composition was determined by GC using a 12-ft, 10% Carbowax 20M column at 150 °C.

Calculations. The molecular mechanics calculations were carried out with the parameters of Boyd[7] and also with MMI.[16] The ab initio calculations were carried out by using the program GAMESS[33] which is derived from HONDO.[34] The optimization was continued until the largest gradient was less than 0.001 hartree/bohr.

Acknowledgment. This investigation was supported by a grant from the Office of Basic Energy Science, Department of Energy.

Registry No. 1, 71032-67-2; **2**, 71032-66-1; **3**, 13757-43-2; **4a**, 39124-79-3; **5a**, 286-08-8; **6**, 54376-67-9; **7**, 16526-90-2; **8**, 21370-66-1.

(33) Dupuis, M.; Spangler, D.; Wendoloski, J. J. National Resource for Computer Chemistry, Program QG01, 1980.
(34) Dupuis, M.; Rys, J.; King, H. *QCPE* **1977**, *11*, 338.
(35) Rossini, F. D. "Experimental Thermochemistry"; Interscience: New York, 1956; Vol. I, Chapter 14.

π-Complexes as Intermediates in Reactions. Biomimetic Cyclization[1]

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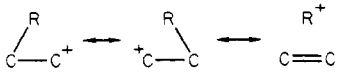
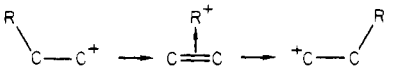
Abstract: The advantages of the π-complex representation of "nonclassical carbocations" are pointed out, with special reference to the electrophilic additions of carbocations to CC multiple bonds involved in biomimetic cyclizations. Studies of the cyclizations of *cis*- and *trans*-2-undeca-6,10-dienyl cations to decalin derivatives, using MINDO/3, indicate them to take place stepwise via intermediate olefin–carbenium ion π-complexes.

When the π-complex theory[2-9] was introduced[2] nearly forty years ago, one of the first applications[2,3] was to the intermediates in the Wagner–Meerwein rearrangement of carbenium ions. At that time there was no rational explanation of the extreme ease with which these rearrangements take place in contrast to the difficulty of analogous rearrangements of radicals or anions. The transition states for all three reactions are equivalent in terms of resonance theory, being represented as hybrids of three contributing structures:



(1)

This problem was immediately solved by the recognition that the intermediate in the rearrangement of a carbenium ion can be represented as an olefin π-complex:



(2)

The bond linking the apical and basal groups in the π-complex is effectively a two-center dative bond, differing from ordinary two-center bonds only in that one of the contributing orbitals is a π MO rather than an AO. This analogy shows that only two electrons can be accommodated in it, any additional electrons having to go into an antibonding MO. The π-complexes derived from radicals or cations as apical groups are therefore much less stable than those from cations. Rearrangements of alkyl radicals or carbanions should therefore be much less facile than those of carbenium ions, as indeed they are.

The π-complex representation also makes it immediately clear that a π-complex isomer of a classical carbenium ion may well be more stable than the latter. Since the bond energy of a C=C double bond is less than twice that of a C—C single bond by only ca. 20 kcal/mol, the π-complex should be more stable than the isomeric carbenium ion (see eq 2) if the bond energy of the bond between the basal (olefin) and apical groups is greater than this difference. Since there is no essential difference between this bond and a normal two-center bond and since even the weakest covalent two-center bond (F–F) has a bond energy >30 kcal/mol, it is very likely that this condition will usually be met. Indeed, high-level ab initio calculations[10] and calculations[11] by MINDO/3[12] suggest that carbenium ions are generally less stable, in the gas phase, than isomeric π-complexes.

These arguments were given[4] at a conference at Montpelier in 1949, together with the representation of metal–olefin complexes as π-complexes stabilized by back-coordination and a discussion of the relationship between the classical and π-complex representations of species containing three-membered rings (see ref 9).

(1) Part 64 of the series "Ground States of Molecules". Part 65, submitted for publication.
(2) Dewar, M. J. S. *Nature (London)* **1945**, *156*, 784; *J. Chem. Soc.* **1946**, 406; *Ibid.* **1946**, 777; "The Electronic Theory of Organic Chemistry"; Clarendon Press: Oxford, 1949.
(3) (a) Dewar, M. J. S. *Faraday Discuss. Chem. Soc.* **1947**, *2*, 50. (b) Coulson, C. A.; Dewar, M. J. S. *Ibid.* **1947**, 2.
(4) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1950**, *18*, c71, c86.
(5) Dewar, M. J. S. (a) *Annu. Rep. Prog. Chem.* **1950**, *47*, 112; **1951**, *48*, 112. (b) *Ibid.* **1951**, *48*, 112.
(6) Dewar, M. J. S.; Marchand, A. P. *Ann. Rev. Phys. Chem.* **1965**, *16*, 323.
(7) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969.
(8) Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Publishing Corp.: New York, 1975.
(9) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783.
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(11) (a) Bischof, P. K.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1975**, *97*, 2278. (b) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1977**, *99*, 7432. (c) Dewar, M. J. S.; Reynolds, C. H., to be presented at the ACS National Meeting in St. Louis, April 1984.
(12) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285, 1294, 1302, 1307.

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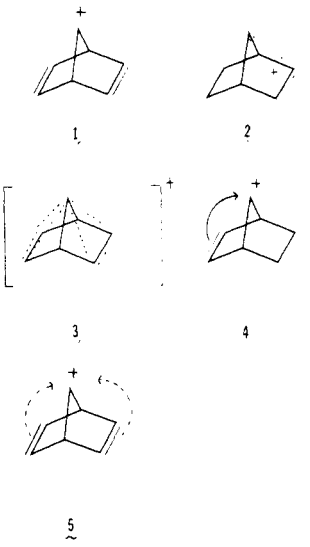
Winstein, at the same conference, presented[13] for the first time definite evidence that a nonclassical carbocation might be more stable than an isomeric carbenium ion (2-norbornyl) but he preferred to describe the former in terms of resonance theory (eq 1), a description which he summarized by the dotted-line symbolism still in common use. The latter can of course be used equally well to represent the MO description of a multicenter bond and this is the meaning now commonly attributed to it. The π-complex notation refers only to one particular kind of multicenter bond and is therefore much more specific. While the importance of π-complexes in inorganic chemistry soon became obvious, organic chemists have never fully realized that they are equally important in organic chemistry, nearly all the known "nonclassical carbocations" being in fact of this type.[6] Their resulting continued use of the ambiguous dotted line symbolism for such species has been unfortunate, for several reasons.

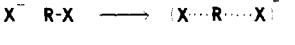
(a) The dotted-line symbolism gives no direct indication of the relative stabilities of classical and nonclassical isomers. It completely fails to explain why π-complex forms of carbenium ions are so stable. It is always easy to write a variety of other nonclassical structures involving three-center bonds of other types. Such species are more stable than their classical counterparts only in a few very exceptional cases. The same problem arose in resonance description of such ions (eq 1). This indeed is why Wilson's original suggestion[14] that such a "nonclassical" ion (derived from camphene hydrochloride or isobornyl chloride) might exist as a stable species was completely ignored. The interpretation in terms of resonance theory carried no conviction and was indeed dismissed at the time as ridiculous. As noted above, it is immediately obvious from the π-complex formalism that such an ion must in fact be at least comparable in stability with the isomeric carbenium ion.

(b) The dotted-line symbolism draws no distinction between different types of three-center bonds. In particular, it draws no distinction between π-complexes (where two of the three atoms involved are also linked by a normal two-center covalent σ bond) and species XYZ^+ where the groups X, Y, and Z are linked *only* by the three-center bond. Bonds of the latter type are common in the boron hydrides, carboranes, and other "electron-deficient" molecules, e.g., $Al_2(CH_3)_6$. They are, however, only rarely[6] found in carbocations. The reason for this is simple. The AOs of quadricovalent boron or aluminum are much larger than those of carbon. Three-center σ-type overlap involving such AOs can therefore be efficient. Since quadricovalent carbon has much smaller AOs, it cannot easily form three-center bonds of this type because the atoms involved cannot usually get close enough together without congestion. This difficulty can be avoided if two of the carbon atoms are linked by a single bond because not only are they then close together but the AOs used to form the three-center bond are also p AOs which are sterically accessible to a third atom. Such a species is of course by definition a π-complex. The dotted-line symbolism would moreover be more meaningful if it were confined to systems where three atoms are linked *only* by a three-center two-electron bond.

(c) A π-complex has a clearly defined geometry, corresponding in effect to a special kind of localized bond. The consequences can be immediately visualized. A good analogy is provided by a classical conjugated polyene, e.g., butadiene. A dotted-line (MO) description ($H_2C\cdots CH\cdots CH\cdots CH_2$) of such a molecule fails to describe its essential feature, i.e., the qualitative difference between the central and terminal π bonds. This of course is emphasized in the conventional localized bond representation. Another example is provided by the 7-norbornadienyl carbon (**1**). When its nonclassical nature was recognized, there was much discussion concerning its structure. Do both double bonds participate in the delocalized MOs or only one? In the dotted-line descriptions (**2** and **3**) both structures look equally reasonable. In the π-complex description, however, **4** and **5** are clearly analogous to the reactants (**6**) and transition state (**7**) in an S_N2 reaction. This analogy at



once suggests that **5** must be the transition state for the interconversion of **4** and its mirror image, rather than a stable species, as indeed is now known to be the case (see ref 6).

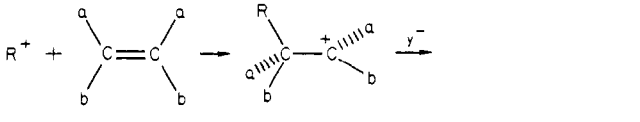


The subject treated here represents a further example of confusion being caused by the representation of nonclassical carbocations by the dotted-line symbolism, i.e., the formation of carbocyclic rings by intramolecular addition of carbocations to carbon–carbon double bonds. Such reactions play an important role in biology, successive additions of this kind being apparently involved in the in vivo synthesis of triterpenes and steroids.[15] For this reason such reactions are now commonly described as biomimetic polyene cyclizations.[16]

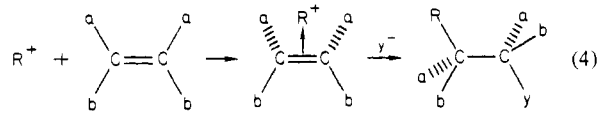
A basic mechanistic problem in these reactions is to determine the nature of the intermediate ions. Because of their failure to adopt the π-complex theory, organic chemists have tended to assume that "classical" carbocations are generally more stable than "nonclassical" isomers, the latter being more stable only in certain exceptional cases. As noted above, one of the major advantages of the π-complex description is that it shows very clearly that π-complex carbocations should in general be at least as stable as isomeric carbenium ions. It has in fact become increasingly clear in recent years that the π-complex forms of a number of simple carbocations, including in particular $C_2H_5^+$, $C_2H_3^+$, 2-Bu^+, and protonated cyclopropane, are more stable than the corresponding classical ions, the latter indeed being in some cases unstable species that rearrange to the isomeric π-complexes without activation. The evidence to this effect comes moreover not only from theoretical calculations[10,11,17,18] but also from experiment.[19,20]

(13) Winstein, S. *Bull. Soc. Chim. Fr.* **1951**, *18*, c55.
(14) Nevell, T. P.; de Salas, E.; Wilson, C. L. *J. Chem. Soc.* **1939**, 1188.
(15) For recent reviews see (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (c) Johnson, W. S. *Ibid.* **1968**, *1*, 1.
(16) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9.
(17) Dewar, M. J. S.; Haddon, R. C.; Komornicki, A.; Rzepa, H. S. *J. Am. Chem. Soc.* **1977**, *99*, 377.
(18) Raghavachari, K.; Whiteside, R. A.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5649.
(19) (a) Dymerski, P. P.; Prinstein, R. M.; Bente, P. F., III; McLafferty, F. W. *J. Am. Chem. Soc.* **1976**, *98*, 6834. (b) Ausloos, P.; Rebbert, R. E.; Sieck, L. W.; Tiernan, T. O. *Ibid.* **1972**, *94*, 8939. (c) Chong, S. L.; Franklin, J. L. *Ibid.* **1972**, *94*, 6347. (d) McAdoo, D. J.; McLafferty, F. W.; Bente, P. F., III *Ibid.* **1972**, *94*, 2027. (e) Jaffe, H. M.; Billets, S. *J. Am. Chem. Soc.* **1972**, *94*, 674. (f) Lossink, F. P.; Semeluck, G. P. *Can. J. Chem.* **1970**, *48*, 955. (g) Karabatsos, G. J.; Zioudrow, C.; Meyerson, S. *J. Am. Chem. Soc.* **1970**, *92*, 5996. (h) Lee, C. C.; Woodcock, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 5992. (i) Collins, C. J. *Chem. Rev.* **1969**, *69*, 543. (j) Myhre, P. C.; Evans, E. *J. Am. Chem. Soc.* **1969**, *91*, 5641. (k) Saunders, M.; Hagen, E. L.; Rosenfeld, J. *J. Am. Chem. Soc.* **1968**, *90*, 6882.

The distinction is important so far as biomimetic cyclizations are concerned because the expected stereochemistry of the products depends on which mechanism is involved. If addition of a carbocation to a C=C bond gives a classical carbenium ion, attack on this by a nucleophile can lead to products corresponding to either cis or trans overall addition (eq 3). Steric and conformational effects could lead to stereoselectivity, but there would be no reason to expect the reactions to be stereospecific. If, however, the intermediate ion is a π-complex and if it is significantly more stable than the isomeric classical carbocation, so that the reaction cannot take place via the latter, only the trans adduct would be expected (eq 4).



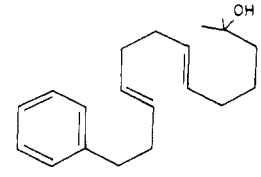
(3)



(4)

Both types of behavior have been observed in electrophilic addition to olefins. For example, attack by Br^+ leads almost invariably to trans addition, the intermediate ion being a π-complex,[21] while attack by Cl^+ often gives a mixture of cis and trans adducts, the intermediate being a classical carbenium ion.[22] Here we are concerned with the situation where the attacking electrophile is itself a carbocation.

The first attempts to establish the stereochemistry of carbenium ion addition to C=C bonds were made nearly thirty years ago by Ansell[23] who carried out very extensive studies of what would now be called biomimetic cyclizations.[16] However, although he was able to prepare the necessary precursors in stereochemically pure form by elegant methods and to effect a number of simple and multiple cyclizations, the most striking being the production of the chrysene derivative (**9**) from **8** in a single step in 60% yield, he was unable to separate and characterize the isomers formed because the necessary techniques, in particular gas-liquid chromatography, had not yet been invented. Their subsequent development enabled Johnson and his collaborators to solve the problem by elegant and detailed investigations,[15,16] which showed that multiple cyclizations of this kind involve essentially stereospecific trans addition to C=C bonds. The only exception is the last step, where the fully cyclized carbocation reacts with a nucleophile to give the final product. Here alone both possible isomers can be formed.



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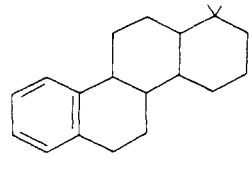

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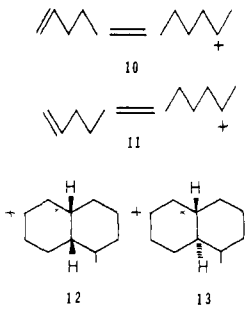
Such stereospecificity would be expected if the cyclizations take place stepwise by successive addition of carbocations to C=C double bonds to form intermediate π-complexes that are significantly more stable than the isomeric carbenium ions. Furthermore, as the π-complex description clearly indicates, each step in the multiple biomimetic cyclization involves electrophilic addition to a C=C double bond, the next double bond acting as the nucleophile. Since electrophilic additions in general are known to take place in steps, the electrophile and nucleophile adding successively, not synchronously, analogy suggests that biomimetic cyclizations must likewise proceed in a nonconcerted manner. Recent work[24] in these laboratories has moreover led to the conclusion that reactions do not normally take place in a synchronous manner if they involve the making and/or breaking of more than one bond. Reactions involving the synchronous formation and/or breaking of two or more bonds require far more activation than analogous one-bond processes.

Because of their failure to represent "nonclassical" carbocations as π-complexes, Johnson et al. have clearly been in two minds concerning the stability of such intermediates. In some papers they seem to favor a stepwise mechanism involving them and in others a synchronous one-step multiple cycloaddition. Stork and Burgstahler[25] and Eschenmoser et al.[26] have also suggested mechanisms of the latter kind. Detailed studies of a number of biomimetic multiple cyclizations by van Tamelen[27] have, on the other hand, indicated that biomimetic cyclizations in fact take place in distinct steps, one ring being formed at a time. Combined with the arguments given above, this work seems to leave little doubt that the overall reaction is not concerted.

However, since the problem is clearly of major significance from the points of view both of theory and of biochemistry, we thought it would be of interest to carry out detailed theoretical calculations for some typical examples that had been studied experimentally. The method of choice for this purpose was clearly MINDO/3.[12] Detailed studies[10,11] have shown that this performs especially well for carbocations, both "classical" and "nonclassical", giving results similar to those from "state-of-the-art" ab initio calculations and in agreement with the available experiment evidence. Unlike comparable ab initio methods, MINDO/3 can moreover be applied to quite large molecules at a cost low enough for their reactions to be studied properly.

Here we report the results of detailed MINDO/3 calculations for the conversions of the *cis*- and *trans*-decalin precursors **10** and **11** to the *cis*- and *trans*-decalin derivatives **12** and **13**.



10 11 12 13

(20) Dannenberg, J. J.; Goldberg, B. J.; Barton, J. K.; Dill, K.; Weinwurzel, D. H.; Longas, M. O. *J. Am. Chem. Soc.* **1981**, *103*, 7764.

(21) Note that the intermediate cannot be represented satisfactorily as a cyclic bromonium ion; see ref 4–9. Such a classical ion would react with nucleophiles at the *less* substituted carbon atom, giving products corresponding to anti-Markovnikov addition, as is observed for species that can be best represented by cyclic structures, e.g., oxiranes, aziranes, thiiranes, and aziranium and thiiranium ions; see ref 9.

(22) See Dewar, M. J. S.; Fahey, R. C. *J. Am. Chem. Soc.* **1963**, *85*, 2248.

(23) (a) Ansell, M. F.; Selleck, M. E. *J. Chem. Soc.* **1956**, 1238. (b) Ansell, M. F.; Selleck, M. E. *Ibid.* **1958**, 1167. (c) Ansell, M. F.; Brown, S. S. *Ibid.* **1958**, 2955. (d) Ansell, M. F.; Gadsby, B. *Ibid.* **1958**, 3388. (e) Ansell, M. F.; Brown, S. S. *Ibid.* **1958**, 3956. (f) Ansell, M. F.; Gadsby, B. *Ibid.* **1959**, 2994. (g) Ansell, M. F.; Ducker, J. W. *Ibid.* **1960**, 5219. (h) Ansell, M. F.; Ducker, J. W. *Ibid.* **1961**, 206.

(24) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.

(25) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068.

(26) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

(27) van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 6480.

Procedure

The calculations were carried out by using the standard MINDO/3 procedure and parameters.[12] Geometries were calculated by minimizing the total energy with respect to all geometric parameters, making no assumptions and using the modified Davidon–Fletcher–Powell[28] algorithm incorporated in our standard computer program.[29] Transition states were located by using a suitable geometrical variable as a reaction coordinate[30–32] and refined by minimizing the scalar gradient of the energy.[33,34] All stationary points were characterized[33,34] by calculating and diagonalizing the Hessian (force constant) matrix.

Bimolecular vs. Unimolecular Reactions

Studies of bimolecular reactions are greatly complicated by the very wide range of possible modes of approach of the reactants to one another. In the case of an association reaction, this problem can be avoided by studying the reverse process which will be a unimolecular dissociation. This point, while obvious, has clearly escaped general notice because numerous calculations of bimolecular reactions have appeared, and continue to appear, in the literature, when time and money could have been saved by studying them in reverse. Worse still, the necessary extensive explorations of the bimolecular potential surface are frequently described in detail under the misapprehension that conclusions can be drawn from them concerning the mode of approach of the reactants to one another during the reaction. The only purpose of such a survey is to locate the transition state for a reaction. Information concerning the detailed dynamics involved can be obtained only from trajectory calculations, which are feasible only for very simple systems, or from even more complex applications of the time-dependent Schrodinger equation.

The reactions of interest in the present connection, while technically unimolecular, are in fact intramolecular analogues of association processes (i.e., addition of a carbocation to an olefin) and present similar problems. We therefore studied them in reverse, i.e., the dissociations of the methyldecahydronaphthyl cations (**12** and **13**) into the undecadienyl cations (**10** and **11**). The methyl groups were included partly to ensure that the latter would have stable classical structures and partly because the cyclizations that have been studied experimentally have involved secondary or tertiary carbenium ions as initiating groups.

Results and Discussion

Because of the preference of methyl for an equatorial position in a cyclohexane ring, the products (**12** and **13**) of the cyclizations of **10** and **11** are expected to have the conformations indicated in **14** and **15**. Calculations were first carried out for these and led to the reasonable structures indicated by the ORTEP plots in Figure 1, together with the corresponding heats of formation. Further study, however, showed the most stable forms of the ions to be the π-complexes **16–19**, whose geometries and heats of formation are likewise indicated in Figure 2. Their calculated heats of formation are also shown in Figure 2.

Here, and subsequently, details concerning geometries are given only when they are relevant to the discussion. Cartesian coordinates for all the species calculated are provided as supplementary material. The only point of interest arising from the geometries calculated for **14–19** is the structure of the $\|\rightarrow H^+$ moiety in **16–19**. In each case the CC bond length was ~1.42 Å and each CH distance ~1.30 Å.

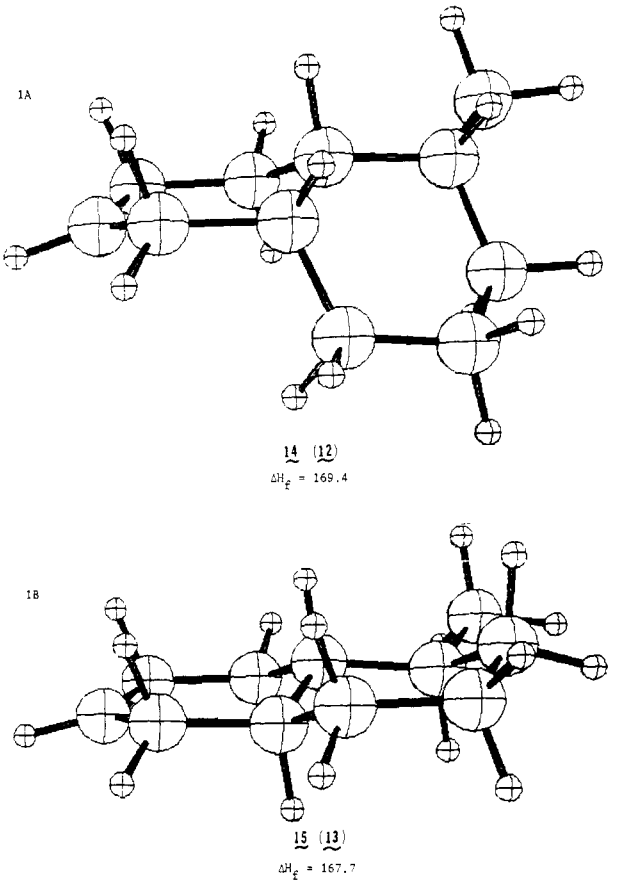
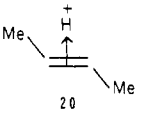


Figure 1. MINDO/3 calculated geometries and heats of formation for **14** and **15**.

This result seems surprising at first sight because it has been generally assumed that secondary carbenium ions are usually more stable than isomeric π-complexes. However a recent experimental study[20] has indicated that the most stable form of *sec*-butyl cation is in fact the π-complex **20**, a conclusion supported by MINDO/3



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calculations.[11] The calculations refer of course to ions in the gas phase. The equilibrium between classical and π-complex isomers is likely to be affected by solvation. Intuition suggests that solvation should favor the classical ion in which the charge is more concentrated. The double cyclizations of **10** and **11** must in any case lead initially to the classical ions **12** and **13**.

The reverse process for the *trans*-decalin derivative **13** was studied first, taking the length of the breaking CC bond (marked by an asterisk in **13**) as the reaction coordinate. A stable intermediate was formed whose geometry is shown in Figure 3 together with the calculated distribution of formal charge.

The results in Figure 3 show that the intermediate is best represented as a π-complex (**21**). This is indicated by the length of the basal CC bond, by the bond angles to the apical atom, and by the calculated formal charges. The apical atom is not symmetrically placed between the basal atoms. This, however, is not in any way surprising. The μ bond linking the apical group to the basal atoms in a π-complex is in effect a dative σ bond in which the ethylenic π MO acts as the donor and a hybrid AO of the apical atom as the acceptor. The μ bond will be strongest when

(28) Davidon, W. C. *Comput. J.* **1968**, *1*, 406. Fletcher, R.; Powell, M. J. D. *Ibid.* **1963**, *6*, 163.

(29) A complete package of MINDO/3 and MNDO programs (MOPAC) is now available from the Quantum Chemistry Program Exchange (Q.C.P.E.).

(30) The term "reaction coordinate" is used here in its original sense, to denote a geometrical variable that changes during a reaction and whose value at any point along the reaction path can be taken as a measure of the extent to which the reaction has proceeded. The normal coordinate in a transition state, corresponding to translation across the saddlepoint, is better termed the *transition coordinate*.

(31) This procedure, which has been used in theoretical discussions of reactions for half a century and which we have ourselves used for many years in our calculations, has recently been "discovered" by other theoreticians who have suggested alternative terms for it; see, e.g. Alagona, G.; Scrocco, E.; Tomasi, J. *Theor. Chim. Acta* **1977**, *51*, 11. There seems no good reason for abandoning the traditional one used here.

(32) See, e.g., Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4290.

(33) McIver, J. W.; Komornicki, A. *Chem. Phys. Lett.* **1971**, *10*, 303.

(34) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

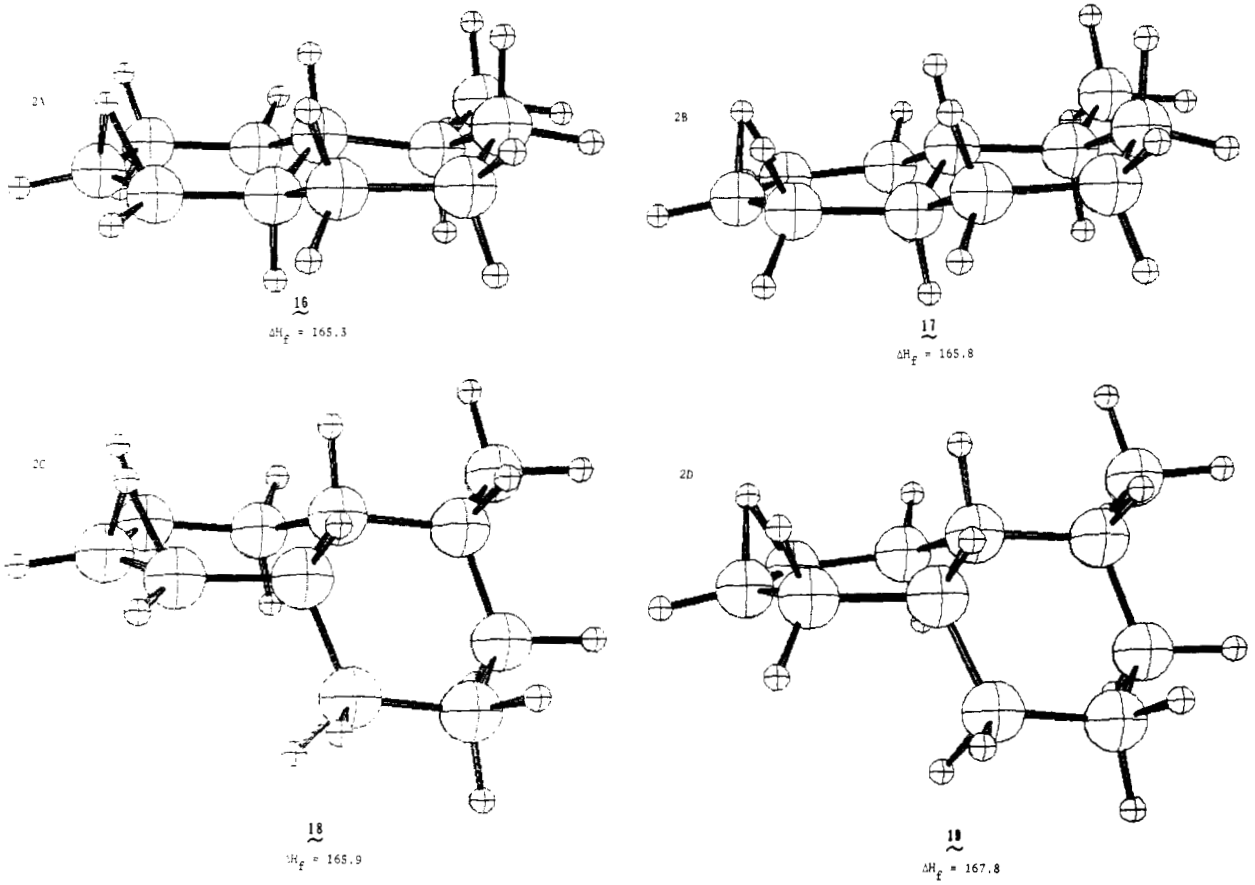
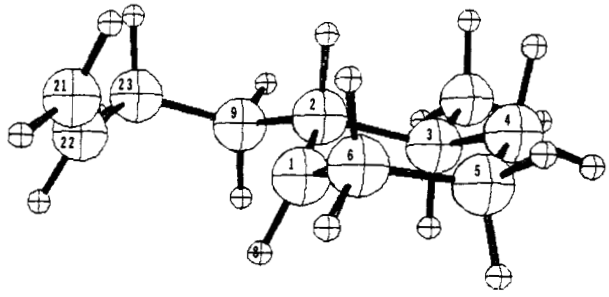


Figure 2. MINDO/3 calculated geometries and heats of formation for **16–19**.



Geometry		Charge			
1-2	1.4733	1	.3774	6	-.0208
2-3	1.6096	2	-.0173	9	.0350
1-3	2.3980	3	.1189	23	-.0350
3-2-1	102.036	4	.0022	22	.0168
3-2-1-8	97.357	5	.0845	21	.0738

Figure 3. MINDO/3 calculated π-complex intermediate (**21**) for the conversion of **13** (**15**) to **11**.

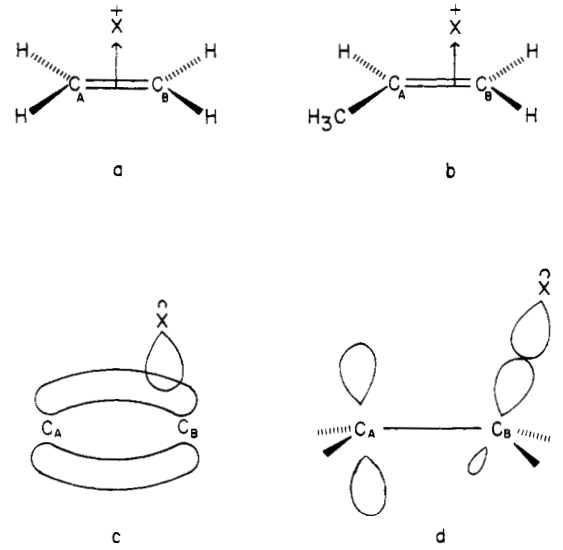


Figure 4. (a) The π-complex between ethylene and an acceptor X^+. (b) The π-complex between propene and X^+. The apical group X^+ is no longer symmetrically positioned between C_A and C_B due to polarization of the π MO by the methyl substituent. (c) Cross section of the π-complex μ bond. (d) The isomeric classical carbenium ion.

these orbitals overlap as efficiently as possible. In a π-complex derived from a symmetrical olefin, the apical atom is best placed symmetrically between the basal atoms (Figure 4a) but substitution of the olefin moiety leads to polarization of its π MO and hence to a corresponding displacement of the apical atom. A displacement of this kind was originally invoked[2-4] to explain Markovnikov's rules and was confirmed by MINDO/3 calculations (see ref 11) of the geometry of the π-complex from propene and methyl cation (Figure 4b). Equally, just as a σ bond can be bent by steric constraints, so also can the μ bond in an olefin π-complex. Indeed, since the cross section of the π MO presented to the apical atom is oval rather than circular, displacement of the apical group in a plane parallel to the basal atoms should be exceptionally easy (Figure 4c).

The discussion so far has been concerned with species in the gas phase. Classical carbocations should be stabilized more effectively by solvation than isomeric π-complexes, both because of the smaller dispersal of charge in the classical ion and because of the possibility in it of dative bonding from the solvent. Unfortunately there is no way at present to estimate quantitatively the effects of solvation on the relative energies of a carbenium ion and an isomeric π-complex. It does, however, seem likely that even if solvation makes the classical ion as stable as the π-complex, the two isomers will be separated by a significant energy barrier,

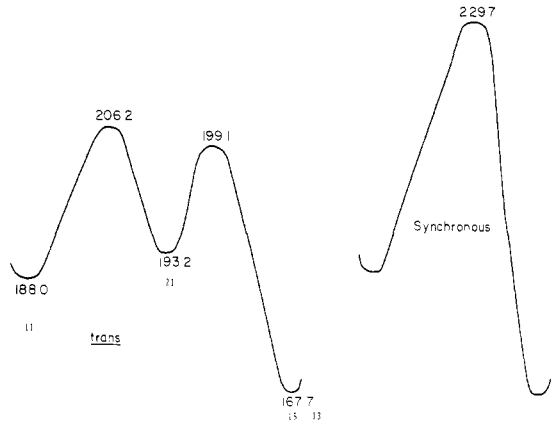
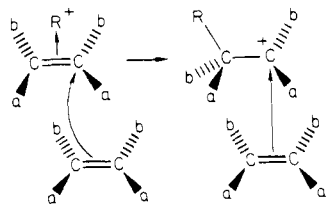


Figure 5. MINDO/3 reaction profile for the conversion of **11** to **15** (**13**).

because a strongly solvated classical carbocation will not be able to rearrange to an isomeric π-complex until the solvent molecule has been displaced from the cationic center. The reaction of a carbocation with a C=C double bond should moreover lead first to the π-complex, because stabilization of the classical ion by solvation will become possible only late in the reaction, after the C=C bond has been broken, so that the charge becomes concentrated on a single carbon atom. It therefore seems very likely that addition in solution will also take place by the π-complex mechanism. Even if solvation makes the classical ion as stable, or more stable, than the π-complex, the barrier between the two should allow the latter to react with a nucleophile before it has time to rearrange. Such an attack will of course lead to overall trans addition to the relevant C=C bond. In the case of a multiple biomimetic cyclization, the nucleophile will of course be the π component of the next C=C bond, the reaction leading to another π-complex (eq 5).

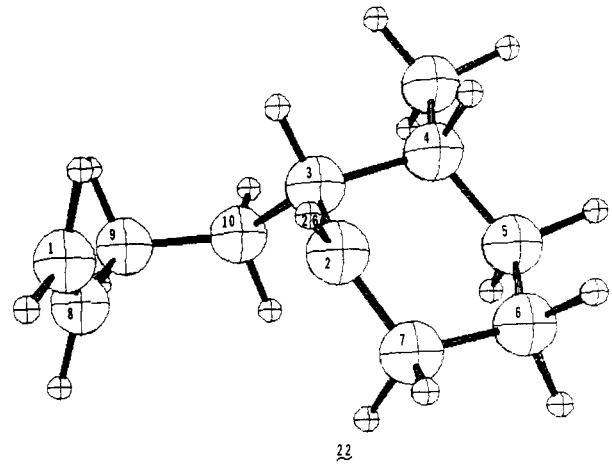


(5)

The cyclization of **21** thus leads stereospecifically to the *trans*-decalin derivative **13**, just as attack by any nucleophile on the intermediate π-complex in electrophilic addition to a C=C double bond leads to overall trans addition. Note how the π-complex notation emphasizes the parallel between the attacking double bond in the cationic cyclization (eq 5), where the donor orbital is a filled π MO, and the nucleophile is electrophilic addition to an olefin (eq 4), where the donor orbital is a filled (lone pair) AO. The π electrons of an olefin are basically no different from a pair of unshared electrons occupying an AO of a conventional nucleophile.

Since the olefinic moiety in an olefin π-complex retains its stereochemistry, rotation about the C=C bond being inhibited, ring opening in **21** to give an open-chain ion necessarily leads stereospecifically to **11**. The transition state for this process was located without difficulty, leading, together with the earlier calculations, to the reaction profile for the overall conversion of **11** to **13** shown in Figure 5, which also indicates its stereochemical course.

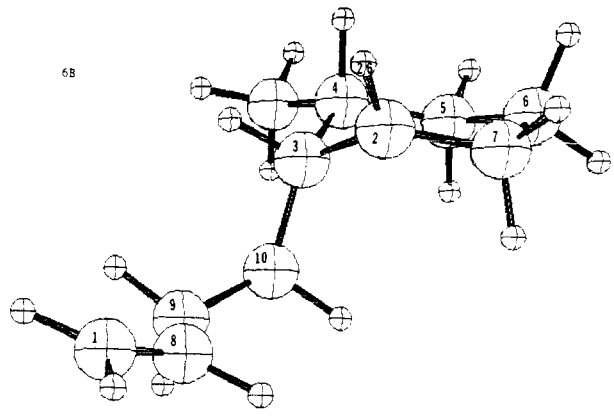
These arguments suggest that carbocations can in general be divided into two distinct types, classical and π-complex,[4-9] that π-complex ions need not be symmetrical, that in such an unsymmetrical π-complex, formed from an unsymmetrical olefin, the apical and basal atoms are still held together by a rather strong two-electron three-center bond, that attack by a nucleophile on such an unsymmetrical π-complex consequently still takes place trans to the apical group, and that solvation of the intermediates



22

ΔH_f = 193.2

Geometry		Charge	
2-3	1.4701	1 -.0288	6 .0814
3-4	1.6028	2 .3974	7 -.0304
2-4	2.4227	3 -.0323	8 -.0245
2-3-4	103.992	4 .1111	9 .0713
4-3-2-26	113.142	5 .0084	10 .0937



23

ΔH_f = 188.3

Geometry		Charge	
2-3	1.4646	1 -.0296	6 .0814
3-4	1.6146	2 .3936	7 .0940
2-4	2.3460	3 -.0253	8 .0900
4-3-2	99.119	4 .1161	9 -.0340
4-3-2-26	104.375	5 .0070	10 .0214

Figure 6. (a) MINDO/3 calculated intermediate (**22**) for conversion of **10** to **14** (**12**). (b) The second intermediate (**23**) found for this process has distorted its geometry slightly from **22** in order to minimize 1,3 axial interactions.

should not alter the course of the overall reaction.

Next we carried out similar calculations for the *cis*-decalin series, i.e, double ring opening in the ion **12**. As in the case of **13**, the classical isomer (**14**) proved to be less stable than the π-complex isomers containing protonated double bonds. Two stable species of this kind (**18** and **19**) were located. The geometries and heats of formation calculated for **14**, **18**, and **19** are shown in Figure 2.

The double ring opening in **14** followed a course similar to that found previously for **15**, taking place via an intermediate π-complex (**22**) whose structure and heat of formation are shown in Figure 6a. The reaction profile for the overall conversion of **12** to **10** (Figure 7) also closely resembled that for conversion of **13** to **11** (Figure 5). In this case, however, an alternative route was found for cyclization of the open chain cation (**10**), leading to a second π-complex (**23**) whose geometry and heat of formation are shown in Figure 6b. The structure of **23** is similar to that of **22**, except in that the axial substituent in **22** has rotated away from the ring to minimize 1,3-interactions.

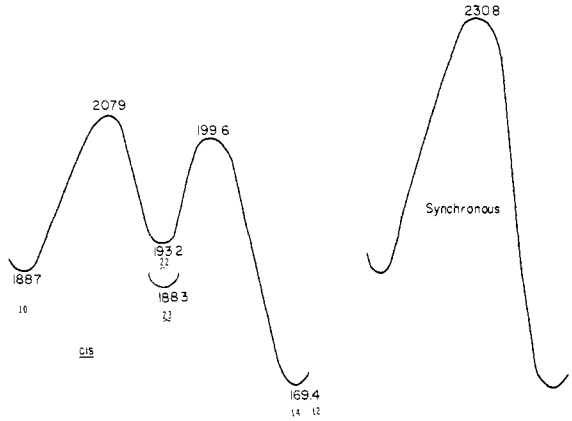


Figure 7. MINDO/3 reaction profile for the conversion of **10** to **14** (**12**).

As a final check on our calculated mechanisms, we examined possible concerted paths for the double cyclizations of **10** and **11**. While no true transition state could be located for either process, an indication of their feasibility was obtained by a calculation in which the lengths of the forming CC bonds were constrained to be equal. The activation energies for these paths were very large, greater than those for the two-step mechanisms by 23 kcal/mol in the case of **10** → **12** and 24 kcal/mol in the case of **11** → **13**.

Summary and Conclusions

The calculations reported here provide very strong support for a stepwise mechanism for biomimetic polyene cyclizations, each step involving the formation of a cyclic π-complex by electrophilic addition to a C=C bond. The reactions consequently take place stereospecifically by trans addition, as has been observed. There seems to be no question that concerted mechanisms are not involved in processes of this kind. The intermediate π-complexes are not, however, symmetrical, being distorted by angle strain. Distortion of an olefin π-complex by displacement of the apical group in a plane parallel to the basal atoms should be very facile, but it should not alter the essential stereochemical integrity of the π-complex because the basal atoms still remain linked by a strong π bond. The role of such distorted π-complexes has been underestimated in the past because of the misleading terminology and symbolism commonly used by organic chemists to describe "nonclassical carbocations". As we have repeatedly pointed out, the majority of such ions can be represented as olefin π-complexes and this description represents their properties far more effectively than the alternative dotted-line notation, which in fact was introduced several years later and for reasons unconnected with chemistry. The relationship between the two parallels that between the localized bond and MO descriptions of classical conjugated systems. The latter obscures the main characteristics of such molecules, i.e., the fact that they contain localized[7,8] single and double bonds.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research (Grant F49620-83-C-0024), the Robert A. Welch Foundation (Grant F-126), and the National Science Foundation (Grant CHE82-17948).

Registry No. 10, 88657-48-1; **11**, 88657-49-2; **12**, 88657-50-5; **13**, 88657-51-6; **16**, 88657-52-7; **17**, 88657-53-8; **18**, 88657-54-9; **19**, 88657-55-0; **21**, 88669-40-3; **22**, 88728-83-0.

Supplementary Material Available: Summaries of MINDO/3 calculations (9 pages). Ordering information is given on any current masthead page.

Base-Catalyzed Fragmentation of 2,3-Dioxabicyclo[2.2.1]heptane, the Bicyclic Peroxide Nucleus of Prostaglandin Endoperoxides: Large Secondary Deuterium Kinetic Isotope Effects[1]

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Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received June 20, 1983. Revised Manuscript Received November 12, 1983*

Abstract: The influence of deuterium substitution on the rates of base-catalyzed rearrangements of 2,3-dioxabicyclo[2.2.1]heptane (**1**) is examined. The kinetic isotope effect observed previously with 1,4,5,6,7,7-hexadeuterio-**1** (k_H/k_D = 7–8) is much larger than that observed with 1-deuterio-**1** (k_H/k_D = 3–4) during fragmentation to levulinaldehyde. This reveals a large cumulative secondary deuterium isotope effect which accompanies rate-determining cleavage of the bridgehead C–H bond. Presumably cleavage of the C4–C7 bond also occurs during the rate-determining step and deuterium substitution on these carbons produces large secondary kinetic isotope effects.

Fragmentation of the prostaglandin (PG) endoperoxide PGH_2 produces the levulinaldehyde derivatives LGE_2 and LGD_2.[1] This process competes with disproportionation of PGH_2, which affords prostaglandins PGE_2 and PGD_2, important natural mediators of cellular activities.[2] As a basis for understanding how in vivo biosynthesis might be channeled to disproportionation or fragmentation, we are carefully studying the mechanisms of these rearrangements for 2,3-dioxabicyclo[2.2.1]heptane (**1**), the strained

(1) Prostaglandin Endoperoxides. 13. For previous papers in this series see: Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 3498–3505 and references cited therein.

(2) For a recent review see: Wolfe, L. J. *J. Neurochem.* **1982**, *38*, 1. Also see van dorp, D. A. In "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergamon: New York, 1979; pp 233–242 and references cited therein.

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