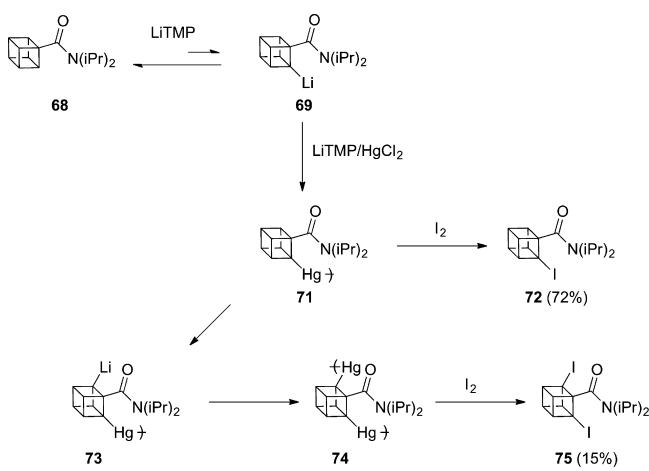
Scheme 20. *ortho*-Lithiation and Anion Trapping with CH₃OD

3.3.2. Transmetalation. Bearing in mind that at any given time in the above reaction, there is only a small concentration of the lithiated cubane 69 in solution, the authors felt that if they were able to trap the anion formed with an additional electrophilic metal, notably mercury, they would be able to make this method useful from a synthetic perspective.⁷⁵ They found that if the above lithiation is performed in the presence of mercury salts, the lithiated intermediate 69 is immediately mercuriated, creating a new C–Hg bond (71). They found that this species readily reacts with molecular halogens, most notably iodine and bromine which gives the monoiodinated species 72, and the corresponding bromide, respectively. In addition, they noted that once the anion has been consumed, the amide can participate in an additional metalation, allowing for the access to doubly halogenated cubanes such as diiodocubecarboxamide 75 (Scheme 21). While the mercury derivatives can be efficiently halogenated, other metal derivatives, including those of zinc, silicon, and tin have demonstrated a larger array of synthetic applications.⁷⁶

The Eaton group followed up with their seminal work by demonstrating the possibility to metolate and transmetallate and then perform a reverse transmetalation on the cubane core. This procedure allows for the access to dilithiated cubanes (80), which were previously inaccessible by direct lithiation of cubanecarboxamides (Scheme 22).^{10,75,77}

In 1988, Bashir-Hashemi et al. published the first transmetalation with magnesium salts in their studies toward the synthesis of phenylcubanes. They found that treatment of diamide 76 with LiTMP and MgBr₂ provided easy access to

Scheme 21. *ortho*-Lithiation and Anion Trapping with HgCl_2^{75}



mono- and bis-Grignard reagents (**81**) through similar activation as discussed above. Upon quenching with iodine (I_2), for example, they were able to obtain the tetraacid bisamide **82** in good yield. In addition, Eaton et al. have reported that, employing this method, the corresponding diacid (**83**) can be generated in high yield (Scheme 23, line 1).^{10,78} After failed attempts to generate phenylcubanes via cross-coupling methods, Bashir-Hashemi et al. discovered that when intermediate **81** is quenched with bromobenzene and followed by aqueous workup they were successful in generating diphenylcubane diamide (**85**) in a 53% yield. Additionally, if the reaction mixture is quenched with iodine (I_2) instead of performing a standard workup, the corresponding diiodinated compound **86** was produced in a 25% yield (Scheme 23, line 2).⁷⁹

While the application of *N,N*-diisopropylcarboxamides were useful in the generation of lithiated cubane derivatives, in a variety of cases it was not advantageous to carry this functionality throughout the whole synthetic sequence. As a result, Eaton and et al. developed a method for the conversion of amides like **83** to

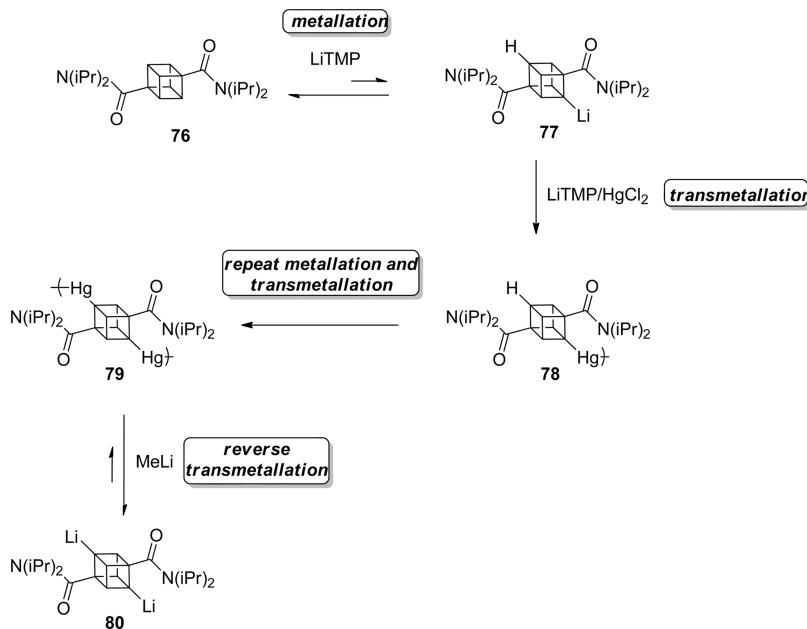
the carboxylic acid functionalities. Initial reduction with lithium aluminum hydride (LiAlH_4) to its corresponding amine (**87**) and subsequent oxidation with dimethyldioxirane to tetraacid **88** was achieved. Although this was effective on smaller scales, they found that initial borane reduction (BH_3) to **87** followed by oxidation with potassium permanganate (KMnO_4) to **88** to be most effective for large-scale preparation of these compounds (Scheme 24).⁸⁰

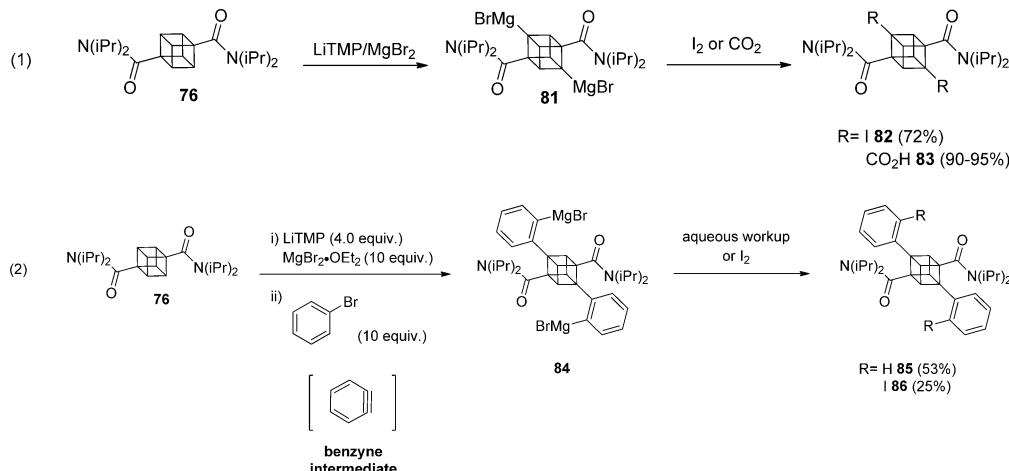
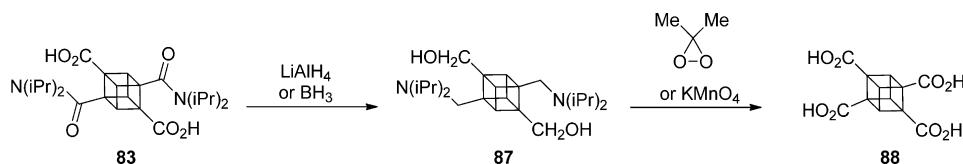
In addition, Bottaro et al. utilized a *tert*-butylethylcarboxamide as the activating group for a β -lithiation on the cubane core.⁸⁰ The advantage of this functionality is the possibility to hydrolyze it through the employment of strong acid. Alternatively, the *tert*-butyl moiety can be cleaved with mild acid treatment.

3.3.3. Proton Abstraction. In pursuit of synthesizing cubane derivatives with a variety of substituents, Eaton et al. found that treatment of 2,4-dicyanocubanamide (**89**) with LiTMP gave a mixture of two isomeric tetrasubstituted cubane carboxylic acids upon carboxylation (**90** and **91**).⁸¹ This was a significant discovery because the electron-withdrawing nature of cyano substituents on the cubane core with assistance from the amide group allows for a facile direct proton abstraction. It only requires a slight excess of base to give complete conversion (Scheme 25).

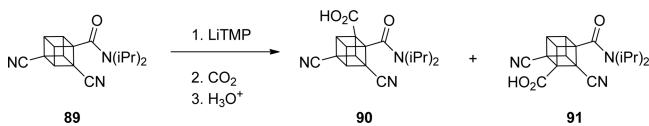
The authors noted that the above reaction, while effective, was not very selective for either **90** or **91**. It was discussed that activation of the cubane C–H bond by two flanking cyano groups is competitive with activation by the amide group of **89**, leading to a mixture of products **90** and **91**. In an effort to favor product **90** and enhance the *ortho*-metalation they envisioned that the addition of MgBr_2 would be suitable. When the employed ratio of LiTMP: MgBr_2 was 1.5:1, the product ratio raised to 9:1 in favor of **90**. This led to the discovery that β -magnesiation was possible with TMPPMgBr and/or by $(\text{TMP})_2\text{Mg}$, referred to as the Hauser base.^{82,83} This idea was further extrapolated upon by the Eaton group and these amide bases have demonstrated their utility in organic synthesis.^{84,85} Eaton et al. developed a protocol for the generation of these bases

Scheme 22. Reverse Transmetalation of Cubane^{10,75,77}

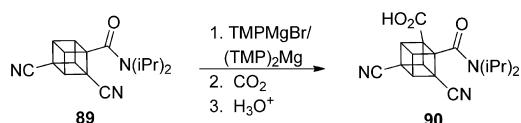


Scheme 23. *ortho*-Magnesiation through Metalation and Transmetalation Sequence⁷⁸Scheme 24. Conversion of the *N,N*-Diisopropylcarboxamide Substituted Cubane (83) to Tetraacid 88⁸⁰

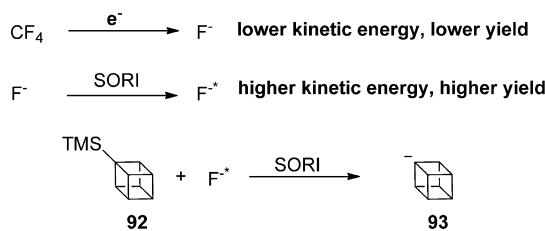
Scheme 25. Direct Deprotonation of the Cubane Core by LiTMP



and employed it with amide 89 to generate product 90, exclusively in 90% yield (Scheme 26).⁸⁴ The employment of these bases has since been further developed on arenes, for the purposes of *ortho*-magnesiation.^{82,85,86}

Scheme 26. Direct Deprotonation of the Cubane Core by TMPMgBr₂/(TMP)₂Mg⁸⁴

3.3.4. Sustained Off-Resonance Irradiation. Following kinetic experiments demonstrating that cubane (**1**) is a particularly acidic alkane and that its carbon–hydrogen bond dissociation energy (BDE) is greater than that of a typical tertiary C–H bond,^{87,88} Kass and et al. became interested in determining the respective homolytic C–H bond dissociation energy for one thermodynamic cycle.⁸⁹ They generated the cubyl anion in the gas phase by treatment of trimethylsilylcubane **92** with in situ generated fluoride ion. They noticed that this was rather poor yielding, so they employed a technique called sustained off-resonance irradiation (SORI) to increase the overall kinetic energy of the fluoride ion, leading to an increased yield of cubyl anion **93** (Scheme 27).⁸⁹

Scheme 27. Sustained off-Resonance Irradiation (SORI) Gas-Phase Experiments with Fluoride Ion to Generate the Cubyl Anion from Trimethylsilylcubane (**92**)⁸⁹

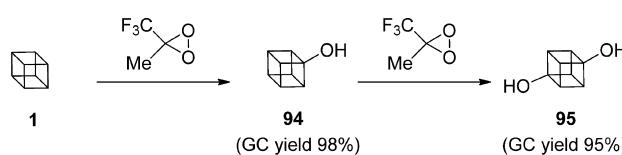
3.4. C–H Insertion Reactions

In 2009, the first direct C–H insertion reaction of cubane (**1**) was discovered. Curci et al. discovered that treatment of cubane (**1**) with (methyltrifluoromethyl)dioxirane (TFDO) performed a mono- and subsequent bishydroxylation of **1** to give mono- (**94**) and bishydroxycubane (**95**), respectively (Scheme 28).⁹⁰ The reaction is thought to proceed through a concerted oxenoid mechanism, in light of ease of formation of cubyl cations (Scheme 29).^{91,92}

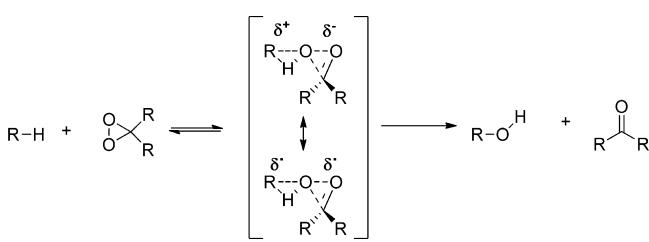
4. REARRANGEMENTS

4.1. Cubene (**1,2**-Dehydrocubane)

Cubene, or **1,2**-dehydrocubane (**42**), would be by far one of the most pyramidalized alkenes conceivable.^{93–96} As one can imagine, the geometry of the olefinic carbon atoms are far

Scheme 28. C–H Oxidation of Cubane⁹⁰

Scheme 29. Proposed Mechanism for C–H Oxidation of Cubane^{91,92}



from planar. In fact, Hrovat and Borden have calculated the pyramidalization angle of cubane to be 84° (Figure 6). As a result, the possible formation of cubene (42) was highly questionable.⁹⁷

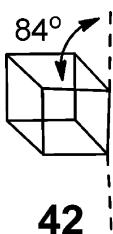
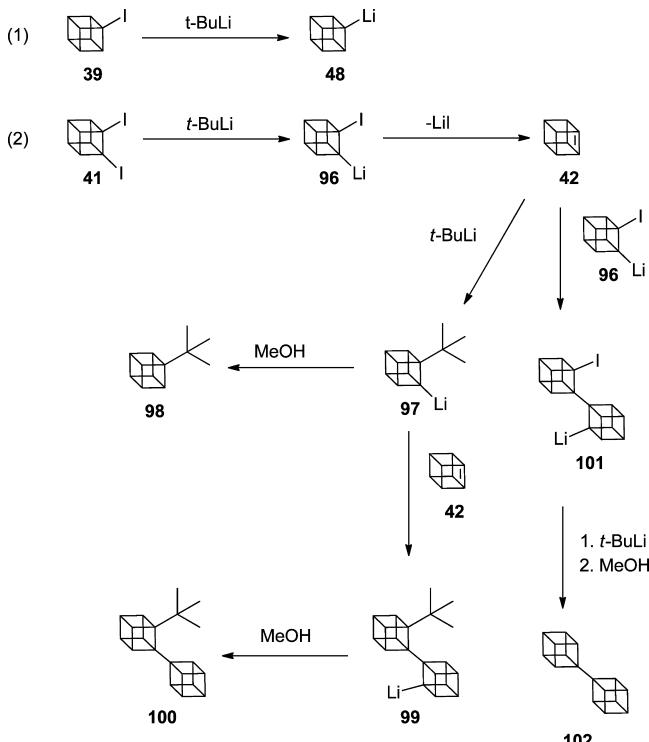


Figure 6. Pyramidalization angle of cubene (42).⁹⁵

Yet, the incredible discovery simultaneously came in 1988, when Eaton and et al. attempted to prepare cubene (42) for the first time. They found that reactions of monoiodocubane (39) with *tert*-butyllithium gave essentially only cubyllithium (48; Scheme 30, line 1), while the same reactions with 1,2-diiodocubane (41) gave mixtures of *tert*-butylcubane (98), and

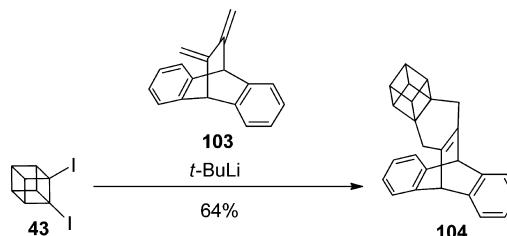
Scheme 30. Reactions of Mono- (39) and 1,2-Diiodocubane (41)⁵⁴



cubylcubanes (100, 102). The authors proposed that all the observed products must have featured the intermediacy of a cubene (42; Scheme 30, line 2). Further proof of cubene was demonstrated using Fourier transform ion cyclotron resonance (FT-ICR) mass spectroscopy which showed reacting cubane with atomic oxygen produced a radical ion of cubene.⁹⁸ Additional work explored the heat of hydrogenation (88 ± 5 kcal/mol), heat of formation (236 ± 5 kcal/mol), strain energy (225 ± 5 kcal/mol), and olefin strain energy (61 ± 5 kcal/mol) for cubene using the bond dissociation energy of the radical anion of cubene.⁸⁹

Given the predicted strain of cubene (42), and its presumed ability to rapidly react with a diene in a Diels–Alder reaction, the authors decided to try trapping it as a Diels–Alder adduct. They conducted the deiodination in the presence of 11,12-dimethylene-9,10-dihydro-9,10-ethanoanthracene (103) and indeed the corresponding 1:1 Diels–Alder adduct 104 was formed in a 64% yield (Scheme 31).⁵⁴

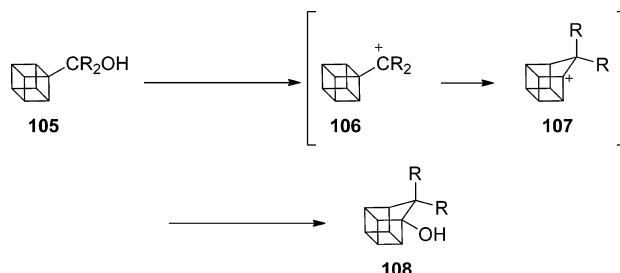
Scheme 31. Diels–Alder Reaction of Cubene (42) Formed in Situ from 1,2-Diiodocubane (41)⁵⁴



4.2. Cubylcarbinyl Cation

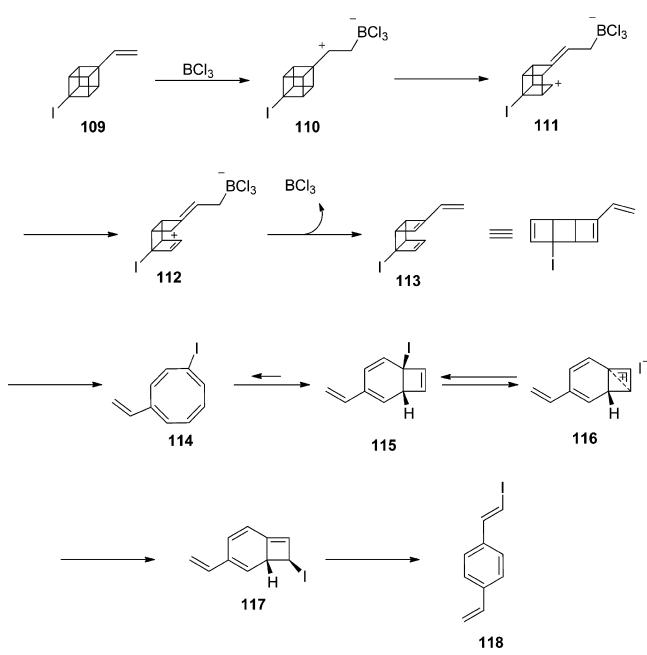
The cubylcarbinyl cation is yet another interesting intermediate that has shown unique intramolecular reactivity.⁹⁹ The first time that this intermediate was proposed was in the explanation of a rearrangement discovered by Eaton et al. in the preparation of cubylmethyl alcohols (105). They found that, if not handled with care, the alcohols have a tendency to rapidly rearrange into homocubyl derivatives (108) most likely via a tight ion pair (Scheme 32).^{10,100,101}

Scheme 32. Rearrangement of Cubylmethylalcohol (105) to Homocubyl Derivatives 108^{10,100,101}



Another interesting discovery and postulated cubylcarbinyl cation came from the work of Priefer et al. In an attempt to perform a polymerization of the iodovinylcubane 109, they found that the monomer in refluxing toluene unexpectedly rearranged to 4-vinyl-trans-β-iodostyrene (118). The addition of as much as 75% BCl_3 shortened the reaction time from 36 to 8 h. The mechanism of this transformation is depicted in Scheme 33.¹⁰²

Scheme 33. Proposed Mechanism for the Conversion of 4-Iodo-1-Vinylcubane (109) to 4-Vinyl-trans- β -iodostyrene (118)¹⁰²



A series of differential scanning calorimetry (DSC) experiments disclosed that, in comparison with other cubane derivatives, 4-Iodovinylcubane **109** gave a unique DSC thermogram due to a side product being generated, which was proposed to be 4-iodocyclooctatetraene **114** (Figure 7).¹⁰³

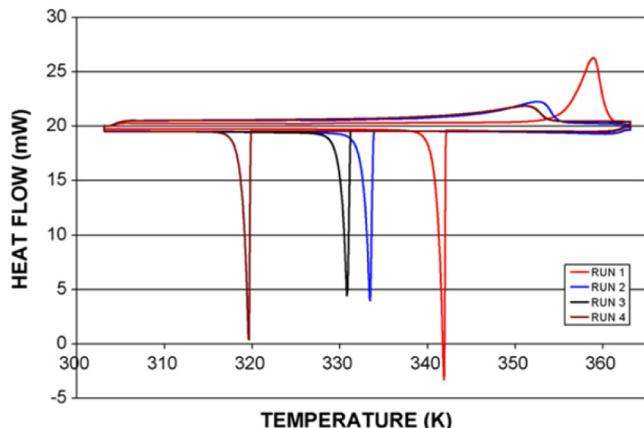


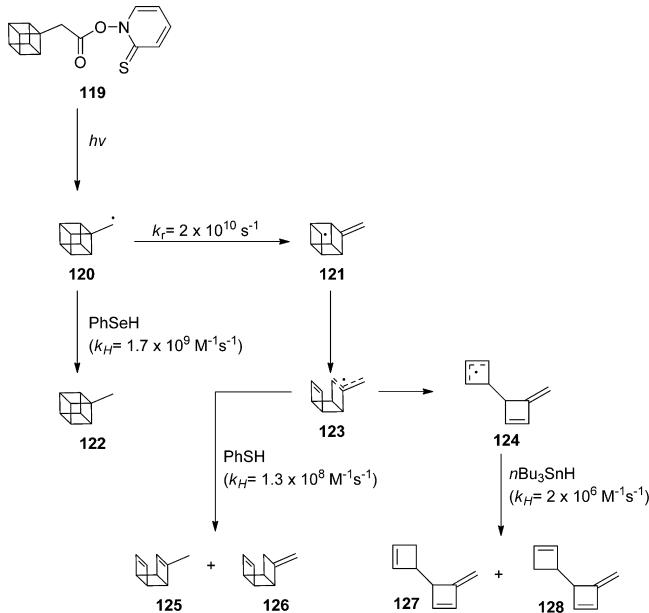
Figure 7. DSC thermogram of **109**.¹⁰³

4.3. Cubylcarbonyl Radical

In the early 1990s, the Eaton group began studying the reactivity of the cubylcarbonyl radical (**120**). They found that **120** can be generated by photolysis of the corresponding *N*-hydroxy-2-pyridinethione ester (**119**). A variety of reaction conditions favor hydrogen-atom transfer to the radical. Methylcubane (**36**) is formed only when a large excess of the PhSeH is present in solution, otherwise a rearrangement of the cubane core occurs. No evidence of a 1,2-shift was seen but cleavage of anywhere between one and three bonds occurs. The distribution of products (**36**, **125**, **126**, **127**, **128**), could be directly correlated to the lifetime of the radical generated. The respective rate

constants for various radical trapping reactions were determined (Scheme 34).^{88,104}

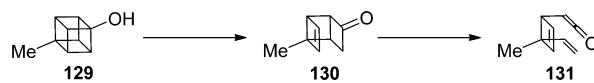
Scheme 34. Generation and Trapping of Cubylcarbonyl Radical with Various Reagents^{88,104}



4.4. Cubyl Alcohol

While cubanols can be prepared they are particularly fragile. For example, 4-methylcubanol (**129**) opens through a homoketalization pathway to tricyclooctenone (**130**), which further rearranges to vinylcyclobutenylketene (**131**) (Scheme 35).^{104,105}

Scheme 35. Rearrangement of 4-Methylcubanol (129) to the Respective Vinylcyclobutenylketene (131)^{104,105}

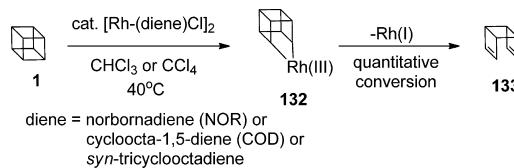


4.5. syn-Tricyclooctadiene and Cuneane

In 1970, Eaton et al. discovered some interesting novel conversions of cubane in the presence of transition metals. In the presence of rhodium(I) complexes, cubane (**1**) rapidly rearranges to *syn*-tricyclooctadiene (**133**). This has been postulated to go through a C–C bond insertion (**132**) followed by a 2-fold carbodemetalation event (Scheme 36).^{104,106}

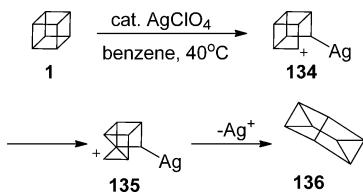
Another remarkable discovery was made by the same group in the same year.¹⁰⁶ In the presence of silver(I) salts and palladium(II) salts, cubane (**1**) undergoes a cation-cascade rearrangement to furnish cuneane (**136**). Shown in the context of AgClO_4 as catalyst, it was proposed that there is an initial

Scheme 36. Rearrangement of Cubane (1) to *syn*-Tricyclooctadiene (120)¹⁰⁶



cleavage of a carbon–carbon bond (**134**) in the cubane core followed by skeletal rearrangement to give cuneane (**136**; Scheme 37). It has also been shown that rearrangement of

Scheme 37. Rearrangement of Cubane (**1**) to Cuneane (**136**)¹⁰⁶

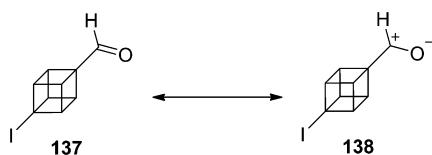


cubane (**1**) to cuneane (**136**) can be initialized by Li(I) with a weakly coordinating carborane anion.¹⁰⁷ Computational and experimental work has since shown that similar skeletal rearrangements can be initialized to generate various derivatives or isomers of cuneane through employment of either derivatives of cubane (**1**) in the above conditions and/or through employment of a proton source (H⁺).^{14,108,109}

4.6. Iodocubanes

After their initial discovery of a cage opening and rearrangement of 4-iodo-1-vinylcubane,^{102,103} Priefer et al. postulated that the aldehyde counterpart (**137**) should also undergo a similar cage opening, as the dipolar character expressed by **138** should facilitate an analogous rearrangement (Scheme 38).

Scheme 38. Dipolar Character of 4-Iodocubane-1-carboxaldehyde ()¹¹⁰



However, upon heating **137** in refluxing toluene for 7 days, it did not rearrange to the expected iodostyrene (**139**). Instead observed a mixture of 4-iodocubanecarboxylic acid (**140**), 1-iodo-4-(hydroxymethyl)cubane (**141**), benzaldehyde (**142**), benzylalcohol (**143**), benzoic acid (**144**), and benzyl benzoate (**145**; Scheme 39).¹¹⁰

The authors explained that the formation of products **140** and **141** are simply those of a Cannizzaro reaction of the aldehyde **137**,

while the others must result by a Cannizzaro reaction of benzaldehyde (**142**), formed from **137** by fragmentation via the cyclooctatetraene **146** and bicyclo[4.2.0]octatriene **147** (Scheme 40). This was substantiated by the observation of iodoacetylene (**148**).

4.7. 1(9)-Homocubenes

One of the most thought-provoking rearrangements comes from chemistry involving 1(9)-homocubenes. In 1987, Eaton et al. demonstrated that cubyl phenyl diazomethane (**149**) upon photolysis or thermolysis undergoes a rearrangement to 9-phenyl-1(9)-homocubene (**151**) based on solvent trapping and olefin trapping experiments.¹¹¹ Only a short time after, Jones et al. reported the same type of transformation in the H-substituted variant (**150** → **152**; Scheme 41).¹¹² This remains one the most remarkable anti-Bredt rule olefins to date.¹¹³ The authors mention that this would be called “*trans* in a five-membered ring.”

Further, it was also found that 1(9)-homocubenes (**153**) rearrange to 9-homocubylidenes (**156**). This type of rearrangement of an olefin to a carbene is extraordinarily rare.^{114,115} Appell et al. have shown that this type of rearrangement occurs reversibly.¹¹⁶ In addition, White et al. have confirmed that one component to the rearrangement is indeed a carbon–carbon shift in the homocubane framework.⁵⁵ Jones et al. have determined the equilibrium constant for the olefin–carbene rearrangement below (Scheme 42).^{10,117}

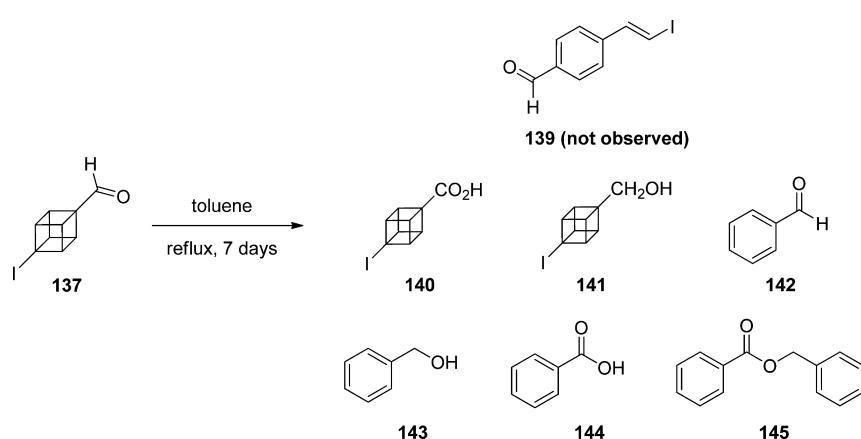
4.8. 9-Azahomocubenes

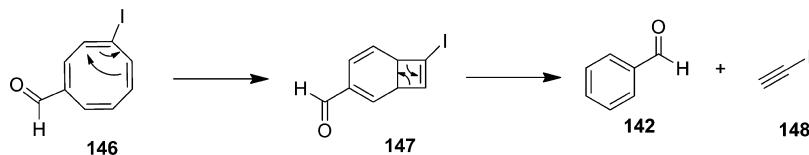
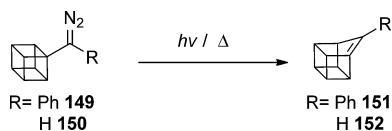
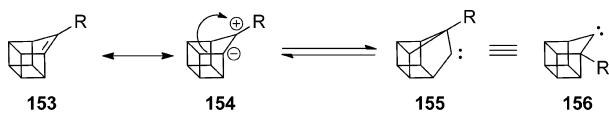
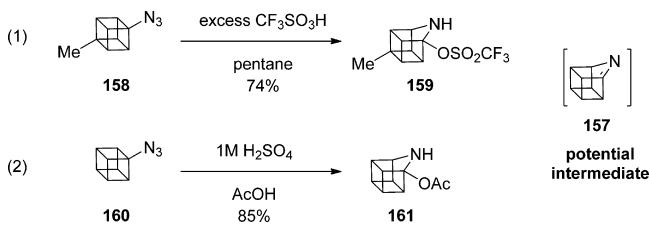
Another reaction that potentially proceeds through the intermediacy of homocubene is that of the formation of 9-azahomocubene (**157**). Eaton et al. found that when cubyl azide **158** was subjected to trifluoroacetic acid (CF₃SO₃H) in pentane that they were able to furnish 1-(trifluoromethylsulfonyloxy)-9-azacubane (**159**) in a 74% isolated yield. They also found that subjecting of cubyl azide **160** went through a similar transformation to give 1-acetoxy-9-azacubane (**161**; Scheme 43). They found that the latter reaction does not proceed without the addition of sulfuric acid (H₂SO₄) and, as a result, came to the conclusion that protonation of the starting azide is the initiating step.¹¹⁸ It should be noted that, while these transformations are thought to proceed through 9-azahomocubene **157**, this still has not been confirmed as an intermediate in the transformation.¹¹⁹

5. ENERGETIC MATERIALS

Energetic materials encompass various classes of chemical compounds that, upon initiation, undergo a rapid reaction,

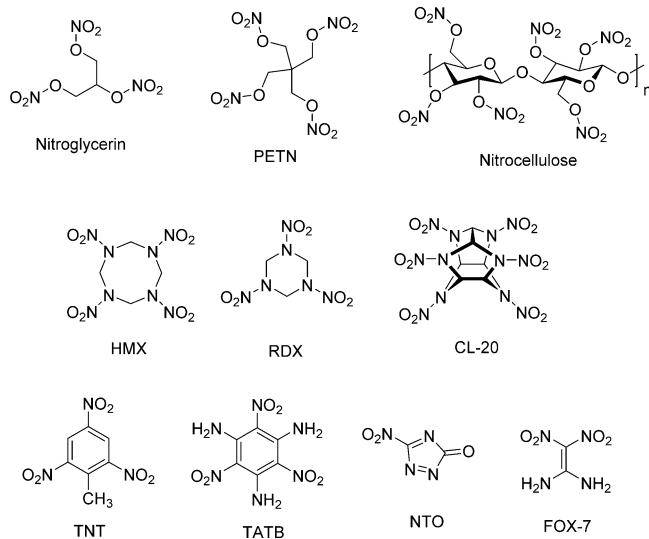
Scheme 39. Thermolysis of 4-Iodocubane-1-carboxaldehyde (**137**)¹¹⁰



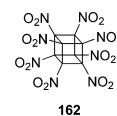
Scheme 40. Mechanistic Rationale for the Formation of Benzaldehyde (142) from 4-Iodocubane-1-carboxaldehyde (124)¹¹⁰**Scheme 41.** Photolytic or Thermal Rearrangement of Cubyl Phenyl Diazomethanes to Their Corresponding 1(9)-Homocubene Derivatives^{112,113}**Scheme 42.** Mechanism of Olefin–Carbene Rearrangement (153 → 156)^{10,117}**Scheme 43.** Examples of Reactions That Likely Proceed through a 9-Azacarbene (157) Intermediate¹¹⁸

releasing a great amount of energy. Typically this is generated by both a large exothermic change that produces heat and a large positive entropic change as solid or liquid material is converted to a high-velocity gaseous species. Such materials are generally classified as explosives, propellants, pyrotechnics, or incendiaries and they have found wide applications for industrial and military purposes. Explosive chemical reactions are strongly thermodynamically favored reactions where preferably the explosive material contains high potential energy and the products are energetically stable small molecules. Ideally, an explosive material would have high density, large potential energy (e.g., bond strain), and an elemental composition that, following decomposition, results in only stable gaseous compounds such as carbon dioxide and nitrogen. For these reasons, most commercial explosives contain nitro or nitrate groups, carbon, and little hydrogen. Examples of these are the nitrate esters such as nitrocellulose (guncotton), nitroglycerin, and pentaerythritol tetranitrate (PENT, which is combined with the common plastic explosive C4 (aka composition C-4) to produce Semtex); nitroamines such as cyclotrimethylenetrinitramine (RDX, the explosive component in C4), cyclotetramethylenetrinitramine (HMX), and the experimental CL-20; and nitro compounds such as trinitrotoluene (TNT), triaminotrinitrobenzene (TATB), 3-nitro-1,2,4-triazol-5-one (NTO), and 1,1-diamino-2,2-dinitroethene (FOX-7; Figure 8).

The cage compound CL-20 has a remarkably high density (2.04 g/cm^3) and a high heat of formation energy (460 kJ/mol),¹²¹ which are desirable properties in an explosive

**Figure 8.** Commercial and experimental explosives.

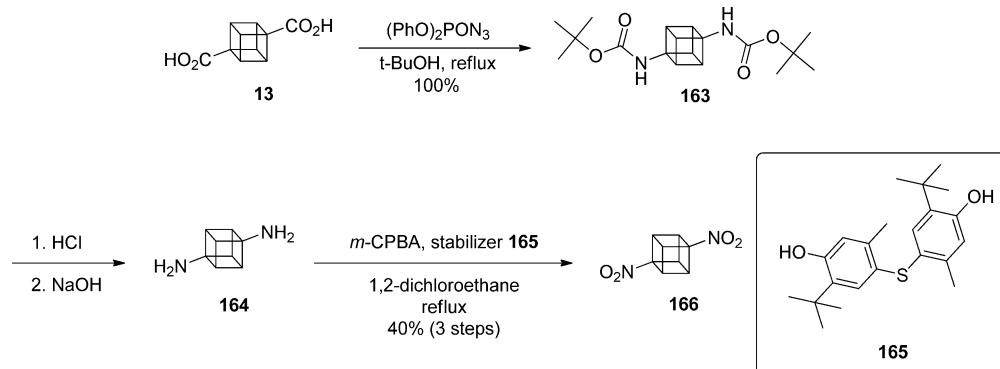
material.¹²² Both high density and high heats of formation are typical characteristics of strained cage compounds. One disadvantage of nitrate esters and nitroamines such as CL-20 is their relative sensitivity to friction and shock compared to the much more stable nitro compounds. These factors led scientists from the U.S. Army Armament Research and Development Center to postulate octanitrocubane (162; Figure 9) as an experimental new explosive at a Working Group Meeting on High-Energy Compounds (Hilton Head, SC, USA) in 1981.¹²³

**Figure 9.** Octanitrocubane (ONC) (162).

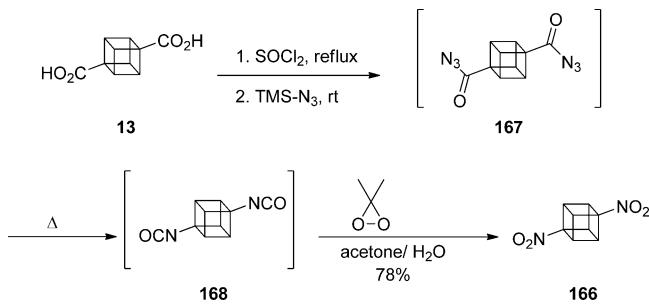
5.1. Nitrocubanes

The family of mono- to octanitrocubane derivatives are potentially useful explosives and have fascinating structures but are synthetically very challenging to access. As a result, it is no surprise that there have been a number of computational and theoretical reports attempting to predict the physical properties of these compounds. Both ab initio and semiempirical methods have been used, for example to predict heats of formation,^{124–130} densities,^{131,132} strain energy,^{133,134} and a variety of other thermodynamic and explosive properties.^{135–144}

The first nitrocubane derivative prepared was 1,4-dinitrocubane (166) by Eaton et al. in 1984 (Scheme 44).¹⁴⁵ The diacid (13) was treated with diphenylphosphoryl azide in refluxing *tert*-butanol to give the biscarbamate (163) after (163) Curtius rearrangement. Subsequent hydrolysis and decarboxylation gave 1,4-diaminocubane (164), which was notably unstable and decomposed overnight but was stored as the corresponding

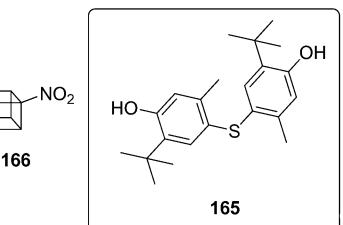
Scheme 44. Synthesis of 1,4-Dinitrocubane (166) from Diacid 13¹⁴⁵

dihydrochloride salt until use. The diamino compound (164) was oxidized to the 1,4-dinitrocubane (166) with *m*-chloroperbenzoic acid in refluxing dichloroethane with 4,4'-thiobis(2-*tert*-butyl-6-methylphenol) (165) as stabilizer, in a yield of 40% over 3 steps (Scheme 44). Differential scanning calorimetry showed that there was no obvious decomposition of 1,4-dinitrocubane (166) below its 260 °C melting point. This synthesis was subsequently improved upon by conversion of diacid 13 to the respective diacid chloride with thionyl chloride (SOCl_2) and subsequent conversion to the diacyl azide 167. This was then followed by Curtius rearrangement to diisocyanide 168 and finally treatment with dimethyldioxirane to furnish 1,4-dinitrocubane (166) in 78% yield (Scheme 45).¹⁴⁶

Scheme 45. Revised Route to 1,4-Dinitrocubane (166)¹⁴⁶

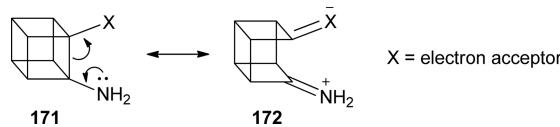
While 1,4-dinitrocubane (166) is a highly energetic material, it is surprisingly quite stable. High pressure studies using a diamond anvil demonstrated that 1,4-dinitrocubane (166) powder when compressed nonhydrostatically at room temperature to a stress of about 7 GPa explodes spontaneously and violently.¹⁴⁷ However, 1,4-dinitrocubane (166) shows no evidence of shock sensitivity under normal conditions and has a decomposition point above 250 °C.¹⁴⁵ In 1993, Eaton reported the synthesis of 1,3,5-trinitrocubane (169) and 1,3,5,7-tetranitrocubane (170; Figure 10).¹⁴⁸ It is noteworthy that neither of these molecules possess adjacent nitro groups (in a 1,2-disubstituted orientation).

An earlier computational study indicated that there would be a considerable C–C bond destabilizing effect having adjacent nitro and amino groups on the cubane core.¹⁴⁹ Indeed, while Eaton's group was able to prepare 1,2-diaminocubane, all attempts to synthesize 1,2-dinitrocubane through oxidation methods failed;¹⁴⁸ leading instead to unstoppable cage cleavage reactions. Such facile cage openings occur when the cubane structure bears an electron-donating group adjacent to an electron-withdrawing

Figure 10. Structural formulas of 1,3,5-trinitrocubane (169) and 1,3,5,7-tetranitrocubane (170).¹⁴⁸

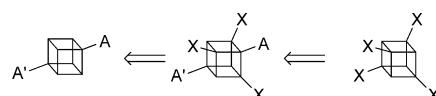
The pathway to decomposition of the cage has been attributed to delocalization through hyperconjugation (Scheme 46), and cubane derivatives bearing a 1–2-disubstituted, electron-

Scheme 46. Hyperconjugative Destabilization of the Cubane Nucleus

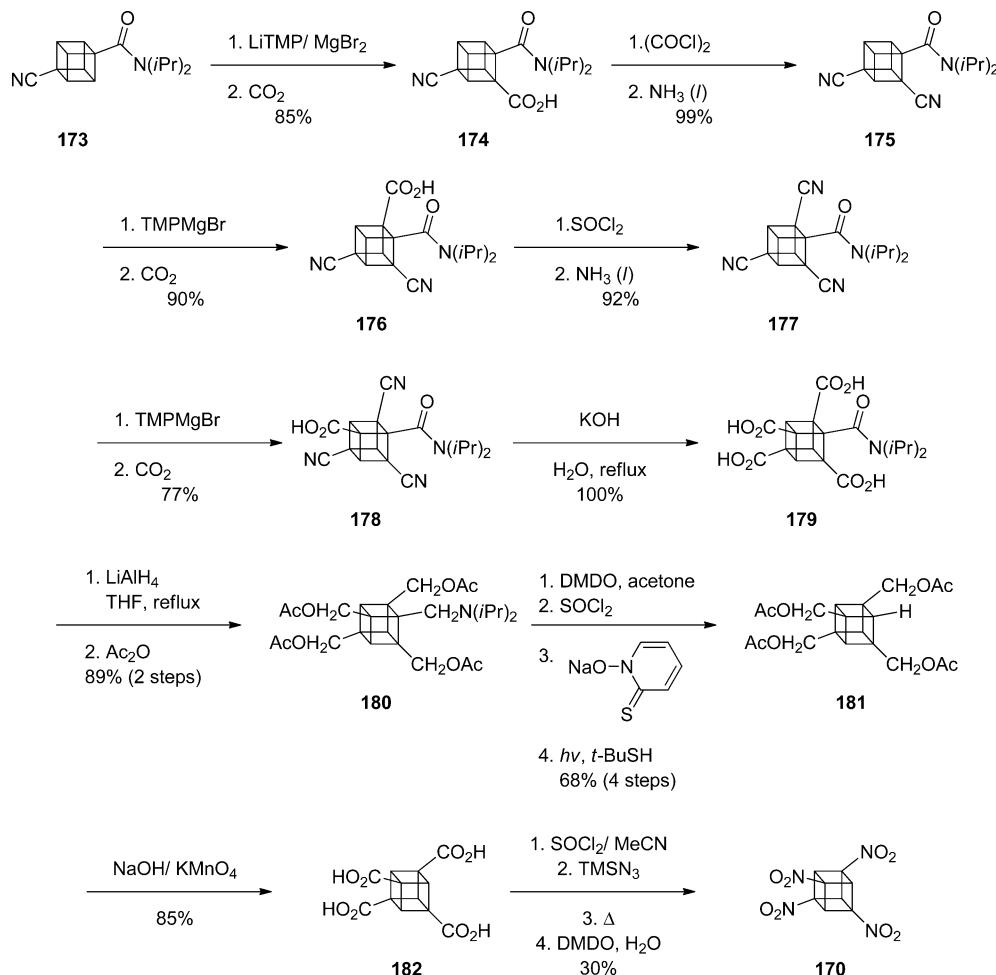


push–pull motif are virtually impossible to isolate. Weakening of the C–C bond between the substituents is enough to lower the kinetic barrier to ring-opening and hence trigger decomposition of the cubane nucleus.¹⁴⁹

The synthesis of 1,3,5-trinitrocubane (169) and 1,3,5,7-tetranitrocubane (170) was achieved by deliberately avoiding *ortho* substitutions of this type. The most accessible cubane starting materials are 1,4-disubstituted. So, the synthetic plan to arrive at a 1,3,5,7-tetrasubstituted cubane was to use *ortho*-directed metatlation to introduce a substituent (X) on each of the three adjacent carbons surrounding an activating group (A, A') followed by removal of the *ortho*-activating group (Scheme 47).

Scheme 47. General Strategy for Tetrasubstituted Cubane Synthesis¹⁴⁸

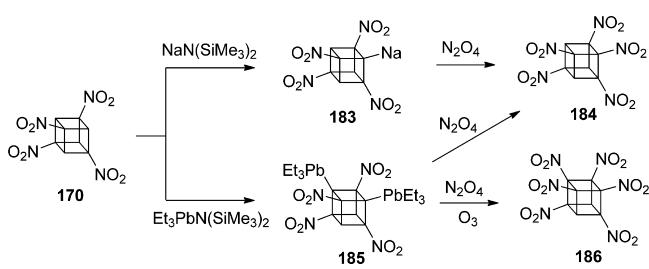
The synthetic sequence toward 1,3,5,7-tetranitrocubane (170) is outlined in Scheme 48. The known 4-cyano-(diisopropylcarbamoyl)cubane (173) was *ortho*-metallated relative to the directing carboxamide with LiTMP/MgBr₂, followed by CO₂ quenching to give carboxylic acid 174. The acid was converted to the corresponding nitrile (175) via a two-step sequence featuring conversion to the acid chloride by treating

Scheme 48. Synthesis of 1,3,5,7-Tetranitrocubane¹⁴⁸

with oxalyl chloride, then to the amide by treatment with liquid ammonia, and finally dehydration with thionyl chloride to furnish dinitrile **176**. The ortho-metallation/carboxylation and functional group manipulation was repeated twice more to arrive at the pentasubstituted derivative (**178**), which was hydrolyzed to the corresponding tetraacid (**179**). The four carboxylic acid groups were reduced with LiAlH₄ and the resulting tetrahydroxymethyl groups were protected as acetates (**180**). Dimethylidioxirane oxidation of the amide gave the corresponding acid, which was then subjected to the Barton decarboxylation sequence: treatment with thionyl chloride, followed by 2-pyridinethiolate N-oxide sodium salt to form the thiohydroxamate ester, and then irradiation in the presence of *t*-butylthiol to give decarboxylated cubane **181**. Oxidation of the resulting decarboxylated product gave the 1,3,5,7-tetraacid (**182**). The tetraacid (**182**) was then simply converted to the tetranitro derivative using a similar sequence of reactions as for converting the 1,4-diacid to the 1,4-dinitrocubane, as described above: thionyl chloride to give the tetraacid chloride, trimethylsilylazide to give the tetrakis-(azidoacyl)cubane, followed by thermal rearrangement in refluxing chloroform to give the tetraisocyanate, which upon oxidation by dimethylidioxirane in wet acetone gave 1,3,5,7-tetranitrocubane (**170**). Both 1,3,5-trinitrocubane and 1,3,5,7-tetranitrocubane (**150**) were found to be remarkably stable, with no thermal decomposition until over 250 °C, very dense, shock insensitive, and powerful explosives.¹⁵⁰

The synthesis of 1,3,5,7-tetranitrocubane (**170**) is undeniably tedious and long-winded with many functional group manipulations. The synthetic strategy is hindered by the instability of the cubane nucleus when there are adjacent electron-withdrawing groups and electron acceptors. The pK_a of 1,3,5,7-tetranitrocubane is in the range of 20.5–22.5, and it can be metalated with, for example, silyl, lead, mercury, and tin reagents. Reaction of the sodium salt of (**150**) with N₂O₄ led to a 60:40 mixture of 1,2,3,5,7-pantanitrocubane (**184**) and recovered tetranitrocubane. 1,2,3,5,7-Pantanitrocubane (**184**) was found to be colorless and highly crystalline, showing no obvious shock sensitivity or special thermal sensitivity, with decomposition occurring only above 250 °C.¹⁵⁰ When the bis(triethyllead) derivative (**185**) was treated with N₂O₄, followed by ozonolysis, a 40% isolated yield of a 40:60 mixture of pantanitrocubane (**184**) with hexanitrocubane (**186**) was obtained (Scheme 49).

The relative acidity of tetranitrocubane (**170**) proved to be the key to preparing the higher nitrocubane compounds. Anion formation with four equivalents NaN(SiMe₃)₂ followed by N₂O₄ at −130 °C gave a 74% yield of heptanitrocubane (**154**) on a 1 g scale.¹⁵¹ Single-crystal X-ray analysis of this compound provided an accurate density of 2.028 g cm^{−3} at 21 °C. While heptanitrocubane was found to be considerably acidic, treatment with excess N₂O₄ failed to produce octanitrocubane (**162**). However, when heptanitrocubane (**187**) was lithiated with LiN(SiMe₃)₂ and then treated with excess nitrosyl chloride followed by ozonation at −78 °C, octanitrocubane (**162**) was

Scheme 49. Synthesis of Hexanitrocubane (186)¹⁵⁰

formed in 50% yield on a millimole scale (Scheme 50). This presumably proceeded via the intermediate nitrosoyl compound, which was not isolated.^{151,152}

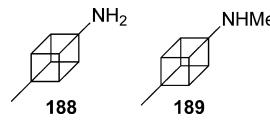
Octanitrocubane (162) was found to be a stable white solid, which crystallized as the monohydrate unless carefully prepared under anhydrous conditions. The density of this material was determined to be 1.979 g cm⁻³ based on X-ray analysis of a single crystal. Neither heptanitrocubane nor octanitrocubane could be detonated by hammer blows, and both decomposed above 200 °C. The density of octanitrocubane (162) disappointingly turned out to be at the lower end of the predicted range. Hence as a shock stable, explosive material it still falls short of materials such as CL-20. Aside from that, the heroic and complex synthesis of octanitrocubane makes it totally impractical as an explosive material. However, as a testament to the ability of organic synthesis to conquer molecules that appear impossible to make, octanitrocubane stands next to cubane itself as an impressive feat of endeavor.

6. CUBANE IN MEDICINE

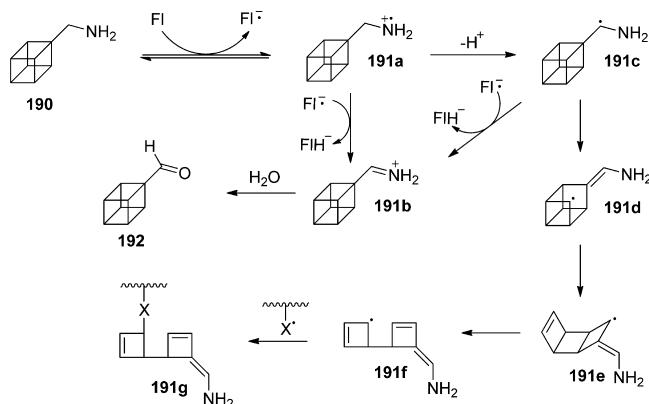
The unique structure of cubane which is derived from being a strained and saturated hydrocarbon system has made it an interesting target for pharmaceutical applications. The ability to functionalize the rigid structure at each carbon of cubane allows for the development of functionally complex compounds which can be valuable when designing drugs for specific active sites of an enzyme. The eight-membered cage also has the benefit of increasing the lipophilicity of a molecule which can allow for easier transport of the compound across cell membranes. The rigid frame is also well suited for achieving substitution patterns akin to benzene; however, one is able to achieve substitution above and below the plane of a benzene ring.

The earliest example of using cubane in medicinal chemistry can be found in a patent in 1971, and the compounds listed were found to be potent antiviral agents. 4-Methylcubane-1-amine 188 and 4-methylcubane-1-methylamine 189 were found to potent against the influenza virus.¹⁵³ Specifically when white mice were infected with influenza virus and treated with 189, their survival rate increased to 70% versus untreated and infected control mice which only had a 20% survival rate (Figure 11).

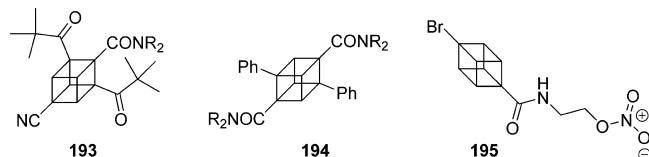
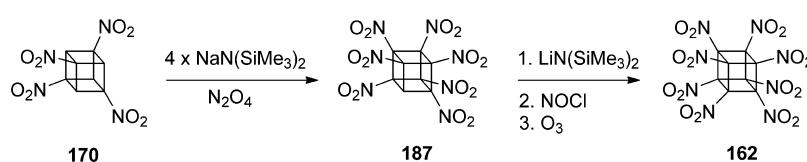
One early application of cubane in medicinal chemistry was the use of (aminomethyl)cubane (191) to probe the mechanism of action of monoamine oxidase-B (MAO-B) in the catalytic

**Figure 11. 4-Methylcubane-1-amine derivatives with antiviral properties.**

oxidation of a variety of amine containing neurotransmitters. (Aminomethyl)cubane (191) was used to study the oxidation because the ring cleavage of a cubylcarbonyl radical is 3×10^{-3} s⁻¹ greater than any other radical derived from a saturated hydrocarbon system.¹⁵⁴ Based on the obtained products, they were able to propose a one-electron transfer from the amine to the flavin, which then forms a α -amino radical (191c) by extraction of an α -hydrogen. This intermediate can then partition to form the aldehyde product 192 by a single electron transfer or ring cleavage to give reactive radical products which causes inactivation by covalently binding to the enzyme (Scheme 51).

Scheme 51. Inactivation of Monoamine Oxidase by (Aminomethyl)cubane¹⁵⁴

A variety of compounds have been synthesized using the cubane scaffold and were evaluated by the National Institute of Health in a preliminary biological-activity screening. The dipivalylcubane 193 showed anti-HIV activity while the phenylcubane derivative 194 displayed anticancer activity.¹⁵⁵ The most notable result from the screening of cubane derived compounds was the lack of any toxicity, suggesting that caged structure is safe in pharmaceutical applications (Figure 12).

**Figure 12. Functionalized cubane derivatives used in biological-activity screenings¹⁵⁵****Scheme 50. Synthesis of Octanitrocubane (162)**

Using the cubane scaffold, specifically 1,4-disubstitution, a library of compounds were synthesized and tested for their activity in cardiac pharmacology. The study found that structure **195** was most active in aorta relaxation and calcium channel blocking, even more active than nicorandil.¹⁵⁶ Nicorandil is used as an antiangina medication which is comprised of a linked nitrate and K⁺-ATP channel agonist, and it is approved for use in Europe, Australia, and the United Kingdom.

Previous work has demonstrated that opioid activity of morphinoids is directly related to its nitrogen substitution. Exploring modification of the alkyl substitution can lead to potent morphine antagonists with *N*-allyl and *N*-cyclopropylmethyl derivatives serving as partial agonists. Since the endocyclic orbitals of cubane are richer in p character, incorporation of the unique scaffold into morphinoids has led to the discovery of potent ligands for both the μ and κ opioid receptors.¹⁵⁷ The antagonist activity of the morphine derivative **196** and the oxymorphone derivative **197** are similar to the *N*-allyl and *N*-cyclopropylmethyl derivatives; however, they have a slightly reduced potency which is attributed to unfavorable steric interactions involving the cubane cage (Figure 13).

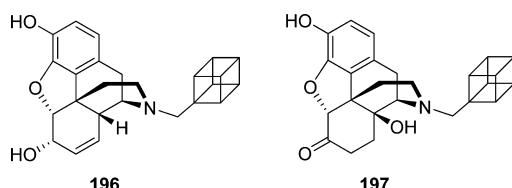


Figure 13. Novel narcotic antagonists.¹⁵⁷

Use of bridged-fused rings (BFRs) in the synthesis of new 5-hydroxytryptamine (5-HT_{1A}) antagonists has been evaluated. 5-HT_{1A} receptors are shown to be involved in various neuropsychiatric disorders including depression, anxiety disorders, Alzheimer's, and schizophrenia. Initial discovery of antagonists for 5-HT_{1A} and subsequent metabolic studies showed that the amide bond is rapidly hydrolyzed, to overcome this metabolic pathway **198a–b** and other BFR derivatives were synthesized in order to obtain compounds with better stability profiles *in vivo*.¹⁵⁸ **198b** was found to bind to the 5-HT_{1A} receptor with high affinity, maintain comparable inhibition activity of the parent compound **199**, maintain a desirable log D_{7,4} of 2.94 ± 0.01 for crossing the blood brain barrier, and improve the metabolic stability of the compound. The fluoromethyl group on the cubane scaffold also prevents any defluorination through loss of hydrogen fluoride, further increasing its *in vivo* stability.¹⁵⁹ The compounds were found to maintain high selectivity for 5-HT_{1A} receptors in rat brain using ¹⁸F-labeling; however, further studies showed that the compounds were unstable toward enzymatic defluorination (Figure 14).

In a more recent publication, the diester **7** was evaluated as a starting material for the synthesis of pharmaceutically relevant

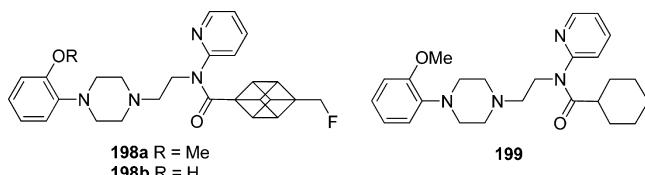
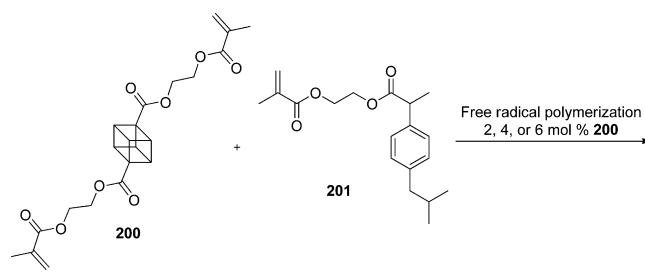


Figure 14. Cubane containing 5-hydroxytryptamine (5-HT_{1A}) antagonists.^{158,159}

cubane containing molecules. Starting with **7** a wide variety of functional group manipulations were carried out on a multigram scale.¹⁶⁰ Taking advantage of the rigid structure and size of the cubane scaffold, the authors produced a library of new molecules and novel heterocycles for incorporation into medicinal chemistry programs. Additional work has evaluated the incorporation of cubane into N-methyl-D-aspartate receptor antagonists for potential use in the treatment of central nervous system pathologies.¹⁶¹ The authors found that incorporation of the cubane scaffold or the larger adamantane group in place of a benzene ring reduced activity of the antagonists, suggesting that steric bulk is not tolerated in the active site.

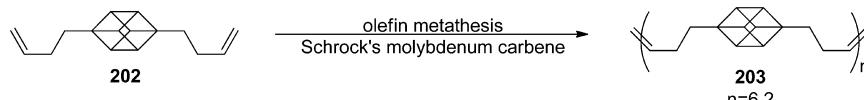
Another application in medicinal chemistry, which is different from the above applications, takes advantage of cubane being generally innocuous in biological systems. In an effort to create macromolecular prodrugs, which can prolong the pharmacological activity of drug, Mahkam and co-workers sought to use cubane-1,4-dicarboxylic acid as a difunctional cross-linking agent in polymers containing ibuprofen.¹⁶² The polymers were produced using either 2, 4, or 6 mol % of cubane-1,4-bis(methacryloyloxyethyl)carboxylate **200** and monomer **201** with a hydrolyzable form of ibuprofen. This results in varying degrees of cross-linking which controls the mobility of the drug on the polymer chain and its sensitivity toward chemical or enzymatic hydrolysis. In addition to ibuprofen another NSAID, indomethacin, was used to make a polymeric prodrug using the same technique (Scheme 52).¹⁶³

Scheme 52. Free Radical Polymerization Using **200** As a Crosslinker Reagent^{162,163}



The polymers made using cubane as a cross-linker were then tested for their thermal properties as well as their rate of hydrolysis to release the active drug. In all cases the polymers with a higher degree of cross-linking (6 mol % **200** used) had higher glass transition temperatures (T_g) and higher temperatures for maximum decomposition rates. They also had slower release rates for the drugs attached to the polymer, which is consistent with a more rigid polymer inhibiting hydrolysis of the ester on ibuprofen/indomethacin.

The polymers produced using **200** and **201** were found to be insensitive to pH, with similar rates of hydrolysis at pH 8 and 1. Further work using additional monomers was completed in order to evaluate their effect on swelling and drug release rates of the hydrogels.^{164–166} Incorporation of glucose, 3,3-azobis(6-hydroxybenzoic acid), silanes, or *N*-vinyl-2-pyrrolidinone has led to polymers with varying release rates (hydrolysis of ester bond) and different swelling properties. This method of controlling the release of a drug is often desired in medical treatment but difficult to achieve; however, using a biologically safe cross-linker like cubane-1,4-dicarboxylate it becomes possible to do so.

Scheme 53. First Example of a Polymer Containing a Cubane Backbone¹⁶⁷

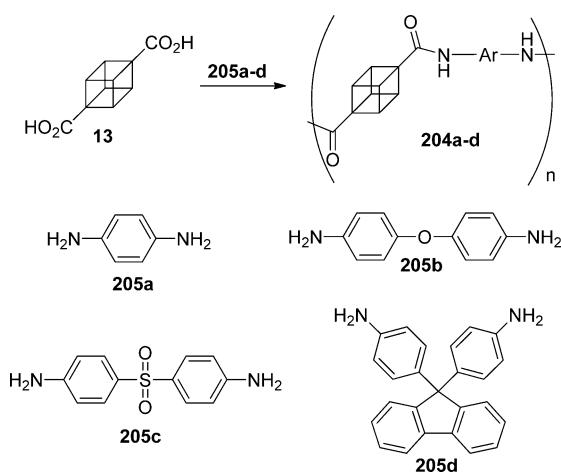
7. CUBANE IN POLYMER CHEMISTRY

It has been postulated that, since cubane has high strain energy, it has many applications in materials and propellant chemistry. Cubane also offers a very rigid three-dimensional structure which can be used to create new materials with interesting properties. Herein are detailed applications of the cubane scaffold in polymer chemistry with unique thermal and physical properties.

The first attempt at synthesizing a polymer containing cubane was the metathesis polymerization of the 1,4-bis(homoallyl)-cubane, **169**. Chauvin reported that **170** with catalyst $[(CF_3)_2MeCO](N-2,6-C_6H_3-i-Pr)Mo=CHC(Me)_2Ph$ afforded an oligomer with an average of 6.2 repeat units per chain (**170**).¹⁶⁷ In hopes of increasing the solubility of the growing polymer, and thus increase the chain length, Chauvin also carried out a copolymerization of **169** and 1,5-hexadiene (1:1). This synthetic procedure yielded a polymer with 14 repeat units (butenylene:cubylene = 0.56:1). The most notable observation was that the oligomer and copolymer were formed without rearrangement of the cube structure (Scheme 53).

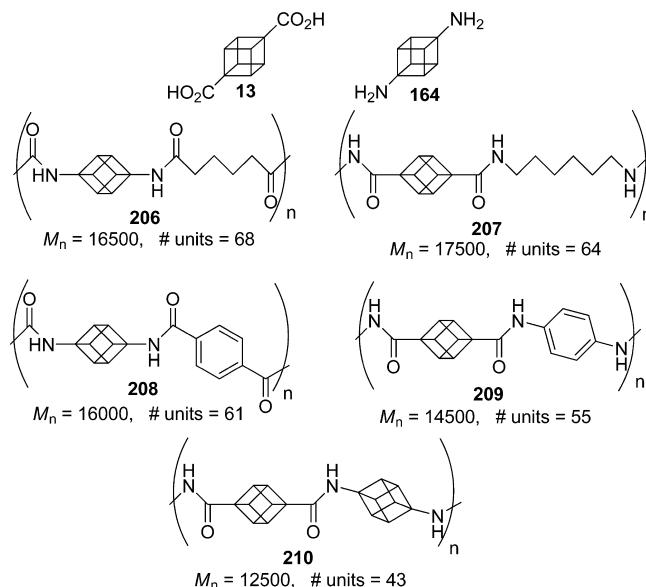
In hopes to circumvent the problem of solubility, Kakuchi performed polycondensation reactions of cubane-1,4-dicarboxylic acid (**13**) to form polymers **204** using a range of aromatic diamines (**205a–d**).¹⁶⁸ He envisioned that, upon formation of polymers **204**, it would be possible to react it with a rhodium catalyst (which is known to open the cage)¹⁰⁶ and with heating and could form the cyclooctatetraene containing polymer. Grubbs has shown that cyclooctatetraene can open via a ring opening metathesis polymerized to form polyacetylene;¹⁶⁹ thus, **204** could ultimately be converted to a grafted or network polymer (Scheme 54).

It was reported that polymers containing diamines **205c** and **205d**, were the only two that were soluble enough to run gel permeation chromatography (however they still required N,N-dimethylformamide to solubilize the polymers).¹⁶⁸ The polymer **204c** had a number-average molar mass (M_n) = 8.3×10^3 and a polydispersity index (PDI) of 3.60. This corresponds to a length

Scheme 54. Polycondensation of Cubane-1,4-dicarboxylic Acid (**13**) and a Variety of Aromatic Diamines (**205a–d**)¹⁶⁸

of ~20 units. With diamine **205d**, they obtained a polymer with a $M_n = 1.2 \times 10^4$ and PDI of 2.41. This corresponds to a length of ~25 units. In all the examples he reported, only concentrated H₂SO₄ could solubilize all of the cubane-based polymers. In addition they were able to show that indeed the cubane moiety could be isomerized with a rhodium catalyst such that cyclooctatetraene units were then incorporated into the polymer.

Another use of cubane in polymer chemistry that has been utilized also deals with polycondensation to generate a cubane containing backbone. Mahkam reported five cubane-based polymers, derived from cubane-1,4-dicarboxylic acid (**13**), 1,4-diaminocubane (**164**), and a variety of different diacids and diamines to form polymers **206–210**.¹⁷⁰ Figure 15 illustrates

Figure 15. Polycondensation of cubane-1,4-dicarboxylic acid (**13**) and 1,4-diaminocubane (**164**) with a variety of diacids and diamines.¹⁷⁰

that the number of monomer units reaches a maximum of 68 when monomers **164** and adipoyl chloride are reacted to form polymer **206**. When the two cubane monomers (**13** and **164**) are reacted together, the polymer, **210**, has 43 repeat units. None of the polymers were soluble in THF, and only partially soluble in DMF and DMSO. Solubility was only achieved in TFA and formic acid (Figure 15).

Other approaches to producing polymers containing cubane in the backbone of the polymer scaffold were evaluated by use of additional monomers. Related to his medicinal applications, Mahkam used silane and hydroxy containing methacrylates with cubane-1,4-bis(methacryloyloxyethyl)carboxylate **200** as a cross-linking agent to perform free radical copolymerization.^{171,172} When analyzed the polymers containing **200** had T_g values higher than the polymers without any cross-linking monomer.

As stated, solubility was an issue in the examples described above. It was postulated, that this problem is due to the lack of free rotation in the systems where the cube is part of the polymer chain. This promotes the polymer to come out of solution and

thus prematurely terminate the polymerization. Therefore, it was envisioned that having the cube tethered to a polymer backbone may increase the free rotation of cubane, and the increase in entropy would thus increase the solubility, allowing for homopolymer formation. Ring-opening metathesis polymerization of cubane tethered norbornene monomers was carried out to obtain **211** and **212**.¹⁷³ Polymer **211** was found to have a M_n of 3.6×10^4 and a PDI value of 1.26 which corresponds to ~143 units. Polymer **212** was found to have a M_n of 2.7×10^4 and a PDI value of 1.11 which corresponds to ~71 units (Figure 16).

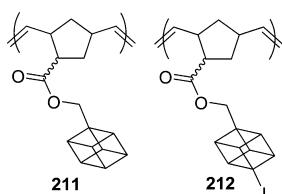


Figure 16. Cubane containing norbornene polymers.¹⁷³

The two polymers synthesized (**211** and **212**) were found to exhibit no glass transition or melting temperature. They are of high molecular weight and soluble in low-polarity solvents. Thermogravimetric analysis (TGA) was performed on the polymers and the iodinated cubane-containing polymer (**212**) underwent rapid thermodecomposition at approximately 250 °C (Figure 16). The nonfunctionalized polymer **211** showed better inherent thermal stability with maximum decomposition occurring above 400 °C (Figure 17).¹⁷³

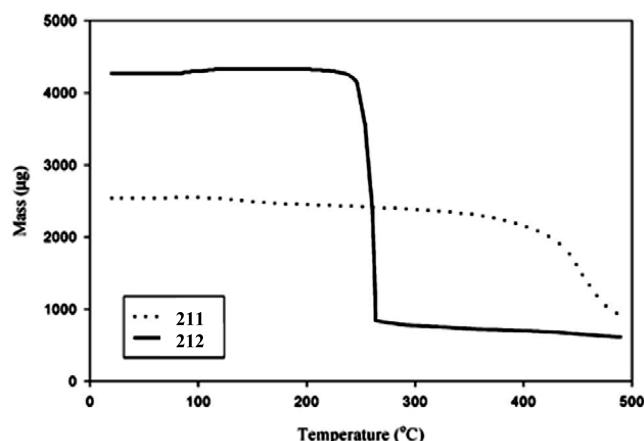
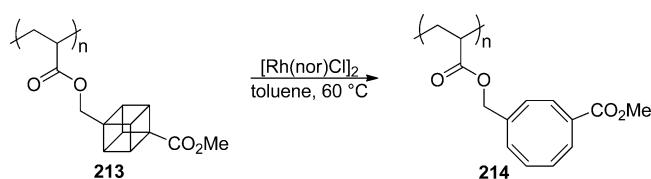


Figure 17. TGA of the norbornene based polymers.¹⁷³

The synthesis of polymers with a cubane moiety attached has been of special interest due to the unique thermal and physical properties of cubane. One interesting project looked at synthesizing a low shrink polymer.¹⁷⁴ There is a loss in volume when a molecule polymerizes which is due to tighter molecular interaction upon formation of covalent bonds that leads to a higher density and lower volume. Poly[methyl 4-(acryloyloxymethyl)cubane carboxylate] (**213**) was synthesized, and then a metal-induced ring-opening was performed to attempt to overcome the volume shrinkage (Scheme 54). A 2.5% volume increase was observed following the opening to the cyclooctatetraene (**214**) (Scheme 55).

More recently cubane was used as a linker in the synthesis of polynorbornene-based double-stranded ladderphanes. The

Scheme 55. Metal-Induced Ring-Opening of Poly[Methyl 4-(acryloyloxymethyl)cubane carboxylate] (**213**)¹⁷⁴



polymers were produced with Grubbs first generation catalyst by ROMP of cubane tethered bis-norbornenes.¹⁷⁵ Monomers **215**, **216**, and **218** readily polymerized in high yields and formed their corresponding polymers (**219**, **220**, and **222**) which consist of 9–16 subunits. The ester linkages could be hydrolyzed postpolymerization to obtain single stranded norbornene based polymers with identical degrees of polymerization (Scheme 56).

Monomer **217**, which is generated by treating **215** with catalytic amounts of $[\text{Rh}(\text{NBD})\text{Cl}]_2$ did not undergo polymerization, and only 20% of the starting material was consumed (20 mol % catalyst was used for the ROMP). In order to investigate this phenomenon, compound **224** was synthesized from the diacetate **223** and subjected to a equimolar amount of Grubbs first generation catalyst to yield **225** in a 58% yield (Scheme 57). The mechanism of this transformation is unreported; however, loss of ethylene occurs, and the alkene of cyclobutene is more reactive than norbornenes. To overcome this decomposition, polymer **221** was made by ring-opening of **219** using rhodium and was obtained in an 85% yield.

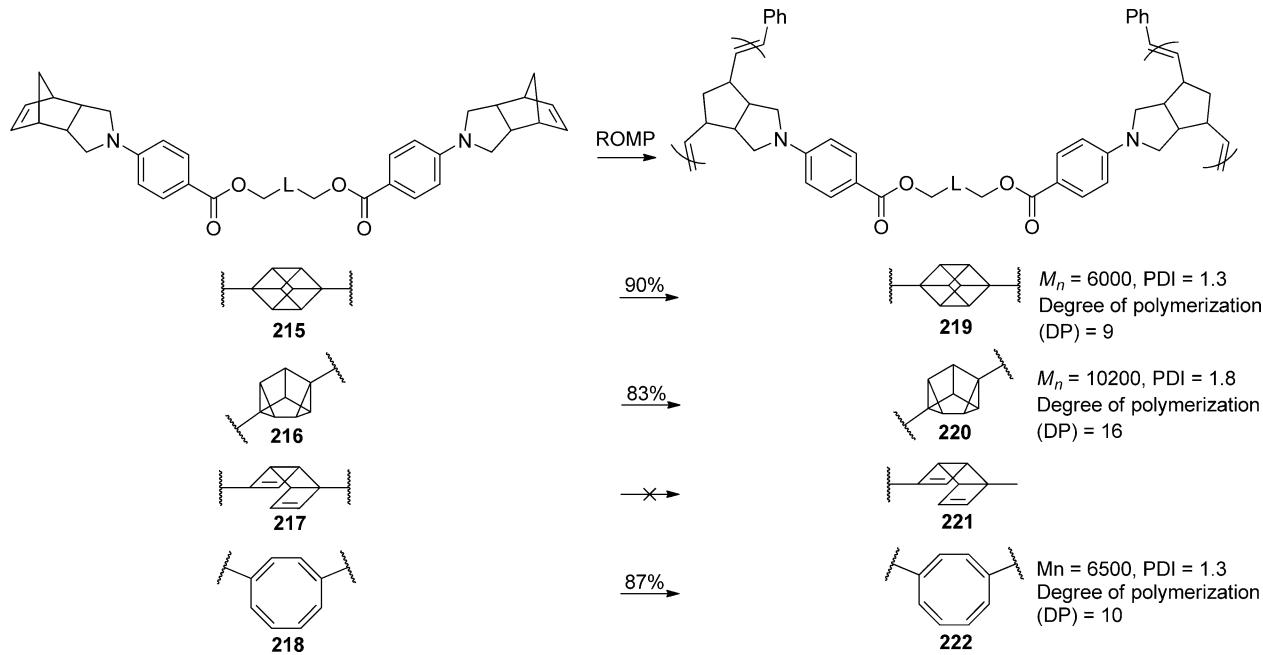
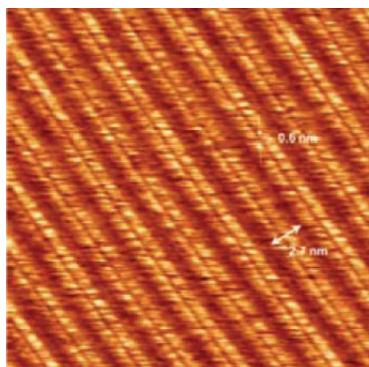
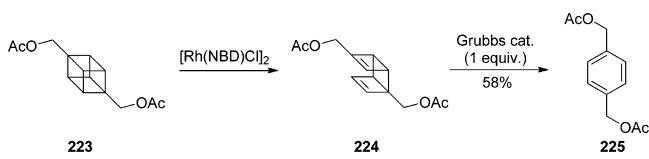
The ladderphanes synthesized above were analyzed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), as well as scanning tunneling microscopy (STM) of **219** was performed.¹⁴³ DSC showed no glass transition temperatures, while TGA showed temperatures ranging from 244 to 304 °C corresponding to a 5% weight loss. The STM images show an ordered pattern by self-assembly on highly ordered pyrolytic graphite (HOPG) with the bright stripe width of 2.7 nm which is consistent with the estimated width of the cubane containing ladderphane **219** (Figure 18).¹⁷⁵

Other work has evaluated the synthesis of cubane oligomers which form rode-like structures with very poor solubility and they have been proposed for use in small gap polymers.¹⁷⁶ The oligomers are synthesized by reacting cubyllithium **226** with 1,4-diiodocubane (**43**) in ether, and halogen exchange equilibrium occurs to give **227** and **228**.¹⁷⁷ Loss of lithium iodide in compound **228** gives the reactive intermediate cubane-1,4-diyl **47** in very small concentrations. This intermediate then reacts with an equivalent of cubyllithium **226** to give the dicubyllithium product **229**. That product can react further with cubane-1,4-diyl to give higher molecular weight oligomers which terminate with a halogen-metal exchange giving **232**. Each cubane adds ~4.15 Å to the length of each rod giving rise to ones as long as 15 Å. Modification of substituents was also evaluated and its effects on solubility and crystal structure (Scheme 58).

8. NOVEL CUBANES

8.1. Cubane β -Cyclodextrin Complex

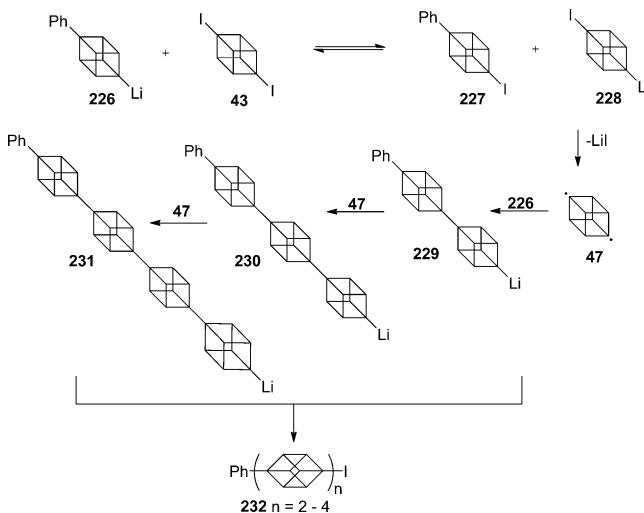
One of the more unique applications of cubane involved tethering the hydrophobic cubane scaffold to β -cyclodextrin and evaluating the resulting intramolecular complexation. The complexes were dissolved in D_2O and evaluated by 2-D NMR to characterize the intramolecular association of the hydrophobic core of β -cyclodextrin and cubane.¹⁷⁸ The solutions of **233** and

Scheme 56. Using ROMP to Generate Cubane and Valence Isomers Containing Double-Stranded Ladderphanes¹⁷⁵Scheme 57. Transition Metal Mediated Decomposition of Tricyclooctadiene¹⁷⁵Figure 18. STM images of 219 on HOPG. Imaging conditions of E_{bias} , $i_{\text{tunneling}}$, and image size: 0.68 V, 174 pA, and 22 × 22 nm².¹⁷⁵

234 readily form 233' and 234' due to the favorable hydrophobic interactions; however, addition of adamantyl carboxylate 235 readily excludes cubane to form 236 and 237. Although this is not a true comparison (the carboxylate ion of 235 vs the Me ester of 233/234) this demonstrated that there is a stronger hydrophobic attraction of the adamantane arising from a closer fit inside the β -cyclodextrin (Scheme 59).

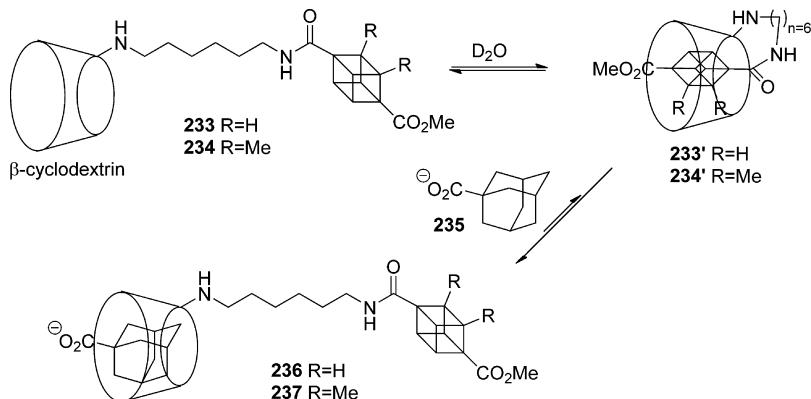
8.2. Cubane Sulfides

Evaluation of new cubane with different heteroatom substitution has been of high interest over the years, previous attempts to incorporate sulfur substitution on the cage was mostly unsuccessful due to the labile nature of resulting structures.¹⁷⁹ It was thought that by oxidizing cubanethiol 206 to dicubyl

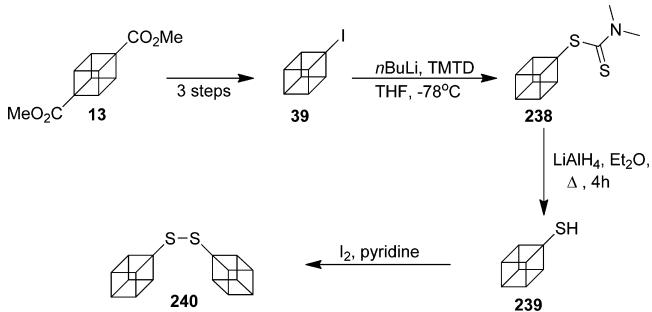
Scheme 58. Cubane Oligomerization¹⁷⁷

disulfide 207 it would be stable enough for X-ray crystal structure as well as NMR studies.¹⁸⁰ Dicubyl disulfide was synthesized in a 47% yield from the starting 1,4-diester (13) and the X-ray structure analysis showed a C–S–S–C dihedral angle of 86.5°. This angle is 20–30° lower than other disulfides bearing tertiary carbons at sulfur. It also exhibits a remarkably short C–S bond which results from stabilization of the torsional transition state by bonding–antibonding interactions between the sulfur π -lone electron pairs and the strained carbon cage.

In 2002, Priefer and Harpp first synthesized and fully characterized cubyl thiol and dicubyl disulfide.¹⁸⁰ Starting from commercially available dimethyl-1,4-cubanedicarboxylate (13) they were able to convert to iodocubane (39). Once 39 was in hand, it was converted to S-cubyl-*N,N*-dimethylthiocarbonate 238 via a base-initiated reaction of monoiodide (39) with tetramethylthiuram disulfide (TMTD) at low temperature. Subsequent reduction with lithiumaluminum hydride (LiAlH_4)

Scheme 59. Intramolecular Complexation of Cubane Tethered to β -Cyclodextrin¹⁷⁸

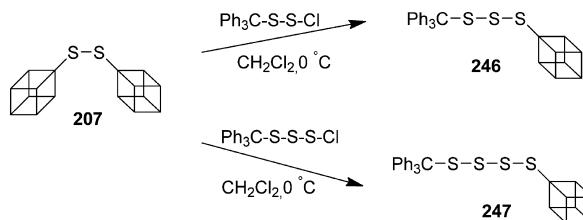
yields thiol **239**, and finally rapid oxidation with I_2 to afford dicubyl disulfide **240** (Scheme 60).

Scheme 60. Synthesis of Cubyl Disulfide, **240**^{145,179,180}

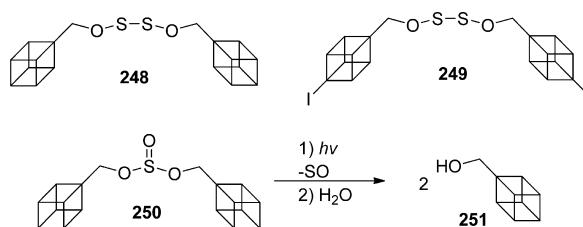
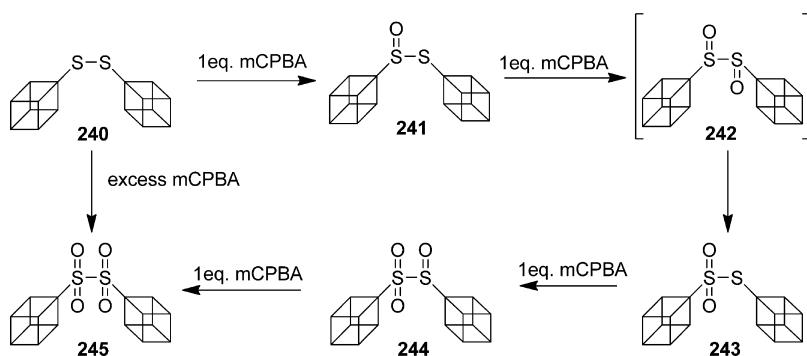
Priefer and Harpp continued their studies with dicubyl disulfide (**240**) with a series of oxidation and sulfur insertion reactions.¹⁸¹ As demonstrated in Scheme 61, starting with dicubyl disulfide, they found that careful stoichiometric additions of *m*CPBA could furnish a variety of oxidized dicubyl disulfides (**241–245**). Of note is that treatment of **240** with excess *m*CPBA furnished *vic*-disulfone (**245**) cleanly.

The authors subsequently explored the preparation of cubyl polysulfides.¹⁸¹ They found that through the employment of triphenylmethylthiosulfenyl chloride and triphenylmethyldithio-sulfenyl chloride that they were able to produce cubyltriphenylmethyl trisulfide (**246**) and the corresponding tetrasulfide (**247**), respectively (Scheme 62).

Another modification of cubane using heteroatoms examined dialkoxy disulfide derivatives; previous work has shown that ones

Scheme 62. Preparation of Trityl Cubyl Sulfides¹⁸¹

with benzyl substitution thermally rearrange to release diatomic sulfur.¹⁸² Synthesis and subsequent thermal and photolytic decomposition was studied for cubanes **248** and **249**.¹⁸³ This was the first report of a nonbenzylic dialkoxy disulfide which liberates trappable diatomic sulfur when heated. More interestingly was that photolysis of **244** in the presence of oxygen proceeds through the sulfite intermediate **250** to give the cubylmethanol **251** (Scheme 63).

Scheme 63. Dialkoxy Disulfide Cubane Derivatives¹⁸³Scheme 61. Successive Oxidations of Dicubyl Disulfide Derivatives¹⁸¹

8.3. Cubyl Amino Acids

The synthesis of the first cubyl amino acid was recently reported including the production of a cubane-substituted dipeptide. Due to the high strain of cubane, use of any transition metal in the synthesis needs to be avoided or it results in the formation of cyclooctatetraene.¹⁸⁴ Cubylglycine derivative **252** was synthesized as a mixture of diastereomers despite using an enantiomerically pure sulfinimine. Reaction of **252** with the hydrochloride salt of leucine allowed for the isolation of **253** as a single diastereomer. Potential applications include the incorporation of **219** into medicinally relevant peptides for the treatment of various disease states (Figure 19).

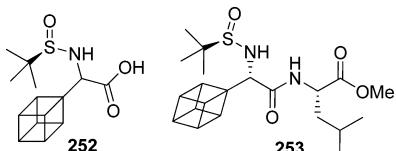


Figure 19. Cubane containing peptides.¹⁸⁴

8.4. Cubyl Chiral Ligand

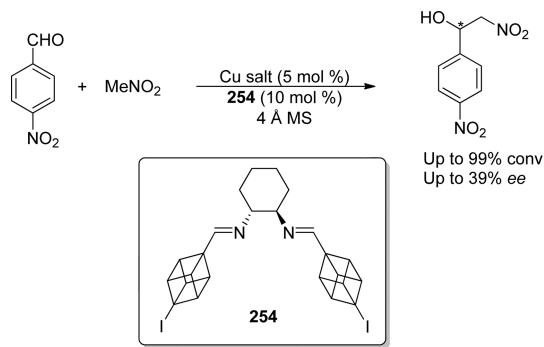
Another novel use of cubane in recent years has focused on using it in catalysis, specifically incorporation of the cubane scaffold into a chiral ligand. The chiral cubane containing Schiff base ligand **220** was developed in 2010 and was applied to an asymmetric Henry reaction.¹⁸⁵ The ligand was able to provide high conversions and moderate enantioselectivity (up to 39% ee).

Further evaluation of the ligand was performed in a Cu-catalyzed Michael addition and a cyclopropanation reaction, and both examples gave poor enantioselectivity.¹⁸⁶ Computational work showed that the poor stereoselectivity is derived from the absence of any steric hindrance on the metal center. Evidence of cubyl hydrogen interaction with the metal center decreases the dihedral angle of the chiral *trans*-1,2-diaminocyclohexane ring (Figure 20 and Scheme 64).¹⁸⁶

9. CONCLUSION AND OUTLOOK

Cubane has come a long way from its first synthesis on January 6, 1964 at the University of Chicago by Philip E. Eaton. Numerous unique and previously believed to be structurally impossible cage molecules have been synthesized in the subsequent 50 years. A number of significant advancements have been observed over

Scheme 64. Application of Cubane in Asymmetric Catalysis



this time: from the most powerful non-nuclear explosive (heptanitrocubane), the most pyramidalized and twisted olefins (cubene and homocubene, respectively), the least likely carbocation (cubyl cation), antivirals, to chiral ligands; cubane continues to fascinate and amaze. A recent *Organic Letters* publication (2014, 16 (16), 4094–4097) from researchers at AstraZeneca entitled “Cubanes in Medicinal Chemistry: Synthesis of Functionalized Building Blocks” is aiming to incorporate cubane as a structural moiety within pharmaceuticals. Now that cubane can be synthesized in near kilogram scale, indeed the future outlook of cubanes’ uses in materials and pharmaceuticals seems bright.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

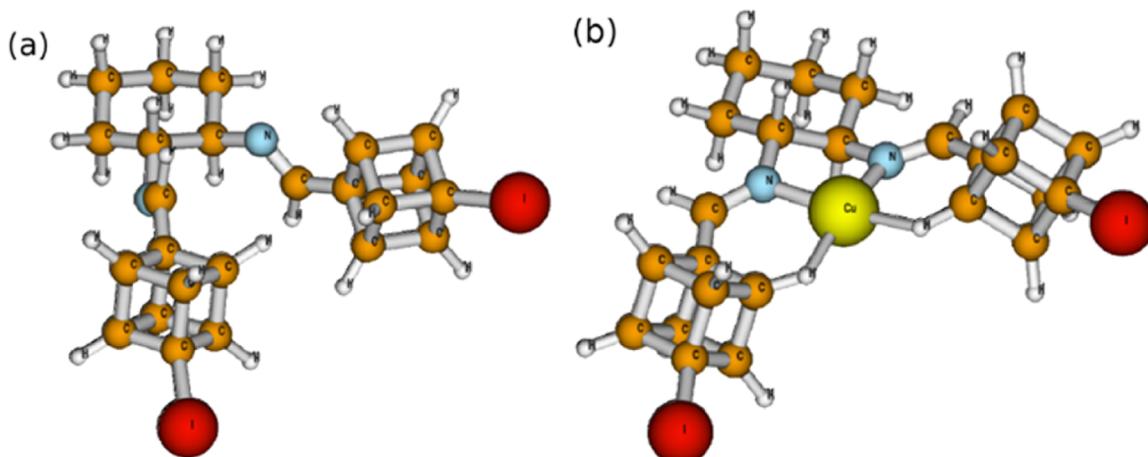


Figure 20. B3LYP Calculations of cubane Schiff base ligand (**254**) unbound (a) and bound (b) to copper salt.¹⁸⁶

Biographies



Kyle F. Biegasiewicz received his Bachelor of Science degree in Chemistry from Niagara University in 2010, completing undergraduate research with Prof. Ronny Priefer. His studies in the Priefer laboratory featured the development of a general approach to the synthesis of isoflavanoid derivatives and the employment of a novel cubane-based Schiff base ligand in Michael addition reactions. He is currently a chemistry graduate student at the University of Rochester in Rochester, NY working under the tutelage of Professor Robert K. Boeckman, Jr. His graduate research areas include studies toward total synthesis of the immunosuppressant natural product FK-506 and enantioselective organocatalytic α -hydroxymethylation of aldehydes.



Justin R. Griffiths received his B.S. in Chemistry from Niagara University in 2010 with his honors thesis focused on the thermal properties of iodinated cubane derivatives. The same year he started his Ph.D. studies at the University at Buffalo—The State University of New York. He is currently a Ph.D. candidate under the supervision of Professor Steven T. Diver. His research interests include the exploration of catalytic processes and decomposition of ruthenium carbenes in olefin and enyne metathesis reactions.



G. Paul Savage received his Ph.D. under the direction of Dr. R. F. Evans at the University of Queensland in 1988, and this was followed by a two-year postdoctoral position with Professor Alan R. Katritzky FRS at the University of Florida. He returned to Australia to take up a research scientist position with CSIRO, Australia's premier government research organization. He completed an MBA in 2005 from the Chifley Business School, La Trobe University. His research interests include heterocyclic chemistry, dipolar cycloaddition reactions, synthesis methodology, and medicinal chemistry. He is currently Research Director of the Biomedical Manufacturing Program in the CSIRO Manufacturing Flagship.



John Tsanaktsidis received his B.Sc. (Hons) and Ph.D. degrees from Flinders University (1988) under the supervision of Dr. Ern Della. Following postdoctoral appointments at the University of Chicago with Prof. Philip Eaton and at the Australian National University with Prof. Athel Beckwith, he joined the faculty at the School of Chemistry, at the University of Melbourne in 1991. Dr. Tsanaktsidis accepted an offer to join the Commonwealth Scientific and Industrial Research Organization (CSIRO) in 1995. His research interests include, process development (flow chemistry), polymer synthesis, fine chemicals from biomass, and cubane chemistry.



Ronny Priefer is a Professor of Medicinal Chemistry within the Department of Pharmaceutical and Administrative Sciences at Western New England University—College of Pharmacy (WNE—COP). He received his B.Sc. degree in Chemistry from the University of Northern British Columbia. He subsequently obtained his Ph.D. in Organic Chemistry from McGill University, Montreal. He was granted a National Sciences and Engineering Research Council-Industrial Postdoctoral Fellowship Award which afforded him the opportunity to work as a Medicinal Chemist at Neurochem Inc. on Alzheimer's and epilepsy small molecule therapies. He began his academic career in 2005 as an assistant professor at Niagara University, NY. There, he ascended the ranks to Associate Professor in 2008, Chair in 2011, and Full Professor in 2012 when he moved to WNE—COP. Throughout his Ph.D., and as a PI, he has worked on cubane chemistry, totaling ten publications on this unique cage system.

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