

THEORETICAL STUDIES OF AZA ANALOGUES OF PLATONIC HYDROCARBONS

Part 1. Cubane and its aza derivatives

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ABSTRACT

MNDO calculations with complete geometry optimization were carried out on cubane and its 21 aza derivatives (from azacubane to octa-azacubane). The calculated heats of formation are discussed using additive models and isodesmic reactions. The empirical models show additivity of the ΔH_f values, but are difficult to rationalize. The isodesmic reactions tend to prove that azacubanes are relatively more stable than cubane itself and are thus reasonable synthetic targets.

INTRODUCTION

The three platonic solids compatible with tetrahedral carbon are tetrahedron, cube and pentagonal dodecahedron. These compounds have exerted a considerable influence in alicyclic chemistry and in organic chemistry in general [1,2], thanks to the pioneering work of Maier, Eaton, and Paquette [3]. Surprisingly enough, nothing is known about their aza analogues. It is the aim of this series of papers to explore, from a theoretical point of view, these aza analogues. A thermodynamic approach (heats of formation) and a semi-empirical method (MNDO) [4] have been chosen for use in the case of cubane and its derivatives.

ISOMERS OF POLYAZACUBANES

An elegant mathematical procedure for calculating the number of isomeric polyazacubanes consists in applying Pólya's theorem [5,6]. According to this theorem, the number of isomers of k -azacubanes (with k nitrogen atoms) are the coefficients of x^k in the polynomial obtained by substituting, in the cycle index expressing the symmetry of the molecular skeleton, y_k by

$$y_k = 1 + x^k \quad (1)$$

The cycle index is a concise way of indicating the symmetry operations which result in isomorphous forms of the cubane skeleton. Thus, the identity operation which leaves all eight CH groups unchanged is expressed as y_1^8 ; and the four rotations by 120° and 240° through two antipodal vertices (three are four-trigonal axes, each of which passes through a pair of antipodal vertices, thus leaving two CH groups unchanged and leading to two circular permutations of triplets of CH groups) are expressed as $8y_1^2y_3^2$. In addition, there are three tetragonal axes connecting pairwise centres of opposed parallel faces, and rotations of 90° and 270° around these axes lead to two circular permutations of quadruplets of CH groups, i.e. $6y_4^4$. Finally, there are three digonal axes coinciding with the preceding tetragonal axes, as well as six other digonal axes connecting the centres of antipodal parallel edges of the cube, giving a total of nine pairwise permutations, i.e. $9y_2^4$. Therefore, the cycle index of the cubane molecule or of the cube as a geometrical object which will result in all isomers, including stereoisomers, is

$$Z = (y_1^8 + 8y_1^2y_3^2 + 6y_4^4 + 9y_2^4)/24 \quad (2)$$

On operating the above substitution according to Pólya's theorem, the following polynomial is obtained

$$x^8 + x^7 + 3x^6 + 3x^5 + 7x^4 + 3x^3 + 3x^2 + x + 1 \quad (3)$$

The coefficients j of each term jx^k in this polynomial indicate the number of isomeric k -azacubanes. One of the tetraazacubanes is chiral, namely compound **14** in which the four nitrogens and, separately, the four CH groups, are arranged as a path with three bonds which determine two mutually perpendicular planes.

If we wish to calculate with the aid of Pólya's theorem the number of constitutional k -azacubanes, ignoring stereoisomerism, the symmetry of the cube must be expressed as a graph rather than as a geometrical object. For this purpose, symmetry operations of reflection [six symmetry planes passing through four vertices and mirroring pairwise the remaining four vertices denoting CH groups ($6y_1^4y_2$)], and three symmetry planes parallel to the faces ($3y_2^4$)], inversion relative to the centre of the cube, (contributing with y_2^4) and reflection-inversion (improper) axes (three tetragonal and four hexagonal axes, contributing the terms $6y_4^2$, $3y_2^4$ and $8y_2y_6$) must be added.

Thus, the cycle index for constitutional isomers is

$$Z = (y_1^8 + 12y_4^2 + 8y_1^2y_3^2 + 13y_2^4 + 6y_1^4y_2^2 + 8y_2y_6)/48 \quad (4)$$

Substitution of y_k by $1 + x^k$ gives, as before, the polynomial

$$x^8 + x^7 + 3x^6 + 3x^5 + 6x^4 + 3x^3 + 3x^2 + x + 1 \quad (5)$$

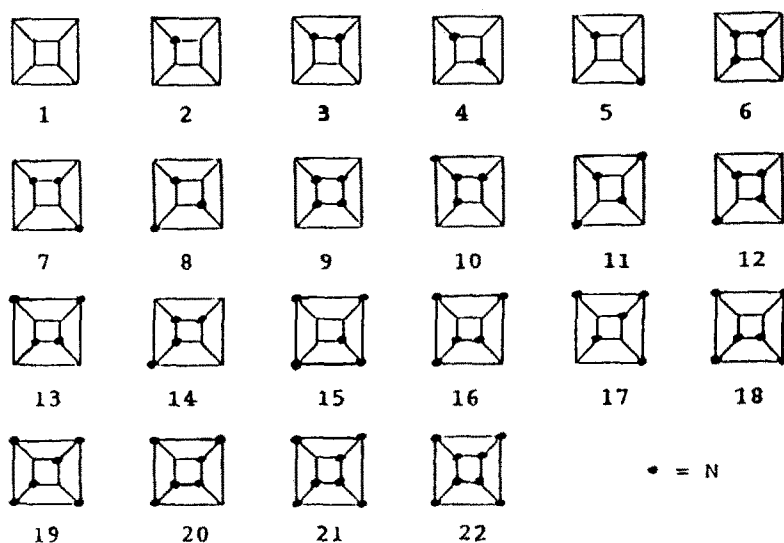


Fig. 1. The 22 isomers of cubane and its aza derivatives.

TABLE 1

Heats of formation (ΔH_f , kcal mol⁻¹) of cubane and azacubanes

Compound	1	2	3	4	5	6
ΔH_f	99.06	115.73	142.68	131.03	133.65	168.25
Compound	7	8	9	10	11	12
ΔH_f	159.34	145.16	204.03	192.84	158.35	183.91
Compound	13	14	15	16	17	18
ΔH_f	186.71	195.25	230.15	221.58	207.76	266.89
Compound	19	20	21	22		
ΔH_f	255.94	258.50	303.41	350.74		

As can be seen, one pair of tetraazacubanes is counted together because it is a pair of enantiomers. The 22 isomers of cubane are shown in Fig. 1.

CALCULATIONS

Using the MNDO approach (MOPAC package) [7] the heats of formation (ΔH_f in kcal mol⁻¹) were calculated for the 22 compounds shown in Fig. 1 (Table 1).

Geometries

There is good agreement between the experimental geometry of cubane [2] (C-C 1.55 Å; C-H 1.10 Å; C-C-C angles 89.3, 90.5 and 89.6°) and the optimized one (C-C 1.54 Å; C-H 1.08 Å; C-C-C angle 90.0°). Since all geometries were fully optimized, the averaged values for C-N and N-N bond lengths, 1.53 and 1.45 Å, respectively, are given here.

Energies

The experimental ΔH_f value of cubane is 148.7 ± 1 kcal mol⁻¹ (quoted in ref. 2). Dewar and Thiel [4] have already discussed this discrepancy which prevents the discussion of absolute values of heats of formation.

ADDITIVE MODELS

In order to find a correlation between the calculated ΔH_f values and the structures five models were examined; in all models cubane **1** served as a reference compound, i.e. only relative energies are discussed.

(i)

$$\Delta H_f = \Delta H_f(^{\circ}) + a_1 x_1 + a_2 x_2 \quad (6)$$

where x_1 is the number of nitrogen atoms, and x_2 is the number of N-N bonds.

A multiregression using the NEMROD package [8] leads to

$$\Delta H_f = 100.88 + 15.26x_1 + 10.70x_2 \quad (7)$$

with a square adjusted regression coefficient of $r_A^2 = 0.9993$.

The drawback of this very simple model is that different constitutional isomers have identical calculated ΔH_f values, whereas the experimental values are quite different (compare the 1,3- and 1,4-diazacubanes **4** and **5**, or the tetraazacubanes **10** and **14**, both with three N-N bonds).

(ii) The preceding model is improved by adding second-order terms, either squared (a_{11} and a_{22}) or rectangular (a_{12})

$$\Delta H_f = \Delta H_f(^{\circ}) + a_1 x_1 + a_2 x_2 + a_{11} x_1^2 + a_{22} x_2^2 \quad (8)$$

$$\Delta H_f = \Delta H_f(^{\circ}) + a_1 x_1 + a_2 x_2 + a_{12} x_1 x_2 \quad (9)$$

However, the new coefficients are not significant and the r_A^2 value is not improved (0.9990 and 0.9993, respectively).

(iii) In an attempt to avoid the problem of model (6) regarding constitutional isomers, we studied the following model

$$\Delta H_f = \Delta H_f(^{\circ}) + a_1 x_1 + a_2 x_2 + a_3 x_3 + a_4 x_4 \quad (10)$$

where x_1 is the number of nitrogen atoms, x_2 is the number of N-N bonds, x_3 is the number of pairs of N atoms separated by two bonds, and x_4 is the number of pairs of N atoms separated by three bonds (with x_3 and x_4 defined as the shortest path).

The matrix corresponding to this model is given in Table 2. As can be seen all the compounds have different entries. The corresponding equation is

$$\Delta H_f = 99.62 + 16.08x_1 + 10.49x_2 - 0.91x_3 + 1.74x_4, r_A^2 = 0.9999 \quad (11)$$

The coefficients a_1 and a_2 are quite similar to those of eqn. (7). The new terms are quite small, but significant; the most remarkable result is the negative value of a_3 : the two nitrogen atoms in positions 1 and 3 slightly decrease the total energy.

(iv) A quite different model was tested which uses the nature and environment of each vertex. Four such situations, represented in Fig. 2, are necessary to describe all the compounds (with compounds 4 and 5 having identical descriptions).

TABLE 2

Matrix corresponding to eqn. (10) and response values

Compound	x_1	x_2	x_3	x_4	ΔH_f	
					MNDO	eqn. (10)
1	0	0	0	0	99.06	99.62
2	1	0	0	0	115.73	115.70
3	2	1	0	0	142.68	142.26
4	2	0	1	0	131.03	130.86
5	2	0	0	1	133.65	133.52
6	3	2	1	0	168.25	167.91
7	3	1	1	1	159.34	159.16
8	3	0	3	0	145.16	145.11
9	4	4	2	0	204.03	204.05
10	4	3	3	0	192.84	192.65
11	4	0	6	0	158.35	158.45
12	4	2	3	1	183.91	183.90
13	4	2	2	2	186.71	186.55
14	4	3	2	1	195.25	195.30
15	5	5	4	1	230.15	230.52
16	5	4	4	2	221.58	221.77
17	5	3	6	1	207.76	207.72
18	6	7	6	2	266.89	267.48
19	6	6	7	2	255.94	256.08
20	6	6	6	3	258.50	258.74
21	7	9	9	3	303.41	303.53
22	8	12	12	4	350.74	350.07

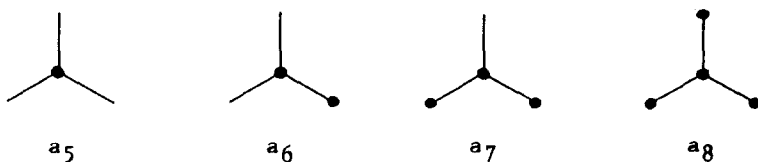


Fig. 2. The environments of the central nitrogen atom corresponding to the parameters a_5 to a_8 .

$$\Delta H_f = \Delta H_f(^{\circ}) + a_5 x_5 + a_6 x_6 + a_7 x_7 + a_8 x_8 \quad (12)$$

where x_i is the number of times the i th environment is present.

By multiregression, the following solution is found

$$\Delta H_f = 100.85 + 14.82x_5 + 20.92x_6 + 26.05x_7 + 31.11x_8 \quad (13)$$

with $r_A^2 = 0.9994$.

The contribution of a carbon vertex bonded to three carbons can be obtained by dividing the constant term by 8 resulting in the value 12.61.

(v) Finally, a model using faces instead of vertices was tested.

$$\Delta H_f = \Delta H_f(^{\circ}) + a_9 x_9 + a_{10} x_{10} + a_{11A} x_{11A} + a_{11B} x_{11B} + a_{12} x_{12} \quad (14)$$

where x_9 is the number of faces with for nitrogen atoms, x_{10} is the number of faces with three nitrogen atoms, x_{11A} is the number of faces with two adjacent nitrogen atoms, x_{11B} is the number of faces with two opposed nitrogen atoms, and x_{12} is the number of faces with one nitrogen atom.

The solution of the multiregression analysis is

$$\Delta H_f = 98.68 + 41.85x_9 + 26.37x_{10} + 16.36x_{11A} + 10.07x_{11B} + 5.62x_{12} \quad (15)$$

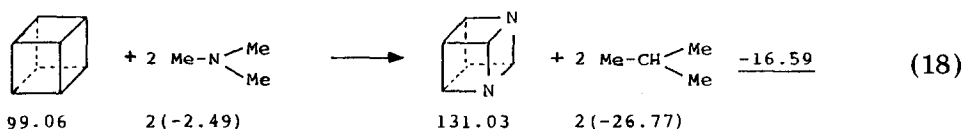
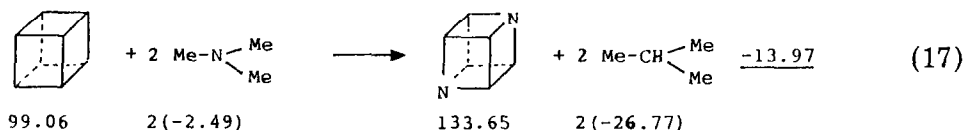
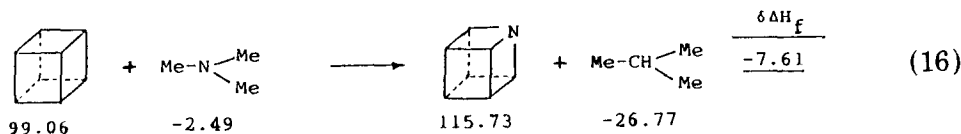
with $r_A^2 = 0.9996$.

All these models correspond to different partitions of the energy that are related. For example, comparing eqns. (7) and (13), it can be seen that $a_5 \approx a_1$, and $2a_6 \approx 2a_1 + a_2$.

ISODESMIC REACTIONS

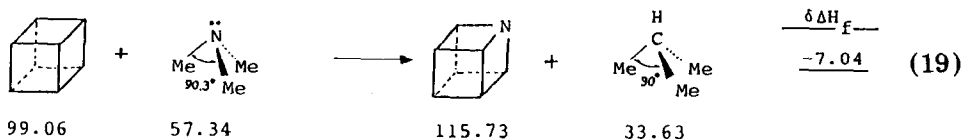
The best way to evaluate strain energies is to use isodesmic reactions [9]. This kind of reaction can also give some idea of the synthetic accessibility of azacubanes, ignoring kinetic aspects.

Thus, the heats of formation of trimethylamine and isobutane were calculated in order to study the following isodesmic reactions



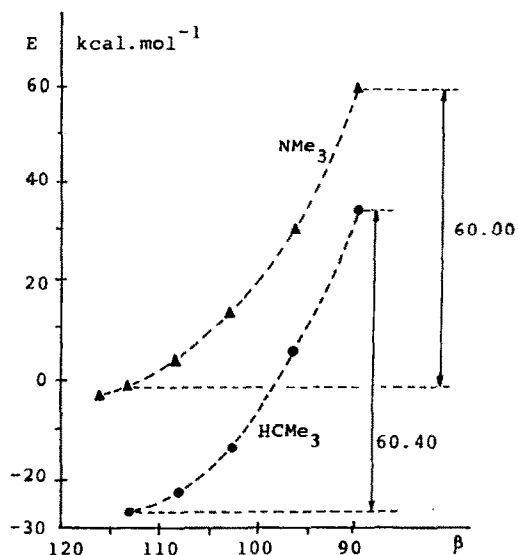
It can be seen that in reactions (17) and (18) the ΔH_f value is approximately twice that in reaction (16). The isodesmic reaction (16) yields a negative balance; i.e. this reaction is favoured. This fact could be explained if nitrogen is more flexible than carbon. For this purpose the energy versus the C-X-C (X=N or CH) angle ranging from the original structure (C-C-C=112.97° and C-N-C=116.02°) to the cubane angle (90°) was calculated and plotted (Fig. 3). The ΔH_f value between both curves at 90° is 25.02 kcal mol⁻¹, i.e. 0.40 kcal mol⁻¹ less than the energy difference at 112.2° (starting point). According to this plot the $\delta \Delta H_f = -7.61$ kcal mol⁻¹ found in reaction (16) does not seem to arise from an easier "folding" of the nitrogen.

In order to reproduce, in trimethylamine, the geometry around the N atom in 1-azacubane (C-N-C=90.29°) the energy of the former with this angle was calculated, resulting in $\Delta H_f = 57.34$ kcal mol⁻¹. The corresponding isodesmic reaction



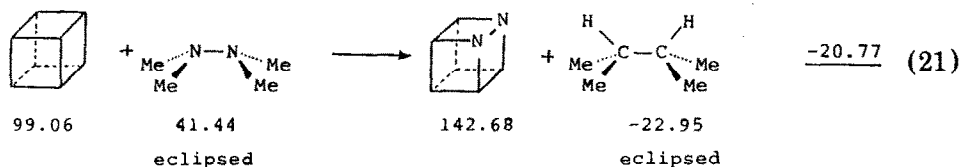
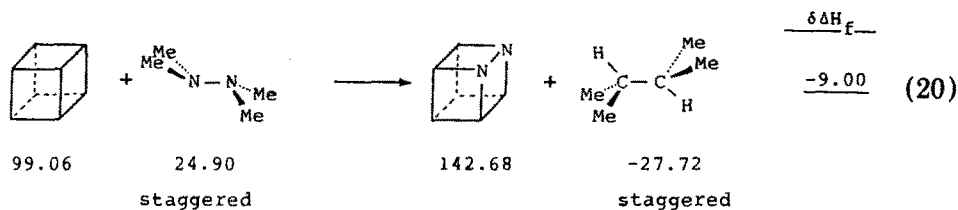
does not explain either of the $\delta \Delta H_f$ values found in reaction (1).

The isodesmic reactions with tetramethylhydrazine (TMH) and 2,3-dimethylbutane (2,3-DMB) were also studied

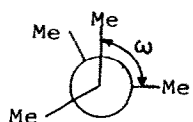


β	$E(\text{NMe}_3)$	$E(\text{HMe}_3)$
116.02	-2.49	-
112.97	-1.35	-26.77
107.70	3.18	-23.67
102.40	13.12	-13.64
96.40	30.77	4.80
90.00	58.65	33.63

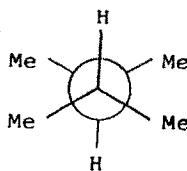
Fig. 3. Energy (kcal mol^{-1}) versus angle ($\text{C-X-C}, ^\circ$) of trimethylamine (\blacktriangle) and isobutane (\bullet).



In reaction (20), TMH and 2,3-DMB are in their calculated minimum conformations



TMH
($\omega \approx 85^\circ$) [10]



2,3-DMB

In order to explain what happened when the methyl groups were in a position similar to that in cubane, the eclipsed conformations of TMH and 2,3-DMB were also calculated [see reaction (21)].

CONCLUSION

The main interest of empirical models is their use in describing a large amount of data by using the simplest equation. According to this criterion, eqn. (11) is the most satisfactory. For compounds with many more constitutional isomers, such as azadodecahedranes, this kind of equation can be used to predict the heat of formation of non-calculated isomers. The isodesmic reactions, with all their uncertainty due to the compounds selected, strongly indicate an increase in stability in azacubane itself and in diazacubanes, even when both nitrogen atoms are adjacent. In conclusion, from a thermodynamic point of view, azacubanes are reasonable targets for synthetic organic chemists.

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