Registry No.—**1a,** 17175-16-5; **1b,** 66398-02-5; DAP, 17448-65-6; CTAP, 41349-78-4; CBDACl, 122-18-9; methyl-*n*-dodecylurethane, 66769-57-1; methyl chlorocarbonate, 79-22-1; dodecylamine, 124-22-1.

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Application of Molecular Mechanics to Predict Solvolysis Rates of Polycyclic Secondary Derivatives

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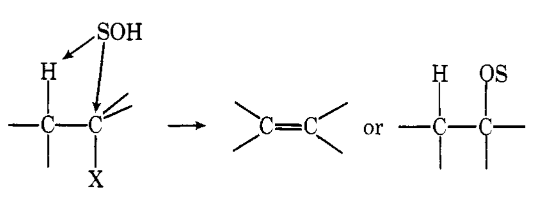
The molecular mechanics method of Schleyer is shown to predict accurately acetolysis rates of rigid, polycyclic secondary derivatives reacting by a k_c mechanism. Calculated rates are compared with experimental rates for substrates which may potentially react with σ assistance, and such assistance is shown to be important for several reactions. Six of these assisted reactions involve either degenerate rearrangement or rearrangement to a less stable carbon skeleton. These six reactions, consequently, cannot be downhill processes for which σ assistance is not controversial, but rather must involve formation of σ-bridged, nonclassical intermediates. In addition, calculated carbocation bond angles are shown to correlate well with the corresponding infrared carbonyl stretching frequencies.

A long-standing goal of organic chemistry has been to predict rates of carbocation formation and rearrangement in solvolysis reactions. The development of molecular-mechanical or empirical-force-field calculations has been a major step toward achieving this goal. The successful calculation of heats of formation, geometries, and strain energies for stable molecules has become practically routine with major efforts now being directed toward parameterization for more atoms.[1–3] Applications to reactivity problems have not been common, but the following reactions have been studied: ester hydrolysis,[4] aldol condensation,[5] nucleophilic addition to ketones,[6] solvolysis reactions,[7–9] carbocation rearrangements,[9,10] alcohol oxidation,[11] alkene dimerization,[12] and free-radical substitution.[13]



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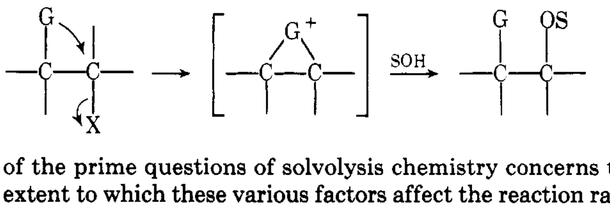

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Application of the molecular mechanics method to solvolysis reactions is particularly interesting because it presents the possibility of separating steric effects from the other factors governing these reactions. Solvolytic heterolysis of the bond between carbon and leaving group can be assisted by nucleophilic or basic solvent attack (a k_s process,[14] eq 1), or by nucleophilic neighboring group attack (a k_Δ process,[14] eq 2), or it may be assisted or retarded by steric effects.[15–18] One of the prime questions of solvolysis chemistry concerns the extent to which these various factors affect the reaction rates of secondary derivatives. The reactions of primary and tertiary derivatives are relatively simple, since these compounds react by competitive k_s and k_Δ processes in the former case and by a simple ionization mechanism (a k_c process)[14] in the latter case.[19] Secondary systems are more complex in that k_c, k_s, or k_Δ processes may be involved, and it has proven extremely difficult to determine which is operating.[18,19] Since methods have been developed recently for detecting k_s processes,[20] much of the remaining uncertainty concerns distinguishing between k_c and k_Δ processes. This problem could be solved if rates of reaction by a simple, unassisted k_c process could be calculated, since k_Δ processes are assisted and would be readily revealed by reaction rates greater than the calculated unassisted ionization rates. Unfortunately, the several attempts at predicting unassisted solvolysis rates have not been wholly successful.[18,21-25] The purpose of the present work is to describe the application of the method of molecular mechanics to the calculation of unassisted solvolysis rates of secondary derivatives.

Molecular mechanics has been applied to the study of carbocations and their rates of formation primarily by Schleyer and his co-workers.[7-12] Since the calculation of force fields for solvolytic leaving groups was still in the developmental stage, Schleyer used hydride as a leaving-group model, eq 3, and further assumed that the carbocation would serve as a transition state model; little experimental information was available for carbocations, so parameterization for carbocations required estimation of several terms.[7d]

$$\mathrm{RH} \rightarrow \mathrm{R}^+ + \mathrm{H}^- \tag{3}$$

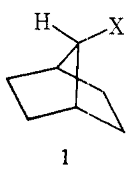
$$\delta\ \text{strain} = (\text{strain energy})_{\mathrm{R}^+} - (\text{strain energy})_{\mathrm{RH}} \tag{4}$$

The validity of this approach (which ignores variation in solvation and entropy contributions) is evidenced by the fact that δ strain was found to correlate solvolysis rates for polycyclic bridgehead alkyl chlorides.[7c,d] The bridgehead chlorides chosen for this initial test are particularly suitable in that there can be no interference from k_s or k_Δ processes, and inductive effects are essentially constant (an isoinductive series).

The goal of the present work is to ascertain whether the Schleyer treatment can be extended to the study of the more complicated secondary derivatives. First it is necessary to provide a rigorous test of whether the Schleyer force field is applicable to secondary carbocations as it is to bridgehead carbocations.[26] Such a test is performed by determining the degree to which the solvolysis rates of a series of rigid, polycyclic, isoinductive secondary derivatives known to react by a k_c mechanism can be correlated with δ-strain values calculated with the Schleyer force field. A test for more flexible secondary derivatives will be the subject of a future report.

The Test Series

Few secondary derivatives have been clearly shown to react by a k_c mechanism. Two compounds which approach reaction by this unassisted process are 7-norbornyl (**1**) and 2-adamantyl (**2**) tosylates.[20] There is evidence that there may be weak assistance in the reaction of these substrates,[7b,27,28] but there is no question that their reaction mechanisms closely approach the k_c limit.[29] Compounds forming an isoinductive series with **1** and **2** must have two "essential" isopropyl groups attached to the reactive center as in **3**; the term "essential" isopropyl group is used here because substitution further down the chain (e.g., isobutyl rather than isopropyl) should cause only minor differences in inductive effects, so such groups can be considered to be isoinductive with an isopropyl group. Acetolysis rates for 21 compounds (other than **1** and **2**) belonging to series **3** were obtained from the literature; these are compounds **4–16** (in these structures, the leaving group position is represented as E for exo, N for endo, Ax for axial, Eq for equatorial, and X when epimers are not possible).



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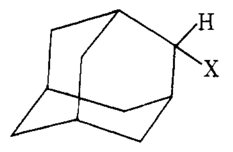

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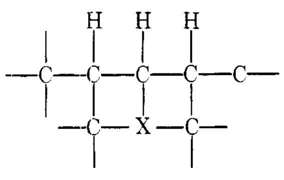

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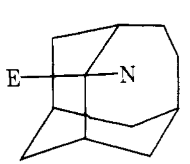
There is evidence that five compounds in this series (**4**-N, **5**-N, **6**-Ax, **9**-N, and **10**-N) react by a k_c mechanism. A review of this evidence follows.

Publication of detailed studies of the 2-homoadamantyl derivatives (**4**) has not appeared, but Grunwald–Winstein *m* values of 0.86 and 0.99 have been measured for the exo and endo derivatives, respectively.[30] Such a sensitivity to variations in solvent polarity has been shown to be characteristic of reaction by k_c mechanisms,[14,20b] so **4**-N seems clearly to be a k_c substrate. The slightly lower *m* value for the exo derivative, **4**-E, indicates involvement of a charge delocalization mechanism not operating in the reaction of **4**-N.



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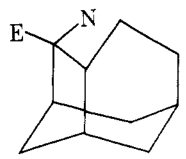

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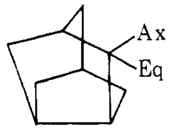

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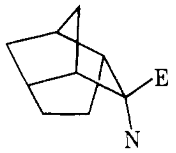

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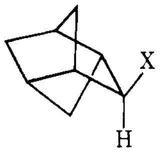

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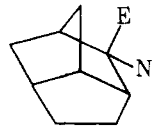

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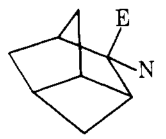

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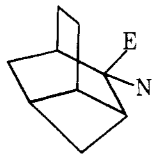

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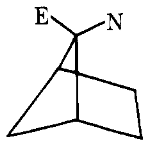

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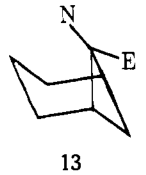

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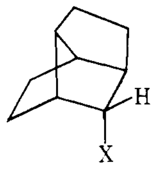

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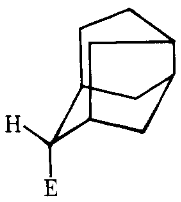

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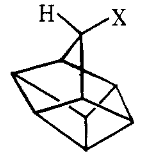

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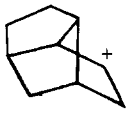

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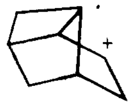

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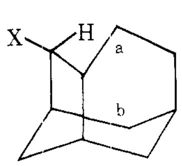
Spurlock[31] has studied the solvolysis of the 2-protoadamantyl derivatives, **5**-E and **5**-N, and has obtained evidence indicating that **5**-E reacts either by a k_Δ or a k_c mechanism and that **5**-N reacts by a k_c mechanism. The evidence is similar to that observed for the solvolysis of *exo*- and *endo*-2-norbornyl derivatives. First, a large exo–endo rate ratio (**5**-E/**5**-N) of 2512 is found for acetolysis. Also, the acetolysis products were the same for both exo and endo and included *exo*-2-protoadamantyl acetate and seven other tricyclic products;

endo-2-protoadamantyl acetate was not formed. Attack from the exo side was shown to be kinetically favored (e.g., reduction of 2-protoadamantanone with $LiAlH_4$ gave only *endo*-2-protoadamantanol). The rearranged products can be obtained from concerted displacement by bonds a or b (**19**) of the leaving group in **5**-E followed by various 1,2 carbon–carbon shifts and 1,3 hydride shifts, or by unassisted ionization of **5**-E and **5**-N to give the 2-protoadamantyl cation which then rearranges. There are two bonds in **5**-N which are approximately antiperiplanar to the leaving group (**20**), but participation by these bonds would give cyclobutyl carbinyl cations, not the products observed. The possibility of a k_Δ process for **5**-N solvolysis can, therefore, be eliminated. It appears that **5**-N must react by a k_c mechanism to give the 2-protoadamantyl cation which enters the same manifold of cations formed by **5**-E. The major question unanswered in this study is whether or not the large exo–endo rate ratio is the result of an accelerated k_Δ process for **5**-E or is of steric origin. Both events seem reasonable in that two carbon–carbon bonds are in the antiperiplanar positions necessary for effective anchimeric assistance (a and b of **19**) of **5**-E solvolysis, and the endo C_5 proton is well situated to sterically impede departure of the leaving group from **5**-N. We will comment on these two possibilities later, but our current interest lies with determining the k_c or k_Δ nature of **5**-N solvolysis, and this is clearly indicated to be k_c.



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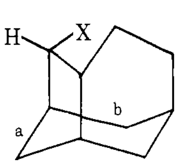

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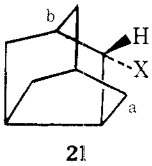
Acetolysis of axial and equatorial 2-noradamantanols, **6**-Ax and **6**-Eq, shows a similar pattern:[32] (1) the axial–equatorial rate ratio is 1190, (2) both derivatives give the same product mixture (95.5% equatorial acetate and 4.5% *exo*-4-brendyl acetate for **6**-Eq, and 92.7 and 7.3%, respectively, for **6**-Ax), (3) rearrangement of carbon–carbon bonds antiperiplanar to the leaving group gives the observed products for **6**-Eq but not for **6**-Ax (**21** and **22**), and those for **6**-Ax give highly improbable strained structures, and (4) reduction of the ketone shows that approach across the equatorial face is kinetically favored (reduction with $LiAlH_4$ gives 98% axial alcohol and 2% equatorial alcohol). Two additional pieces of information are available from deuterium labeling experiments. First, 91.9% of the products from **6**-Eq solvolysis derive from the degenerate rearrangement of bond b of **21**, and the remaining 8.1% derive from rearrangement of bond a to give the 4-brendyl cation, **23**. And second, acetolysis of C_4 or C_2 monodeuterium labeled **6**-Ax gives 10–13% less deuterium scrambling than observed for **6**-Eq. The sum of these experiments indicates either a k_c or a k_Δ mechanism for **6**-Eq acetolysis and either a k_c or a k_s mechanism for **6**-Ax acetolysis. The reduction in deuterium scrambling for **6**-Ax acetolysis is consistent with some nucleophilic solvent assistance for this reaction. That such assistance must, however, be weak can be determined from the observation that products other than inverted, unrearranged acetate are formed and from consideration of the transition state for this displacement process, **24**. As can be seen, the transition state closely resembles that for 2-adamantyl tosylate, a known k_c substrate,[14] in that there are several severe nonbonded interactions between hydrogens and both nucleophile and leaving group.



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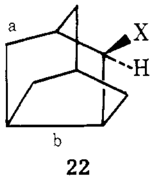

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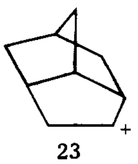

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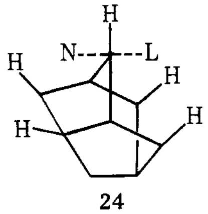

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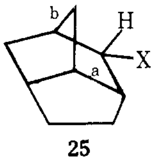
Acetolysis of 2-brendyl derivatives (**9**-E and **9**-N) yields the same product mixture and an exo–endo rate ratio of 1870.[33] Again there are no carbon–carbon bonds antiperiplanar to the endo leaving group which can participate to give the observed products; rather, highly strained cyclobutylcarbinyl cations would be formed by participation of a or b of **25**. As in the previous case, reaction of the exo derivatives by a k_c or k_Δ mechanism and of the endo derivatives by a k_c mechanism is indicated.



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The final member of series **3** which is indicated to react by a k_c mechanism is *endo*-2-tricyclo[3.2.1.$0^{3,6}$]octyl tosylate, **10**-N, for which we suggest the trivial name *endo*-2-norbrendyl tosylate. Sauers, Parent, and Damle[34] studied the acetolysis of **10**-E and **10**-N and found an exo–endo rate ratio of 192, 85% endo and 15% exo alcohol from $LiAlH_4$ reduction of the ketone, and exo acetate as the only reaction product from both **10**-E and **10**-N. Deuterium labeling studies revealed that there were no hidden degenerate rearrangements. These data are consistent with reaction of **10**-N by a simple k_c mechanism and with reaction of **10**-E by a k_Δ mechanism; a k_Δ mechanism is indicated for **10**-E because derivation of products from a classical cation would be expected, on the basis of the ketone reduction, to give some endo product.

The available evidence is, therefore, consistent with the seven compounds **1**, **2**, **4**-N, **5**-N, **6**-Ax, **9**-N, and **10**-N as constituting an isoinductive k_c series. If the Schleyer force field accurately represents the strain energy present in secondary carbocations, the solvolytic rates for this series of k_c substrates should be well correlated by δ-strain values, eq 3 and 4. Table I contains the requisite strain energies and rate constants for all the molecules considered in this work. As models for tosylates we have used both hydrogen and methyl (i.e., R–H and R–Me) since methyl would seem more likely to represent differences in strain energies for epimeric pairs; however, in the present work, no advantage results from using the larger model. Actually, as Dubois has shown, the methyl is probably also too small to model a tosylate group properly.[8]

Figure 1 is a plot of δ strain, using the R–Me model, against acetolysis rate for the seven k_c compounds, and Figure 2 is the corresponding plot using the R–H model. With the exception of *endo*-2-protoadamantyl tosylate (**5**-N) a good correlation results (correlation coefficients of 0.97 in each case); the expressions for the correlations are given in eq 5 and 6. The deviation of the point for **5**-N can be rationalized.

$$-\log k = 0.44(\delta \text{ strain}) + 8.06 \qquad L = Me \qquad (5)$$

$$-\log k = 0.44(\delta \text{ strain}) + 7.22 \qquad L = H \qquad (6)$$

We have used the carbocation as a transition state model, and this model can be expected to work as long as there is no increase in nonbonded interactions with the leaving group upon

Table I. Strain Energies for a Series of Carbocations and Hydrocarbon Precursors and Acetolysis Rates for the Series of Alkyl Tosylates 1–16

		strain energy, kcal/mol[r]			δ strain			
compd	registry no.	R–Me	R–H[a]	R^+	L = H	L = Me	−log k, s^{-1}	assistance[q]
1	10265-27-7	18.77	16.98	30.79	13.81	12.02	13.68[c]	0
2	25139-43-9	8.56	6.87	9.21	2.34	0.65	8.23[b]	0
4-E	66687-78-3	15.80	14.59	15.12	0.53	−0.68	6.69[d]	1.06
4-N	66748-94-5	16.09	14.59	15.12	0.53	−0.97	8.08[d]	0
5-E	66687-79-4	19.10	18.29	20.51	2.22	1.41	6.50[e]	2.18
5-N	66748-95-6	21.84	18.29	20.51	2.22	−1.33	9.90[e]	−2.43
6-Ax	66687-80-7	22.76	20.07	25.70	5.63	2.94	9.66[f,p]	0
6-Eq	66748-96-7	21.85	20.07	25.70	5.63	3.84	6.58[f,p]	3.17
7-E	66687-81-8	37.42	34.17	40.34	6.17	2.92	5.65[g,p]	3.69
7-N	66748-97-8	39.79	34.17	40.34	6.17	0.55	4.74[g,p]	3.56
8	63561-18-2	45.90	(36.86)	54.68	17.82	8.78	4.50[h,p]	7.40
9-E	66687-82-9	22.94	22.57	26.03	3.46	3.09	5.24[i,j,p]	4.18
9-N	66748-98-9	24.78	22.57	26.03	3.46	1.25	8.50[j,p]	0
10-E	6733-62-6	42.46	41.46	48.10	6.64	5.64	7.04[k,p]	3.50
10-N	6239-91-4	43.26	41.46	48.10	6.64	4.84	9.32[k,p]	0
11-E	66687-83-0	41.30	(40.04)	42.79	2.75	1.49	3.83[g,p]	4.88
12-E	3097-76-5	43.05	41.21	69.74	28.53	26.69	10.65[l]	9.17
12-N	10437-83-9	44.36	41.21	69.74	28.53	25.38	2.58[l]	16.66
13-E	6621-20-1	36.34	35.85	51.28	15.43	14.94	9.00[m]	5.64
13-N	6621-28-9	38.49	35.85	51.28	15.43	12.34	2.35[m]	11.15
14	66687-84-1	27.47	25.47	30.98	5.51	3.51	4.79[j]	4.81
15-E	58918-47-1	20.03	18.29	15.03	−3.26	−5.00	6.99[n]	−1.20
16	15291-16-4	117.65	118.13	133.10	14.97	15.45	8.07[o]	6.83
17	66687-85-2			29.18				
18	66687-86-3			51.71				

[a] Values in parentheses from this work, others from ref 3a. [b] Reference 21b. [c] R. K. Lustgarten, J. Lhomme, and S. Winstein, *J. Org. Chem.*, **37,** 1075 (1972). [d] Reference 30. [e] Reference 31. [f] Reference 32. [g] Reference 37. [h] Reference 38. [i] Reference 33b. [j] Reference 33a. [k] Reference 34. [l] Reference 42. [m] Reference 41. [n] Reference 39. [o] Reference 44. [p] OBs/OTs = 3.0. [q] Deviation in rate from the k_c line of Figure 4. [r] Strain energies were calculated using the force fields described in ref 3a and 7d.

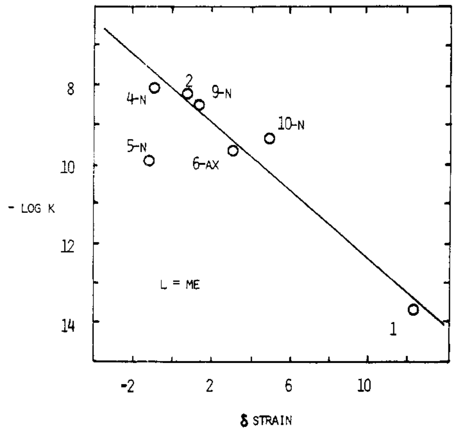


Figure 1. A plot of log k against δ strain for a series of proposed k_c substrates where the leaving group is modeled by methyl. Excluding **5**-N correlation coefficient = 0.97, standard deviation in log k = 0.48 (1.0 including **5**-N).

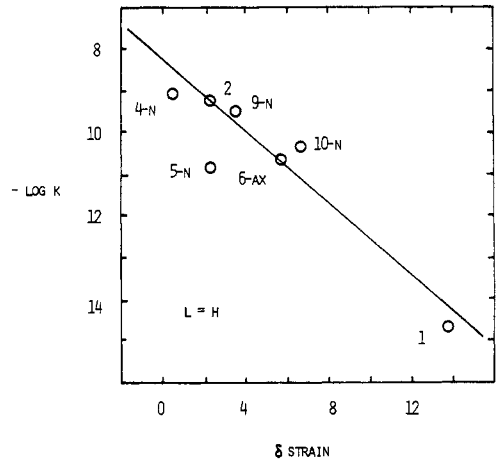


Figure 2. A plot of log k against δ strain for a series of proposed k_c substrates where the leaving group is modeled by hydrogen. Excluding **5**-N correlation coefficient = 0.97, standard deviation in log k = 0.50 (0.79 including **5**-N).

proceeding from the reactant to the transition state. Such interactions would not be reflected in the carbocation and if severe would cause our model to fail. As Spurlock has noted,[31] **5**-N is just such a case; leaving group departure is severely hindered in this molecule by the endo hydrogen at C_5, **20.** Nonbonded hindrance to ionization is not reflected by the molecular-mechanical calculation but can be readily detected by examination of molecular models, or (we propose) by a negative deviation from Figures 1 or 2. Also, it is important to note that deviations of this sort may cause a k_Δ substrate to be classified as a k_c substrate but not vice versa; because of the inability of the present method to detect large increases in nonbonded strain in the transition state, molecules may appear to react too slowly but not too rapidly.

The correlation of unassisted solvolysis rates with strain values in Figures 1 and 2 indicates that the Schleyer molecular-mechanics method accurately calculates the strain energies of polycylic secondary carbocations, and further, that employing hydrocarbons as tosylate models and carbocations as solvolytic-transition-state models is legitimate for these reactions. A further test of the method follows.

Correlation of Infrared Carbonyl Absorptions

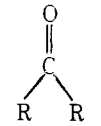
Since both ketones and the corresponding secondary carbocations (**26** and **27**) are trigonal and approximately sp^2 hybridized, their infrared carbonyl stretching frequencies and carbocation stabilities exhibit similar dependencies upon conformation (upon bond angles in particular) about the trigonal center.[35] If it can, therefore, be assumed that infrared

Table II. Infrared Carbonyl Absorption Frequencies (ν_{CO}) for Ketone 26 and C–C$^+$–C Bond Angles (θ) for 27

Compd	$1715 - \nu_{CO}$, cm^{-1}[a]	θ, deg	ref
1	−58	112.9	21
2	−12	118.5	21
4	15	120.3	*b*
5	−28	116.7	31
6	−40	115.5	32
7	−38	114.5	37
8	−55	112.6	38
9	−32	116.2	*c*
10	−35	115.5	34
11	−20	117.7	37
12	−83	110.4	*d*
13	−60	112.6	41
14	−36	115.0	*c*
15	4	120.1	39
16	−42	112.7	44
17	−34	116.3	37

[a] The absorption at 1715 cm^{-1} is that for cyclohexane.[21] [b] R. K. Murray, Jr., K. A. Babiak, and T. K. Morgan, Jr., *J. Org. Chem.*, **40,** 2463 (1975). [c] A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87,** 1613 (1965). [d] K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, **83,** 3998 (1961).

carbonyl stretching frequencies are proportional to CCC bond angle, and further, that the CCC bond angle of a ketone will be similar to the same bond angle in the corresponding secondary carbocation, then a further test of the accuracy of the Schleyer force field for calculation of structure and energy of secondary carbocations is provided. Thus, a direct correlation should exist between experimental infrared carbonyl absorption frequencies and calculated C–C$^+$–C bond angles. We have collected in Table II the carbonyl infrared absorptions and the appropriate bond angles from molecular mechanical calculation for the 16 carbocations considered in the present study. These data are plotted in Figure 3, and with the exception of the homocubyl point (**16**) an excellent correlation results.



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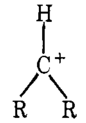


27

The success with which molecular-mechanical calculations using the Schleyer force field correlate with infrared carbonyl absorption and with solvolysis rates for known secondary k_c systems justfies the following conclusions: (1) these calculations accurately predict the structure and energy of secondary carbocations; and (2) differences in strain energies between hydrocarbons and carbocations approximate the energies of activation for unassisted solvolysis of polycyclic alkyl tosylates. In the following section these concepts are applied to identify the operation of neighboring carbon assistance.

Neighboring Carbon Assistance

As discussed earlier, it is often very difficult to distinguish between k_c and k_Δ processes. In the present study of polycyclic alkyl derivatives, neighboring group assistance can potentially be provided by σ electrons of carbon–carbon bonds. There is, of course, much debate about the existence of σ-bridged or nonclassical intermediates,[18] but there is no doubt regarding the importance of σ bridging in the transition states for secondary solvolyses. Actually, σ bridging is common in transition states for processes in which rearrangement to a more stable ion occurs (a so-called downhill process).[36]

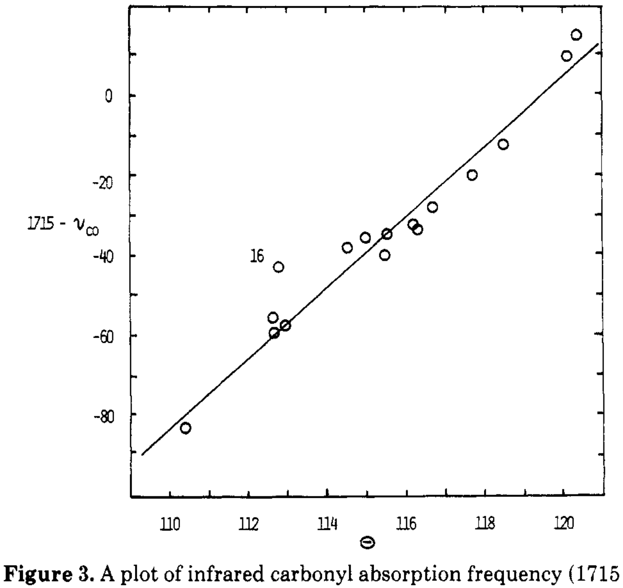


Figure 3. A plot of infrared carbonyl absorption frequency ($1715 - \nu_{CO}$) against calculated C–C$^+$–C bond angles (θ) for compounds **1–17.** Correlation coefficient = 0.97, standard deviation in carbonyl absorption = 5.7 cm^{-1}.

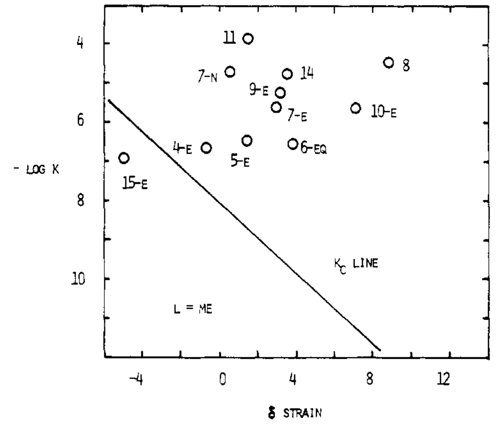


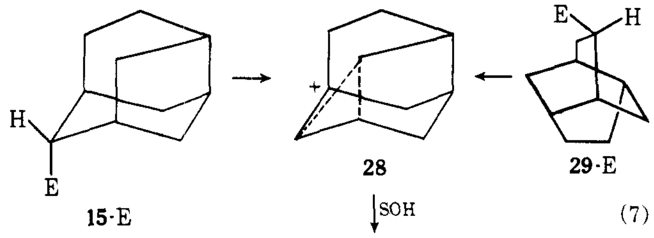
Figure 4. A plot of log k against δ strain for substrates other than the k_c models.

In Figures 1 and 2 the relationship between unassisted acetolysis rates and δ strain is defined. If a secondary substrate, isoelectronic with **3**, undergoes acetolysis by a k_c mechanism, it should lie on the correlation lines of Figures 1 and 2 unless nonbonded interaction involving the leaving group increases significantly upon proceeding to the transition state; in this latter case the point should be below the line defined by the other k_c substrates. In addition to the seven model k_c substrates, we have performed strain calculations for 16 other isoinductive compounds which are either known not to be k_c substrates or for which there is insufficient evidence available to specify reaction by a k_c or a k_Δ mechanism. Figure 4 is a plot of acetolysis rate against δ strain for 11 of these additional 16 substrates; included in the plot is the line defined by the k_c substrates. Five substrates were not included in the plot because their points were so far above the k_c line that they distorted the figure. These five substrates are discussed below.

In Figure 4 the points for ten compounds lie above the k_c line as would be expected for k_Δ processes. One compound, *exo*-10-protoadamantyl tosylate (**15-E**), lies slightly below the k_c line and is thus indicated to be a k_c substrate. Table I contains an assistance column in which is presented the rate acceleration for each compound relative to the predicted k_c rate (i.e., the amount the point is above or below the k_c line).

To discuss the implications of Figure 4 for each compound would be prohibitively lengthy, but it should be noted that in the cases of **4**-E,[30] **5**-E,[31] **6**-Eq,[32] and **9**-E[33] the available evidence was not sufficient for the original authors to distinguish between k_c and k_Δ processes. Figure 4 clearly shows that, with the possible exception of **4**-E, each of these compounds reacts by a k_Δ mechanism. The amount of assistance calculated for **4**-E is only $10^{1.06}$, Table I, and one of the k_c substrates is this far above the k_c line.

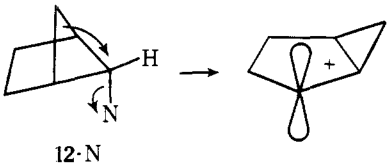
The other seven compounds of Figure 4 (**7**-E and **7**-N,[9,38] **8**,[38] **10**-E,[34] **11**,[37] **14**,[37] and **15**-E[39]) were said by the original authors either to ionize with neighboring carbon assistance (**7**-E, **8**, and **10**-E) or to form bridged ions (**7**-N, **11**, **14**, and **15**-E); of course, formation of a bridged ion implies a neighboring-carbon-assisted process. The results of Figure 4 support the original analyses in every case except that of **15**-E, *exo*-10-protoadamantyl tosylate.[40] The solvolysis of **15**-E has been studied by Tichy, Kniezo, and Hapala[40] who found that both **15**-E and *exo*-4-twistly tosylate (**29**-E) gave the same product mixtures of approximately three parts **15**-OS and one part **28**-OS in 70% acetone, acetic acid, and ethanol, eq 7. A deuterium labeling experiment was consistent with the scrambling expected from the bridged ion **28** and not with that expected from a series of equilibrating classical ions. Regarding the discrepancy between our study of this solvolysis and that of Tichy et al., one possibility is that **15**-E does react with assistance to form a bridged ion, but the assistance is too small to detect with our method. It should be recalled that theoretical studies indicate there may be little difference in stability between bridged and classical ions.[41]



15-E **28** **29**-E (7)

15-E-OS + **29**-E-OS

Four compounds not included in Figure 4 because of the large degree of deviation from the figure are the cyclobutyl compounds **12**-E, **12**-N, **13**-E, and **13**-N. Wiberg and his coworkers have extensively studied the reactions of these compounds and have found that the endo compounds undergo acetolysis by k_Δ mechanisms.[41-43] Both endo compounds react much faster than cyclobutyl tosylate (**12**-N/cyclobutyl = 880, **13**-N/cyclobutyl = 1467), and both compounds have available a symmetry-allowed disrotatory pathway to a highly stable cyclopropylcarbinyl cation, eq 8. The concerted rearrangement is not possible for the exo derivatives, **12**-E and **13**-E, and they react much more slowly than cylobutyl (**12**-E/cyclobutyl = 7.46×10^{-6}, **13**-E/cyclobutyl = 3.37×10^{-4}). Consequently, Wiberg and his co-workers described the exo isomers as having "particularly low reactivity".[43] Actually, the exo isomers only appear to be unreactive when compared to the highly reactive parent cyclobutyl system. Examination of Table II shows that the C–C$^+$–C bond angles in the carbocations **12** and **13** are far less than the desired 120°, and examination of Table I shows that the strain increase upon ionization of the compounds **12** and **13** is tremendous and is higher than that for any other compound treated, including the notoriously unreactive 7-norbornyl derivative. Comparison of the rates of **12**-E and **13**-E with the more appropriate model 7-norbornyl shows **12**-E and **13**-E reacting 3.51×10^3 and 1.58×10^5 times as fast, respectively, as 7-norbornyl. Thus, our δ-strain prediction that **12**-E and **13**-E receive neighboring carbon assistance of $10^{9.17}$ and $10^{5.64}$, respectively (Table I), appears to be quite reasonable.



12-N (8)

A final compound not included in Figure 4 is 9-homocubyl tosylate, **16**. Experimental[44,45] and theoretical[46] studies of the acetolysis and accompanying degenerate rearrangements of this system have been performed. Schleyer used the approximate relationship between infrared carbonyl absorption frequency and solvolysis rate to predict that the acetolysis of **16** was accelerated by a factor of approximately 400 (see discussion of the Foote–Schleyer relationship below).[44] According to Figure 4 the assistance is even greater, amounting to $10^{6.83}$, Table I.

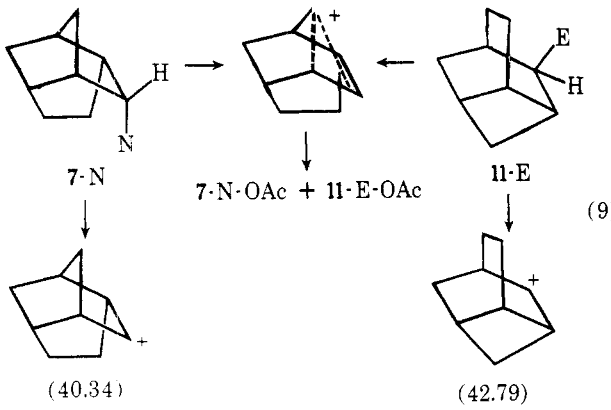
Intermediacy of Nonclassical Ions

In addition to the downhill process discussed above, two other mechanisms can result in a solvolytic reaction which appears to be accelerated relative to appropriate models under the same conditions. These mechanisms are neighboring group assistance to yield a bridged ion and enhanced hyperconjugation. Several workers have noted[18,47,48] that highly strained bent σ bonds can provide an exceptional degree of hyperconjugative stabilization to a developing carbocation, and thus lead to solvolytic rate enhancement. The cyclopropylcarbinyl system has been identified as having this property,[18] while the 2-norbornyl system has been identified as not having it.[49] It appears, therefore, that a high degree of strain such as is present in cyclopropyl systems is necessary for enhancement of hyperconjugative ability. Since none of the systems examined in the present study has cyclopropyl groups, it appears unlikely that reaction of any of these systems involves enhanced hyperconjugation; however, it should be noted that the importance of this phenomenon remains to be clearly delineated.

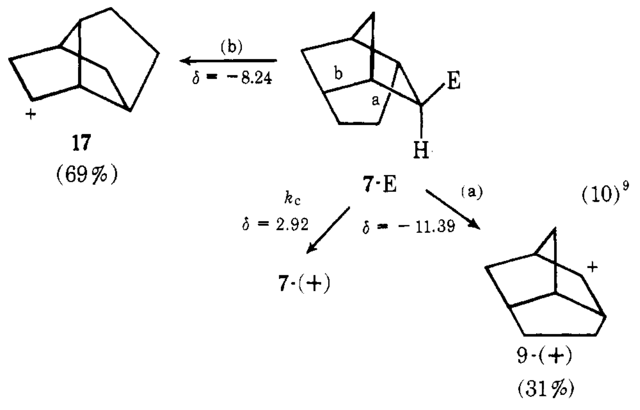
The importance of neighboring carbon participation to yield a σ-bridged or nonclassical intermediate is a matter of longstanding debate.[18] The molecular mechanics method permits the identification of several reactions which are clearly assisted yet which are not downhill processes; i.e., rearrangement to a more stable carbocation does not occur. If there is σ bridging in the transition states for these processes (indicated by accelerated rates if enhanced hyperconjugation is ruled out, as it seems to be for the molecules under consideration in the presented study), and if rearrangement to a more stable classical cation can be ruled out, then it must be concluded that these σ-bridged transition states are leading to σ-bridged, nonclassical intermediates.

Compounds **10**-E and **16** fit the above description in that both compounds react at greatly accelerated rates, Table I, and both give products in which the original carbon skeleton is retained.[33,44,45] Also, reaction of **10**-E yields only the exo product, and as discussed earlier, the results of ketone reduction by $LiAlH_4$ indicate that nucleophilic attack on the classical cation (**10**$^+$) should yield some endo product as well as exo product; it should be recalled, however, that $LiAlH_4$ is a rather unselective reagent.[18] The reaction of **14**-X is similar to that of **10**-E or **16** in that an accelerated rate is observed, yet the reaction involves several degenerate rearrangements followed by a hydride shift to give the same nonclassical ion (below) as **9**-E; a downhill process is not occurring.[37]

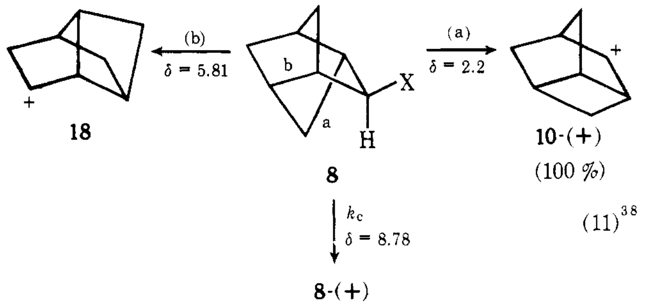
The reaction of **7**-N, eq 9, provides another example of acceleration without downhill rearrangement. In this instance some rearrangement does occur, but it is uphill to yield products derived from cation **11** (in eq 9 the strain energies



(9)



(10)[9]



(11)[38]

of the two cations are given in parentheses below the structure).[37] Reaction of 11-E yields the same product mixture as does reaction of 7-N. Also, $LiAlH_4$ reduction of the ketone corresponding to 7 (i.e., 2-twistbrendanone) results in less than 1% of attack from the endo direction to give *exo*-2-twistbrendanol.[37] In contrast, solvolytic substitution of 7-N proceeds entirely from the sterically disfavored endo direction. Similarly, $LiAlH_4$ reduction of the ketone corresponding to 11 favors approach from the endo direction over approach from the exo direction by a factor of approximately 2. Again, the solvolytic results are in contrast, with attack coming exclusively from the exo direction to yield 11-E-OAc. These results are consistent only with formation of a nonclassical ion as shown in eq 9.

As a final example, the reaction of 9-E is analogous to that of 7-N in that the reaction is accelerated, and unrearranged acetate (9-E-OAc) and a more strained *exo*-4-brexyl acetate (17-OAc) are formed;[33] formation of a nonclassical ion is indicated from reaction of 9-E and 17-E.

These results indicating formation of nonclassical ions, combined with those of Coates,[50] Brown,[51] and Schleyer,[7b] demonstrate that nonclassical ions can be formed in solvolysis reactions. Much debate in this area has centered on deciding the classical or nonclassical nature of the 2-norbornyl cation, and this question still has not been settled.[18–25] However, the present results and those referenced above show that whether the norbornyl cation is classical or nonclassical does not affect the following general principle: carbocations generated in solvolytic processes *can* have positive centers (carbonium carbons)[52] which are pentacoordinate; such nonclassical cations[52] are more stable than their classical counterparts, in which the positive centers are tricoordinate, and they will thus be formed at accelerated rates relative to the rate of formation of the corresponding classical carbocations.

Prediction of Rearrangement Rates. The molecular mechanics method permits accurate calculation of relative energies of carbocations and their precursors, and therefore offers the possibility of predicting the relative formation rates of isomeric carbocations. For example, the k_Δ substrates 7-E and 8 are known[9,38] to rearrange as shown in eq 10 and 11 (in these equations the experimentally observed yields are given beneath the figure and δ-strain values [in kcal/mol] calculated from differences between the cation formed and the neutral precursor are given below the reaction arrows). According to the δ-strain values presented in eq 10, compound 7-E should rearrange upon acetolysis to give 9-(+). Nickon has shown that the favored cation is actually 17, the less stable isomer.[9] Also, if the δ-strain value for the rearrangement process is used to predict the rate of reaction according to Figure 4, the predicted rate is approximately 10^3 times too slow. The reason for this failure, as has been made clear for this specific case by Nickon and co-workers[9] and for the general case by Schleyer and co-workers,[10] is the result of competition between bond-alignment control and product-stability control. As these workers have pointed out, rearrangement pathways are controlled not only by product stabilities but also by the geometric alignment of the involved bonds and orbitals, with dihedral angles of zero and 180° being preferred. The rearrangement of 7-E is unusual in that considerations of bond alignment and product stability lead to opposite predictions; since formation of the less stable product is favored by bond alignment, bond alignment is seen to be the dominant factor.[9]

In the case of rearrangement of 8, bond-alignment and product-stability predictions are the same: 10^+ is 3.61 kcal/mol more stable than 18, and the a–x dihedral angle is 165.2° and the b–x dihedral angle is 158.8° (for the methyl derivative). Again, however, using the rearrangement δ strain of 2.20 kcal/mol in conjunction with Figure 4, one fails to obtain the observed rate; instead, a predicted rate which is $10^{4.5}$ times too fast is obtained.

Thus it appears that the δ-strain method in its present, simple formulation is useful for accurately predicting k_c rates but not k_Δ rates. As others have noted,[9,10] prediction of k_Δ rates requires consideration of both bond alignment and energy factors.

Foote–Schleyer Correlation. Foote has shown that the rate of acetolysis for a large number of secondary tosylates can be correlated with the infrared carbonyl absorption frequency of the corresponding ketones.[21] More recent research has shown that k_s (e.g., cyclohexyl[20]), k_c (e.g., 7-norbornyl[20]), and k_Δ (3-methyl-2-butyl[20a]) substrates lie on the correlation line, implying that compensating factors must be involved in producing the correlation. As noted above, carbonyl frequencies are primarily a function of C–C(O)–C bond angle, and it is surprising that a parameter which depends only on this one factor should be so well correlated with rates. Inclusion of our seven k_c substrates (1, 2, 4-E, 5-N, 6-Ax, 9-N, and 10-N) in the Foote plot, Figure 5, shows poor agreement between experimental and calculated rates (compounds 1 and 2 were part of the original correlation).

Schleyer expanded the Foote correlation to include, in addition to carbocation angle strain, contributions from reactant torsional strain, differences in nonbonded strain in ground and transition states, and inductive effects, eq 11. In applying this Schleyer treatment to the isoinductive k_c substrates, the inductive contribution can be ignored. The third term in the equation, (GS − TS)/1.36, accounts for differences in non-

Table III. Foote–Schleyer Parameters for Calculation of Acetolysis Rates.[22]

Compd	$1715 - \nu_{CO}$, cm^{-1}	ϕ_i	$(-\log k_{calcd})^a$	$(-\log k_{exptl})^a$	(exptl − calcd)
1	−58	60.60	7.25	6.37	0.88
2	−12	60,60	1.50	0.92	0.58
4-N	15	60,50	−2.05	0.77	−2.82
5-N	−28	60,30	3.5	2.59	0.91
6-Ax	−40	60,51	4.86	2.35	2.51
9-N	−32	60,24	2.27	1.19	1.08
10-N	−35	59,55	4.33	2.01	2.32

[a] Relative to cyclohexyl tosylate.

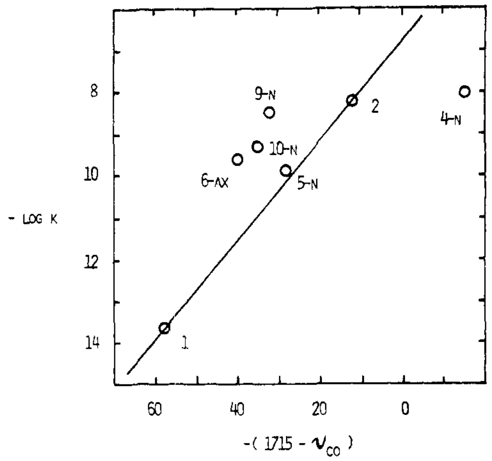


Figure 5. A Foote plot for seven k_c substrates (points 1 and 2 were on Foote's original plot).[21]

bonded strain and is estimated by referring to model systems. There is a degree of arbitrariness in the assignment of the strain values, and we have omitted this term from our calculations. The results of applying eq 11 to our seven k_c substrates are given in Table III, and, as is evident, there are significant discrepancies between calculated and observed rates. Inclusion of the term for nonbonded strain would give calculated rates slightly closer ($<10^{0.5}$) to the experimental rates in every case except 4-N, for which the calculated rate is already too large; relief of nonbonded strain, of course, gives larger calculated rates.

$$\log k_{rel} = (1715 - \nu_{CO})/8 + 1.32 \sum_i (1 + \cos 3\phi_i) + (GS - TS\ strain)/1.36 + inductive\ term \quad (12)$$

It should be noted that Schleyer has pointed out that the Foote–Schleyer correlation is not expected to work for crowded substrates such as those considered in the present study.[53] Our purpose in applying the method to these molecules is not intended as a criticism of the Foote–Schleyer treatment, since its limitations have already been discussed by one of the original authors, but rather to emphasize that prior to the present work the Foote–Schleyer approach was the best available method for predicting acetolysis rates of polycyclic secondary tosylates. The present molecular-mechanical method should be superior since it accounts, with a high degree of accuracy, for differences of all four components of strain energy in both reactant and product carbocation.

Conclusions

The present work demonstrates that the molecular mechanics method of Schleyer can be used to predict accurately the acetolysis rates of rigid, polycyclic secondary derivatives reacting by a k_c mechanism. Comparison of these calculated k_c rates with experimental rates for several substrates permits the identification of accelerated reactions and involvement of σ assistance. Operation of σ assistance for substrates in which there is no downhill rearrangement is consistent only with the formation of nonclassical, σ-bridged intermediates for these substrates, and several such intermediates are identified.

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Synthesis and Reactions of Chloroalkene Epoxides

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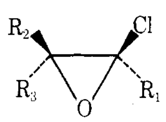
The chloroalkene epoxides, vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), *cis*- and *trans*-1-chloropropene oxide (4 and 5), and *cis*- and *trans*-1,3-dichloropropene oxide (6 and 7), were synthesized from their respective chloroalkenes via either autooxygenation (in the case of 2 and 3) or *m*-chloroperbenzoic acid oxidation (in the case of 1 and 4–7). Dichlorobenzene was a byproduct in the synthesis of both 6 and 7. In the case of 6, its formation was determined to be a result of a bimolecular reaction involving an intermediate in the synthesis of 6. Kinetics of hydrolysis at pH 7.4 and 37 °C were determined for compounds 2–7. Kinetics of thermal decomposition in dilute hydrocarbon solution were determined for compounds 2, 4, 5, and 7. The hydrolysis and thermolysis rates are discussed with respect to structure and mechanism of product formation.

Halogenated alkenes are widely employed as insecticides, industrial monomers, as solvents, and for other uses. Vinyl chloride has been shown to be carcinogenic to animals and man.[1] Trichloroethylene has been shown to be carcinogenic to mice.[1] These compounds and others including *cis*- and *trans*-1,3-dichloropropene are potent mutagens.[2] Vinyl chloride and trichloroethylene have been shown to bind covalently to cellular macromolecules.[3] This binding requires metabolic oxidation of the compounds and there is some evidence which suggests that epoxides may be intermediates involved in the binding.[4] Such epoxides have been proposed as potential activated carcinogenic intermediates[5] based on their structural similarity to known epoxide and chloroether carcinogens.[6] We have undertaken the synthesis and characterization of a number of such epoxides including vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), *cis*- and *trans*-1-chloropropene oxide (4 and 5), and *cis*- and *trans*-1,3-dichloropropene oxide (6 and 7). We determined and compared the rates and products of hydrolysis of these epoxides at physiological conditions. In addition, we have carried out thermal degradations of several of these epoxides and determined the rate of degradation and the nature of the products formed.



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = H; R_2 = R_3 = Cl$
3, $R_1 = R_2 = R_3 = Cl$
4, $R_1 = R_3 = H; R_2 = CH_3$
5, $R_1 = R_2 = H; R_3 = CH_3$
6, $R_1 = R_3 = H; R_2 = CH_2Cl$
7, $R_1 = R_2 = H; R_3 = CH_2Cl$

Trichloroethylene oxide (2), synthesized by the autooxidation of trichloroethylene,[7] has been previously characterized in this laboratory.[8] Frankel et al.[9] had reported the synthesis of tetrachloroethylene oxide (3) by the chlorine-initiated photooxygenation of tetrachloroethylene. We modified this procedure by eliminating the chlorine initiator (which was found to catalyze the decomposition of the product) and allowing the reaction to go to completion. In this way the yield was improved and the purification of the product was greatly simplified.

Kirrman and co-workers synthesized 1-chloropropene oxide via dehydrohalogenation of 1,1-dichloro-2-hydroxypropane.[10] They obtained an unseparated mixture of cis and trans epoxides in low yield. Pure 4 and pure 5 were obtained in excellent yield by the *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of the respective *cis*- and *trans*-1-chloropropenes. The NMR spectrum of each of the pure compounds was superimposable on the NMR spectrum of the mixture obtained by the method of Kirrman.

cis- and *trans*-1,3-dichloropropene oxide (6 and 7) were likewise synthesized by the *m*-CPBA oxidation of the corresponding alkenes. NMR, IR, and mass spectra of the major products were consistent with two possible structures, i.e., the assigned epoxide structure (A) or the cyclic ether (B). Incremental addition of the lanthanide shift reagent Eu(fod)^{TM} to compound 6 moved the chemical shifts of the methine (CH_2) protons (H(b), assigned on the basis of peak shape and integration) at a rate slower than that of either of the other protons H(a) or H(c) (Table I). The lanthanide reagents are known to

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