Modeling Chemical Reactivity. 7. The Effect of a Change in Rate-Limiting Step on the Stereoselectivity of Electrophilic Addition to Allylic Alcohols and Related Chiral Alkenes

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Abstract: The stereoselectivities of electrophilic additions to acyclic allylic alcohols with and without internal nucleophiles have been assessed with use of previously developed chemical reactivity modeling techniques. Reactions normally assumed to proceed via onium-type intermediates have been investigated. The diastereofacial selectivity of attack by I_2, Br_2, PhSeCl, $Hg(OAc)_2$, and related electrophiles, known to be *opposite* for substrates containing an internal nucleophile compared with those without, is explained in terms of a change in the rate-limiting step for the reaction. Specifically, where intramolecular nucleophilic attack is possible, cyclizations proceed via a transition state that resembles a (reactant-like) π complex, whereas reactions that involve intermolecular addition of the nucleophile are governed by one that resembles an "onium" ion, e.g., iodonium. Calculations show that these two extremes should exhibit opposite diastereofacial selectivity of attack on the acyclic allylic π bond by the electrophile, in agreement with available experimental results.

The use of electrophiles to promote the addition of a nucleophile to an otherwise unactivated olefin under mild conditions has become a standard synthesis strategy, most notably in the construction of highly functionalized heterocycles from acyclic precursors. The presence of an allylic heteroatom, such as an alcohol or amide derivative, often results in significant asymmetric induction.[1-3] Interestingly, for electrophiles that normally are assumed to react via onium intermediates, e.g., I_2, Br_2, PhSeCl, and $Hg(OAc)_2$, the preferred diastereomer that results from electrophile-induced cyclization usually is opposite to that observed in the analogous intermolecular electrophilic addition.

This reversal of diastereofacial selectivity parallels a rather subtle difference in mechanism between the kinetically controlled addition and cyclization processes. Thus, the rate-limiting step in many addition reactions is the formation of an onium ion intermediate[4] that subsequently is trapped rapidly by a nucleophile from the medium, whereas electrophilic cyclization reactions proceed via intramolecular attack on a π complex, *not* an onium ion, at least in a few cases that have been studied carefully.[5] For a chiral allylic alcohol, either face of the π bond can react, so that there is a duality of reaction pathways represented as shown in Figure 1. The starting allylic alcohol can be attacked on either face to give the π complexes A and B, which probably form reversibly. In turn, each π complex can proceed either directly to the corresponding product diastereomer by reaction with a nucleophile or indirectly by first collapsing to an onium ion before undergoing nucleophilic attack. For addition reactions (no internal nucleophile), onium ion formation is expected to be rate-limiting, i.e., $k_2 < k_3$ and $k_5 < k_6$. On the other hand, direct intramolecular nucleophilic addition is so much faster for cyclizations that it becomes the predominant pathway ($k_1 > k_2$ and $k_4 > k_5$). Obviously, however, the *diastereofacial selectivity* of the process is dependent upon additional factors, including the relative abundances and reactivities of the complexes and the ratio of rate constants k_2:k_5 (for additions) or k_1:k_4 (for cyclizations). These issues are addressed herein both theoretically, using newly developed reactivity modeling techniques,[6] and via an analysis of representative experimental data for electrophilic additions and cyclizations.

The theoretical approach[6] involves probing a substrate, e.g.,

(1) (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (b) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *Ibid.* **1981**, *103*, 4114. (c) Nakaminami, G.; Shioi, S.; Sugiyama, Y.; Isemura, S.; Shibuya, M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2624. (d) Walker, F. J. *Ph.*D. Thesis, Yale University, New Haven, 1981. (e) Snider, B. B.; Johnston, M. I. *Tetrahedron Lett.* **1985**, *26*, 5497. (f) Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneco, I.; Shimada, Y. *Chem. Pharm. Bull.* **1980**, *28*, 1509. (g) Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885. (h) Tamuru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Ibid.* **1984**, *25*, 1063. (i) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (j) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123. (k) Freeman, F.; Robarge, K. D. *Carbohydrate Res.* **1985**, *137*, 89. (l) Nicotra, F.; Panza, L.; Ronchetti, F.; Toma, L. *Tetrahedron Lett.* **1984**, *25*, 5937. (m) Pouguy, J.-R.; Mahamoud, A. M. N.; Sinäy, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375. (n) Lancelin, J.-M.; Pouguy, J.-R.; Sinäy, P. *Carbohydr. Res.* **1985**, *136*, 369. (o) Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Gazz Chim. Ital.* **1984**, *114*, 193. (p) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *Tetrahedron Lett.* **1985**, *26*, 3915. (q) Kane, P. D.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 657. (r) Freeman, F.; Robarge, K. D. *Tetrahedron Lett.* **1985**, *26*, 1943. (s) Paquet, F.; Sinaÿ, P. *Ibid.* **1984**, *25*, 3071. (t) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1985**, *26*, 2529. The original stereochemical assignments as published in this paper are reversed and will be revised shortly. We thank Professor Williams for informing us of this fact. (u) For a recent review of electrophilic cyclization reactions in the formation of heterocyclic rings, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 411.

(2) Harding, K. E.; Stephens, R.; Hollingsworth, D. R. tetrahedron *Lett.* **1984**, *25*, 4631. (b) Geise, B.; Bartmann, D. *Ibid.* **1985**, *26*, 1197. (c) Overman, L. E.; Campbell, C. B. *J. Org. Chem.* **1974**, *39*, 1474. (d) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. (e) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887. (f) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Ibid.* **1982**, *47*, 4626. (g) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465. (h) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Itô, S. *Tetrahedron Lett.* **1984**, *25*, 4963.

(3) (a) Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron* **1984**, *40*, 2297. (b) Midland, M. M.; Halterman, R. L. *J. Org. Chem.* **1981**, *46*, 1229. (c) Santelli, M.; Viala, J. *Tetrahedron Lett.* **1977**, *18*, 4397.

(4) For reviews covering the mechanism of addition of electrophilic halogen to alkenes, see: (a) V'yunov, K. A.; Ginak, A. I. *Russ. Chem. Rev.* **1981**, *50*, 151. (b) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Suppl. A, Part 2, Chapter 9.

(5) Several kinetic studies of iodocyclization are consistent with a mechanism in which it is a π complex—not an iodonium ion—that undergoes cyclization: (a) Bernett, R. G.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 2048. (b) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864. (c) do Amaral, L.; Melo, S. C. *J. Org. Chem.* **1973**, *38*, 800. This picture also is consistent with known rate enhancements caused by internal nucleophiles.[14]

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Table I. Type A Cyclizations: Direction Group *On* the Tether[a]

electrophile	internal nucleophile (Nu:)	direction group (X)	R	major product diastereomer	typical ratio	ring size	reactive conformer	ref
I_2, NBS, or Br_2	CO_2^-	OH	H	cis	20:1	5,6	OH in-plane	1a–f
I_2	CO_2^-	$OSiR_3$	H	cis	20:1	5	OH in-plane	1a
I_2	CO_2R	OH	H	cis	20:1	5	OH in-plane	1a
I_2	OH	OH	H	cis	20:1	5	OH in-plane	1g
I_2 or NBS	$NHSO_2Ar$	OH	H	cis	20:1	5	OH in-plane	1h
I_2	$CONMe_2$	OH	H	cis	10:1	5	OH in-plane	1i
I_2 or Hg^{2+}	NHBn	OBn	H	cis	7:1	6	OH in-plane	1j
I_2, Hg,$^{2+}$ or PhSeCl	OH	$OCMe_2OR$	H	cis	10:1	5	OH in-plane	1k,l
Hg,$^{2+}$ NBS, or PhSeX	OH	OBn	H	cis	10:1	5,6	OH in-plane	1m,n,o,p
I_2 or PhSeCl	OH	$OCMe_2OR$	CO_2Et	trans	1:10	5	H in-plane	1q,r
Hg^{2+}	OH	OBn	OR	trans	1:10	6	H in-plane	1s
I_2	OH	OH	CH_3	trans	<1:50	5	H in-plane	1t

[a] See Figure 2 for structures of substrates.

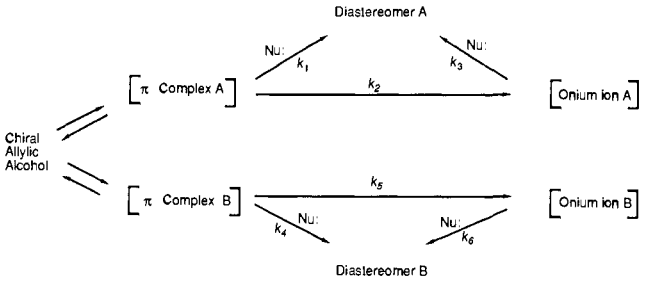
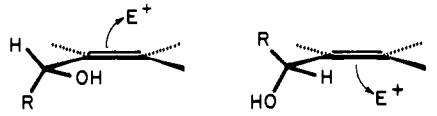


Figure 1. Mechanism of electrophilic addition to an allylic alcohol.

a chiral olefin, with a "test" electrophile, i.e., a proton. The preferred diastereoselectivity of electrophilic addition then follows from assignment of which olefin face is the more reactive, as a function of conformation. For cyclic allylic alcohols, where conformations were fixed, the stereochemical predictions of the reactivity model appear to agree quite well with experimental results.[6] On the other hand, application of the theory to acyclic systems is more problematic, due to the conformational mobility of acyclic substrates and the uncertainty of which conformer(s) plays a dominant role in determining product distribution. Nevertheless, it was concluded that attack by electrophiles occurs either syn to H in an OH in-plane conformer (**1**) or syn to OH in an H in-plane conformer (**2**), although no rationale was provided



1, OH in plane **2**, H in plane

to explain what factors would cause one to be favored over the other for any particular reaction. Further, there are examples of selective attack on *either* face, depending upon specific circumstances. Although this variable behavior may simply reflect the similar reactivities and abundances of conformers **1** and **2**,[6] a clear division of stereochemical preferences between examples with internal nucleophiles and those without suggested a more concrete explanation. Since the presence of an internal nucleophile can affect the nature of the rate-limiting step for the overall process, we chose to extend the previously described reactivity models to take this possibility into account. Specifically, an attempt is made here to address the effect that a change in rate-limiting step has on conformer selection. This refinement provides a basis for rationalizing (and ultimately predicting) the stereoselectivity of many electrophilic addition and cyclization reactions of allylic alcohols and related compounds.

Computational Methods

All calculations have been carried out at the single-determinant (Hartree–Fock) level with the 3-21G split-valence basis set[7] (3-21G(*) for molecules containing second-row elements[8]) or the 6-31G* polarization basis set.[9] Optimum (3-21G) geometries have been employed throughout,[10] and are either reported elsewhere[6] or follow in Table IV. All ab initio calculations have been performed with the GAUSSIAN 85 program system,[11] as implemented on a Harris H800 digital computer. Electrostatic potentials have been obtained according to previously described methods[12] and have been superimposed onto electron-density surfaces corresponding to $\Psi^2 = 0.002$ e/bohr^3.[13]

Results and Discussion

Previously described reactivity models[6] provide an indication of which face of an allylic π bond will be attacked by an electrophile in a kinetically controlled addition reaction. This analysis assumes a reactant-like (early) transition state, which is not necessarily applicable to all electrophiles, or even to a given electrophile under all conditions. In order to assess the generality of this assumption, the literature on kinetically controlled additions to allylic π bonds by electrophilic halogen, selenium, and mercury reagents has been surveyed. The data clearly show that the

(6) (a) For Part 6, see: Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.*, in this issue. (b) Part 4: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.*, in this issue. The model electrophile is a point positive charge. The interaction energy within the Hartree–Fock framework, termed the *electrostatic potential* (for recent reviews, see: (c) Scrocco, E.; Tomasi, J. *Adv. Quantum Chem.* **1978**, *11*, 115. (d) *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum: New York, 1981), comprises a repulsive component, E^{nn}, describing the interaction between the nuclei on the reagent and substrate, and an attractive term, E^{en}, accounting for interaction of the substrate electron distribution with the reagent nucleus.

$$E^{nn} = \sum_{A}^{substrate} \frac{Z_A}{R_{AX}}$$

$$E^{en} = \sum_{\mu}^{substrate} \sum_{\nu} P_{\mu\nu}^{substrate} \int \phi_\mu^*(1)[1/r_{1X}]\phi_\nu(1)\, d\tau_1$$

The summation which makes up E^{nn} is carried out over all nuclei A in the substrate molecule. Z_A are the atomic charges (atomic numbers) of the nuclei, and R_{AX} are the distances between these nuclei and the test reagent, X, with charge $Z_X = 1$. The double summation which makes up E^{en} involves atomic orbitals on the substrate. The incorporated integrals involve a single electron (on the substrate), and the distance r_{1X} separates this electron from the test charge. $P_{\mu\nu}^{substrate}$ are elements of the substrate density matrix.

$$P_{\mu\nu}^{substrate} = 2\sum_{i}^{occ} c_{\mu i} c_{\nu i}$$

(7) Binkey, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(8) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039.

(9) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.

(10) Subject only to the constraint that the contained olefin remain planar. For a discussion of olefin pyramidalization upon asymmetric substitution, see: Houk, K. N. *Methods Stereochem. Anal.* **1983**, *3*, 1.

(11) Hout, R. F., Jr.; Francl, M. M.; Kahn, S. D.; Dobbs, K. D.; Blurock, E. S.; Pietro, W. J.; McGrath, M. P.; Steckler, R.; Hehre, W. J. *Quantum Chemistry Program Exchange*; Indiana University: Bloomington, Indiana, to be submitted.

(12) (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (b) Pau, C. F.; Hehre, W. J. *J. Comput. Chem.*, submitted. (c) Hehre, W. J.; Pau, C. F.; Hout, R. F., Jr.; Francl, M. M. *Molecular Modeling. Computer-Aided Descriptions of Molecular Structure and Reactivity*; Wiley: New York, 1986.

(13) Francl, M. M.; Hout, R. F., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 563.

Table II. Type B Cyclizations: Direction Group *In* the Tether[a]

electrophile	internal nucleophile (Nu)	directing group (X)	R′	R	product diastereomer	typical ratio	ring size	reactive conformer	references
Hg^{2+}	NHR OC=NH	O	alkyl	H	trans	10:1	5	O in-plane	2a
Hg^{2+}	COR, $CH(OH)CCl_3$	O	alkyl	H	trans	5:1	5	O in-plane	2b,c
"Br^+", NBS	NR_2COOMe	N	alkyl	H	trans	10:1	5	N in-plane	2d,e
I_2,NIS	$OCOO^-$	O	alkyl	H	trans	5:1	5	O in-plane	2f,g
I_2	OCONHR	O	alkyl	H	cis	1:2	5	O in-plane	2h

[a]See Figure 2 for structures of substrates.

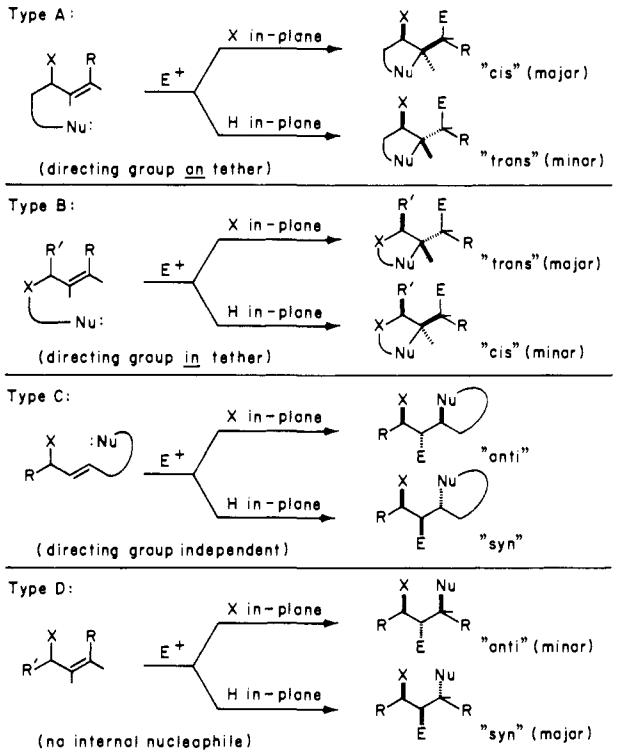


Figure 2. General reaction types (X = oxygen or nitrogen).

presence of an internal nucleophile reverses the "normal" diastereoselectivity of electrophilic attack. It is argued here that the reason for this difference is that the presence of an internal nucleophile changes the rate-limiting step for the overall reaction, and that in doing so affects which face of the π bond preferentially reacts with the electrophile. In other words, facial preferences in electrophilic addition reactions are *not* invariant with respect to the location of the transition state along the reaction coordinate.

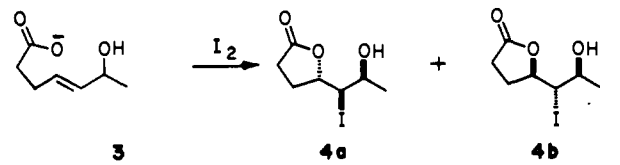
The stereochemistry of kinetically controlled electrophilic additions to four substrate types (A–D) has been surveyed (Figure 2). Specifically, reactions of type A allow scrutiny of electrophilic cyclization when the directing group (X = oxygen or nitrogen) is incorporated *on* the trapping tether; systems of type B enable examination of electrophilic cyclizations in which the directing element is incorporated *in* the tether; type C cyclizations elucidate the stereochemical preference when the directing group and internal nucleophile act independently; lastly, type D additions provide the means to determine the stereoselectivity in the absence of an internal nucleophile. Taken as a whole, data for this group of substrates should reveal the fundamental stereochemical dictates in electrophilic additions and cyclizations.

Examination of known electrophilic addition reactions[1-3] in these categories reveals many examples of stereoselective trapping in reaction types A and B. For example, the preferential formation of *cis*-4,5-disubstituted furans, lactones, pyrans, and piperidines (Table I) and of *trans*-3,5-disubstituted oxazolidines, cyclic carbonates, and carbamates (Table II) by intramolecular electrophilic cyclization reactions is well established. However, the directing group in each reported case is incorporated *on* or *in* the tether that bears the internal nucleophile. Because of conformational restrictions in the cyclic transition state[14] that might override inherent stereochemical preferences, a chiral olefin having the directing alcohol group on the "other side" of the alkene (relative to the internal nucleophile) was sought, i.e., type C. Since no cyclizations of this type have been reported, **3** was prepared. Subjected to kinetically controlled iodocyclization,[1a] it gives nearly equal proportions of the two diastereomers (**4a** and **4b**). On the other hand, type D electrophilic additions (Table III) exhibit a definite preference for attack by the electrophile from the *opposite* face as compared with reaction types A and B. Thus, the internal nucleophile that is present in types A–C cyclizations alters the face of the double bond that is attacked by electrophiles to an extent which appears to be partially dependent upon the position of the nucleophile.

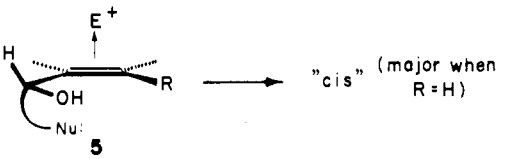
Table III. Type D Additions: No Internal Nucleophile[a]

electrophile	directing group (X)	R	R′	typical ratio	reactive conformer	ref
I_2	OH, OBn	H	alkyl	1:20	H in-plane	3a
I_2	OH	alkyl	alkyl	1:10	H in-plane	3a
Br_2	OH	H	alkyl		H in-plane	3b,c
Hg^{2+}	OH	H	alkyl	1:10	H in-plane	2b

[a]See Figure 2 for structures of substrates.



Several important implications emerge from the results of these four reaction types. First, the pronounced stereochemical preferences for cyclizations directed by an OR group *on* the tether generally are in accord with the reactivity model, wherein attack is preferred on the OH in-plane conformer **5**, from the face of the π bond syn to the allylic hydrogen.[6] Note that in this conformation the internal nucleophile is constrained to reside in a nearly ideal position for antarafacial attack on the (activated) π bond.[15] Attack on the less abundant[16,17] H in-plane conformer



from the opposite face gives rise to the minor diastereomer in type

(14) For a review of electrophilic cyclization, including the effect of internal nucleophile upon rates of reaction, see: Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272. See also: Williams, D. L. H.; Bienvenue-Goetz, E.; Dubois, J. E. *J. Chem. Soc.* **1969**, 517.

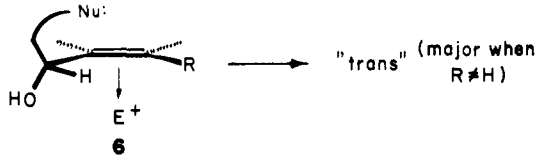
(15) For an interesting recent discussion of reactivity as a function of proximity, see: Menger, F. M.; Venkaturam, U. V. *J. Am. Chem. Soc.* **1985**, *107*, 4706.

(16) For a discussion of the balance between conformer abundance and reactivity, see: (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(17) For conformational studies of chiral allylic alcohols, see: (a) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647. (b) Smith, Z.; Carballo, N.; Wilson, E. B.; Marstokk, K.-M., Møllendal, H. *J. Am. Chem. Soc.* **1985**, *107*, 1951.

A cyclizations. This bias is consistent with anticipated steric effects, although it should be noted that steric considerations are *not* incorporated into the simple electrostatic model.[18]

There are a few type A cyclizations that show *reversed* facial selectivity. For example, substrates with a *cis* substituent (R ≠ H) on the double bond (relative to the stereogenic allylic center) react selectively on the opposite face, i.e., as in **6**, and not as in **5**. These reversals may be rationalized on the basis of the *cis*



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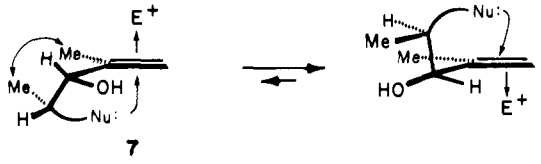
substituent destabilizing the (normally favored) OH in-plane conformer, thereby making the conformer **6** energetically more accessible than **5** in those cases. Similarly, destabilization of the analogous OH in-plane conformer **7** caused by a steric repulsion between C-2 and C-4 methyl groups has been suggested[1a] as being responsible for an observed reversal of the usual O in-plane preference in iodocyclizations.



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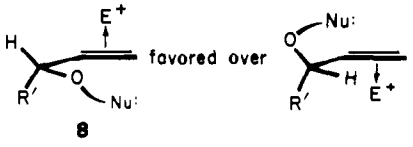
Substrates that incorporate the directing group (oxygen or nitrogen) *in* the tether (type B) give analogous results, although with somewhat reduced selectivities. Once again, preferential reaction via conformers with OR or NHR in-plane (**8**) gives rise to the major product.



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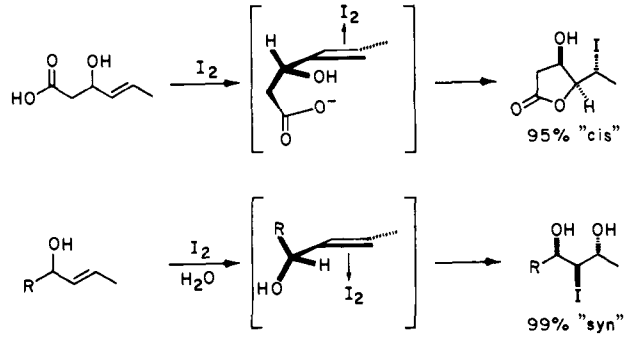
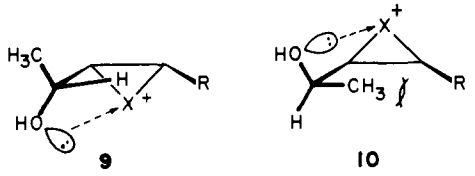
In contrast to both type A and type B cyclizations, the selectivity of electrophilic attack on allylic alcohols *lacking* an internal nucleophile (type D) ranges from a slight preference in the opposite direction to a complete reversal. For example, while iodolactonization shows a ~20:1 preference for reaction via a conformer in which OH is in-plane, i.e., as in **5**,[1a] iodohydrin formation from a nearly identical allylic alcohol (but lacking an internal nucleophile) occurs preferentially from the opposite face, via the alternative H in-plane conformer, with preferences as high as 99:1.[3a] Reversals of this kind also are observed for other electrophiles (Table III). The stereoselectivity of type C cyclization lies midway between the two extremes (types A and D). Thus,



when the nucleophile and directing group act independently, little selectivity is noted despite the fact that the analogous type A and D reactions of *trans*-1,2-disubstituted allylic systems both are very selective (but for opposite faces of the π bond).

Because an obvious variable in these examples is a minor difference in rate-limiting step, i.e., π complex trapping for cyclizations vs. onium ion formation for additions, we have explored the possibility that stereoselectivity might be dependent upon how far along the reaction coordinate (π complex to onium ion) the transition state actually lies (it is appropriate to discuss this change of rate-limiting steps in terms of transition-state timing because both transition states lie on the reaction coordinate between π complex, "early", and onion ion, "late"). Therefore, an onium ion like transition state was modeled theoretically; practical considerations dictated the use of a chloronium ion for this purpose. Interestingly, one of the two possible onium ion diastereomers, **9** (shown in the most stable conformation), is several kcal/mol^{-1} more stable than the lowest energy conformer of the alternative diastereomer **10** (see Table IV). The conformational preference of both **9** and **10** to position the hydroxyl group "syn" to the



9 **10**

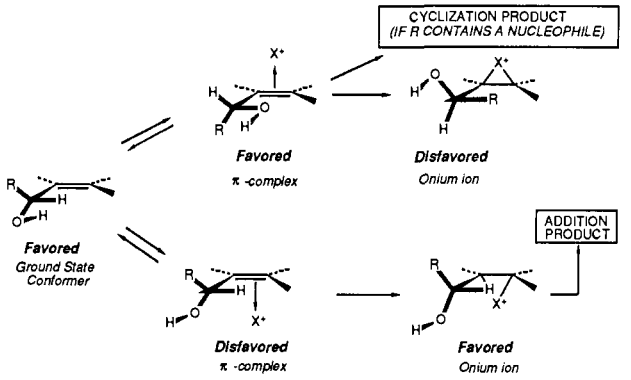
halogen presumably arises because of stabilizing interactions between the developing positive charge and the oxygen lone pairs. The intermediate **9** that resembles the favored transition state for additions is formed by attack as in conformer **2**, whereas **10** is obtained by attack as in **1**, followed by rotation about the C_2–C_3 bond. The instability of **10** is easily rationalized in terms of an unfavorable steric interaction between the eclipsed allylic methyl group and the terminal methylenic center[19] in the conformation that would allow stabilization of the incipient positive charges by the heteroatom lone pair. Thus, in both cases stabilization of the positive charge by the oxygen lone pairs is favorable, but in **10** it is energetically more costly because of steric repulsion between the methyl and "R" groups.

The conclusion drawn from this result is that if the transition state for electrophilic attack resembles an onium ion intermediate, attack of the electrophile will occur predominantly as in **9**, rather than as in **10**, a selectivity that is opposite to most of the type A and type B cyclizations discussed, and to that predicted by the early transition state model.[6] A comparison of the two transition-state models leads directly to the inference that attack on the face of an acyclic alkene experiencing a stronger initial long-range attraction of the electrophile (reactivity model) becomes increasingly disfavored as the reaction proceeds toward an onium ion intermediate (onium ion model). As a consequence, the stereoselectivity of electrophilic attack reverses when the rate-limiting step changes. Specifically, an internal nucleophile traps the initially formed, favored π complex *before* it collapses (or as it begins to collapse) to an energetically unfavorable onium ion,[5] whereas in the absence of an internal nucleophile the initially formed π complex must progress further along the reaction coordinate to an onium ion (or revert to starting alkene) before bimolecular nucleophilic attack can occur. *These two processes are predicted to favor attack on opposite faces of the π bond.*

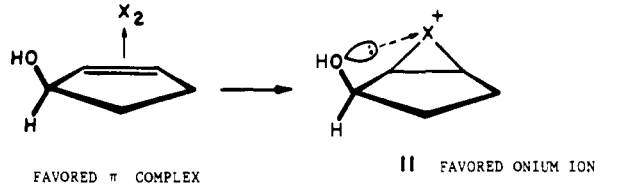
Note also that **10**, although highly disfavored in acyclic cases, corresponds to one of only two possible onium ion diastereomers in reactions of *cyclic* allylic alcohols. On the basis of the analysis presented above, a transition state resembling an onium ion intermediate in reactions of *cyclic* allylic alcohols thus should favor **11** over the alternative anti diastereomer. Paradoxically, this is

(18) Attack on the OH in-plane and H in-plane conformers as shown corresponds approximately to "OH inside" (or "inside alkoxy") and "H inside" modes of attack, respectively, postulated by Houk: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(19) The "inside" allylic hydrogen in **9** is 33.9° out of plane, whereas the "inside" methyl group in **10** is 42.6° out of plane. See Appendix for complete geometrical details.



the *same* face predicted to be more reactive by the reactivity models, i.e., π-complex-like transition state, in contrast to acyclic systems, for which the two models predict reaction on opposite faces.



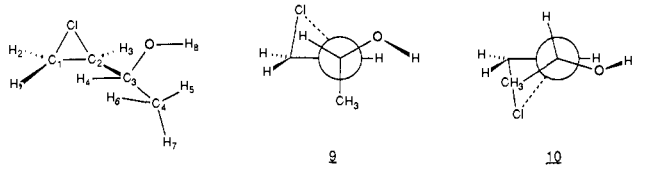
To summarize, type A and type B cyclizations occur via an "earlier" pair of transition states,[20] resembling π complexes and described by the original reactivity model.[6] Conversely, type D additions progress through a "later" pair of transition states best modeled by the corresponding onium ions. The type C cyclization apparently lies between these two extremes; we theorize that because of the extra degree of rotational freedom in the nucleophilic appendage (relative to type A) the internal nucleophile is less effective, and as a result, the transition state is somewhat less reactant-like than in type A or type B reactions, but still more so than in type D. For *cyclic* allylic alcohols, on the other hand, both early and late transition-state models predict attack on the same face of the π bond, leading to the paradox that while stereoselectivity is a function of transition state timing in acyclic systems, in cyclic substrates it is not.

Conclusions

The face of a chiral acyclic allylic alcohol or amine derivative selected for attack by electrophiles such as I_2, Br_2, NBS, HgX_2, and PhSeX is highly dependent on the exact nature of the transition state. An "early", reactant-like transition state results in preferential attack on the OR in-plane conformer (for alkenes without a cis substituent), syn to the allylic hydrogen, to give a π complex that reacts directly with the internal nucleophile to give the cyclic product. In contrast, a "later" transition state (resembling an onium ion) leads to preferential reaction on the opposite face, i.e., electrophilic attack occurs syn to the heteroatom in a conformer with hydrogen in plane, followed by onium ion formation and subsequent nucleophilic attack. Thus, the presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of the transition state. For cyclic derivatives, models for early and for late transition states are in agreement: attack is predicted to occur syn to the heteroatom regardless of transition-state timing.

Other types of electrophilic reactions, such as epoxidation, Simmons Smith cyclopropanation, and osmium tetroxide hydroxylation,[21] that proceed via a different pathway (no separate external nucleophile is involved) are more difficult to characterize, in part because the reaction pathways are less well understood than the examples cited in this paper. Still, it is plausible that transition-state timing also is an important factor in determining stereoselectivity in those reactions, a possibility that is currently under investigation.

Table IV. 3-21G(*) Optimized Geometries[a] For Model Chiral Onium Ions



Structure **9**: E = -686.78176 hartrees

C_1C_2 = 1.463, C_2C_3 = 1.465, C_3C_4 = 1.573, C_1Cl = 1.836, C_3O = 1.421, C_1H_1 = 1.075, C_1H_2 = 1.075
C_2H_3 = 1.077, C_3H_4 = 1.082, C_4H_5 = 1.081, C_4H_6 = 1.084, C_4H_7 = 1.082, OH_8 = 0.967
$C_1C_2C_3$ = 123.9, C_2C_1Cl = 89.9, $C_2C_3C_4$ = 103.7, C_2C_3O = 104.8, $C_2C_3H_4$ = 112.0, $C_3C_4H_5$ = 110.3
$C_3C_4H_6$ = 106.7, $C_3C_4H_7$ = 112.4, C_3OH_8 = 113.6, $C_1C_2H_3$ = 119.6, $C_2C_1H_1$ = 116.3
$C_2C_1H_2$ = 115.9, $C_1C_2C_3C_4$ = -84.6, $C_1C_2C_3O$ = 158.6, $C_1C_2C_3H_4$ = 33.9, $ClC_1C_2H_3$ = 83.4
$ClC_2C_1H_1$ = 112.2, $ClC_2C_1H_2$ = -110.6, $C_2C_3C_4H_5$ = 60.2, $C_3C_4H_5H_6$ = 116.3, $C_3C_4H_5H_7$ = -125.2
$ClC_1C_2C_3$ = -97.2

Structure **10**: E = -686.77857 hartrees

C_1C_2 = 1.459, C_2C_3 = 1.477, C_3C_4 = 1.540, C_1Cl = 1.845, C_3O = 1.425, C_1H_1 = 1.073, C_1H_2 = 1.074
C_2H_3 = 1.076, C_3H_4 = 1.100, C_4H_5 = 1.080, C_4H_6 = 1.081, C_4H_7 = 1.082, OH_8 = 0.967
$C_1C_2C_3$ = 125.6, C_2C_1Cl = 87.2, $C_2C_3C_4$ = 116.3, C_2C_3O = 103.7, $C_2C_3H_4$ = 101.9, $C_3C_4H_5$ = 109.1
$C_3C_4H_6$ = 112.4, $C_3C_4H_7$ = 108.6, C_3OH_8 = 113.4, $C_1C_2H_3$ = 118.7, $C_2C_1H_1$ = 117.3
$C_2C_1H_2$ = 116.1, $C_1C_2C_3C_4$ = -42.6, $C_1C_2C_3O$ = -167.8, $C_1C_2C_3H_4$ = 75.9, $ClC_1C_2H_3$ = -82.2
$ClC_2C_1H_1$ = -110.5, $ClC_2C_1H_2$ = 108.9, $C_2C_3C_4H_5$ = 68.3, $C_3C_4H_5H_6$ = 122.3, $C_3C_4H_5H_7$ = -118.5
$ClC_1C_2C_3$ = 100.2

[a] Bond lengths in angstroms, bond and dihedral angles in degrees.

Experimental Section

General. THF was distilled from K metal. EtOAc and CH_2Cl_2 were distilled from calcium hydride. All other solvents were commercial reagent grade and dried over 3A molecular sieves. IR spectra were recorded on a Perkin-Elmer 283 spectrophotometer. ^1H NMR spectra were obtained on a Bruker WM 250 (250 MHz) spectrometer. Mass spectra were recorded on a Finnigan 9610 spectrometer at 70 eV. High-pressure liquid chromatography (HPLC) was performed on a Waters Analytical instrument with a 30 cm μ-Porasil column and a 254-nm UV detector. Gas chromatography was conducted on a Hewlett-Packard Model 5830 A chromatograph equipped with a flame ionization detector. Thin-layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel plates (60 F-254). Flash chromatography was carried out on silica gel, 230–400 mesh (Merck).

Preparation of 6-Hydroxy-4-heptenoic Acid (3). A solution of 2.00 g (13.7 mmol) of 4-dioxolanebutanoic acid,[22] 30 mL of 0.5 M HCl, and

(20) "Early" transition state in this context is essentially the same as the normal usage that refers to the position along the reaction coordinate between the two intermediates involved in the rate-limiting step. Here, though, there are two possible rate-limiting steps, and the one that resembles a π complex occurs "earlier" than the one that is onium ion-like.

(21) Of electrophiles other than those discussed in this paper, most exhibit addition stereoselectivities analogous to the addition reactions listed in Table III.[6] The glaring exception is osmium tetroxide, which generally reacts selectively from the opposite face compared with most other electrophiles.[28] Although one might explain this phenomenon by postulating a reactant-like transition state,[29] there is a fascinating alternative possibility: OsO_4 is a *transvestial* reagent. Specifically, its outward "appearance" is that of a *nucleophile* (8 oxygen lone pairs confined to a relatively small volume of space), so that the favored long-range attraction to the π bond is to the opposite face as compared with most electrophiles. It is only when the metal itself reaches close proximity to the π electrons that its true electrophilic nature is exposed. Thus, the stereoselectivity pattern for OsO_4 is as a nucleophile, while the reactivity is electrophilic, i.e., more highly substituted alkenes react faster.[30]

(22) 4-Dioxolanebutanoic acid was prepared according to Shea and Wada (Shea, K. J.; Wada, E. *J. Am. Chem. Soc.* **1982**, *104*, 5715).

10 mL of acetone was stirred for 12 h at 25 °C. The solution was then saturated with NaCl, extracted 5 times with diethyl ether, dried over $MgSO_4$, and concentrated in vacuo to yield 0.903 g (65%) of 4-hydroxybutanoic acid which was used immediately. The crude acid aldehyde (0.903 g, 8.85 mmol), 5.64 g (17.7 mmol) of $Ph_3PCHCOCH_3$,[23] and 50 mL of THF were heated at reflux for 24 h under an argon atmosphere. The reaction mixture was quenched to yield 0.612 g (49%) of crude 6-keto-4-heptenoic acid, which was submitted to immediate $NaBH_4$ reduction (0.64 g, 17.2 mmol) in 20 mL of MeOH for 1 h, giving 0.350 g (56%) of the hydroxy acid (**3**) after column chromatography (1:2, petroleum ether: diethyl ether, SiO_2): ^1H NMR (250 MHz, $CDCl_3$) 5.62 (m, 2 H, H-4, H-5), 4.28 (app quintet, J = 6.2 Hz, H-6), 2.50-2.34 (m, 4 H, H-2, H-3), 1.26 (d, J = 6.2 Hz, 3 H, H-7); IR (neat) 3600-3100, 2980, 2940, 1710, 1065, 970; MS m/e (relative intensity) 145 ($M^+ + 1$, 1.32), 143 ($M^+ + 1 - H_2$, 2.17), 127 ($M^+ + 1 - H_2O$, 100.00); high resolution mass spectrum (EI) calcd for $C_7H_{10}O_2$, $M^+ - H_2O$ 126.0681, found 126.0677.

***rel*-[5*R*]-Dihydro-5-(*rel*-[1*S*,2*R*]-2-hydroxy-1-iodopropyl)-2(3*H*)-furanone (4a) and *rel*-[5*S*]-Dihydro-5-(*rel*-[1*R*,2*R*]-2-hydroxy-1-iodopropyl)-2(3*H*)-furanone (4b).** The general procedure for iodolactonization of hydroxyalkenoic acids as reported by Chamberlin et al.[1a] was followed by using 127 mg (0.882 mmol) of **3** and 672 mg (2.65 mmol) of iodine to yield 186 mg (78%) of crude **4a** and **4b**. **4a**: ^1H NMR (250 MHz, $CDCl_3$), 4.77 (m, H-5), 4.10 (dd, J = 9.5, 1.9 Hz, H-6), 3.44 (m, H-7), 2.60 (m, 3 H), 2.08 (m, 1 H), 1.29 (d, J = 6.2 Hz, 3 H, H-8). **4b**: ^1H NMR (250 MHz, $CDCl_3$), 4.56 (m, H-5), 4.35 (dd, J = 9.0, 4.5 Hz, H-6), 3.63 (m, H-7), 2.60 (m, 3 H), 1.88 (m, 1 H), 1.35 (d, J = 6.2 Hz, 3 H, H-8) based on integration, the ratio of **4a**:**4b** was 2:1; IR (neat) 3600-3250, 2990, 2940, 1780, 1340, 1175, 1020, 915, 730; mass spectrum, *m/e* (relative intensity) 270 (M^+, 0.74), 226 ($M^+ - C_2H_4O$, 16.34), 127 (I^+, 2.15), 99 ($M^+ - I - C_2H_4O$, 100.00), 85 ($C_4H_5O_2^+$, 49.44); HPLC (1:5, hexane:diethyl ether, 2.1 min, 72%, 3.3 min, 28%); high resolution mass spectrum (EI) calcd for $C_7H_{11}IO_3$, M^+ 269.9753, found 269.9762.

In order to assign stereochemistry to each diastereomer, the lactone mixtures were converted into the corresponding epoxides by methanolysis according to the following procedure. To a dried flask was added the lactone mixture (42.3 mg, 0.157 mmol), 3.0 mL of MeOH, and K_2CO_3 (21.7 mg, 0.157 mmol), and the resulting solution was stirred for 1 h, diluted with water, saturated with NaCl, extracted 3 times with diethyl ether, dried with $MgSO_4$, and concentrated in vacuo to yield a mixture of epoxides which were analyzed by capillary gas chromatography. Authentic methyl ester epoxy alcohols for comparison were prepared by using the erythro-selective vanadium-catalyzed Sharpless epoxidation procedure[24] on the methyl ester of **3** prepared by treatment of **3** with diazomethane.[25] Epoxy methyl esters from iodolactone mixture: ^1H NMR (250 MHz, $CDCl_3$) 3.94 (m, H-6), 3.70 (s, 3 H, OMe), 3.05 (dt, J = 5.9, 2.0 Hz, H-4), 2.81 (appt, J = 2.0 Hz, H-5), 2.48 (t, J = 7.2 Hz, 2 H, H-2), 1.91 (m, 2 H, H-3), 1.25 (d, J = 6.6 Hz, 3 H, H-7); minor isomer observed at 3.00, 2.78, 1.29; GC (5.5 min, 78%, 5.6 min, 22%); this mixture of epoxides closely resembled the Sharpless mixture by 250-MHz ^1H NMR and gave identical retention times and a very similar diastereomer ratio by capillary GC (5.5 min, 73%, 27%).[26] It thus follows that the major iodolactone is **4a** and the minor diastereomer is **4b**.

Acknowledgment. Partial support of this work in the form of an NSF grant to A.R.C. (CHE 8401197) is gratefully acknowledged. A helpful suggestion by Professor Collum (Cornell University) was incorporated into the introductory section.

Registry No. 3, 105728-84-5; **3** methyl ester, 105762-40-1; **4a**, 105728-87-8; **4a** epoxy methyl ester, 105728-88-9; **4b**, 105814-95-7; **4b** epoxy methyl ester, 105834-46-6; $Ph_3P{=}CHC(O)CH_3$, 1439-36-7; $OHC(CH_2)_2CO_2H$, 692-29-5; 4-dioxolanebutanoic acid, 105728-85-6; 6-oxo-4-heptenoic acid, 105728-86-7.

(23) $Ph_3PCHCOCH_3$ was prepared according to Ramirez and Dershowitz (Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41).

(24) Sharpless, K. B. *Aldrichim. Acta* **1979**, *12*, 63.

(25) Diazomethane was prepared according to Moore and Reed (Moore, J. A.; Reed, D. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 351.

(26) It is not totally clear why these two epoxide regioisomers are formed preferentially. Methanolysis of the lactone ring must be faster than direct epoxide formation, since we observe neither the lactone epoxides derived directly from **4a** and **4b** nor their subsequent methanolysis/Payne rearrangement[27] epoxy alcohol products (neither of which correspond to the Sharpless diastereomers). There most likely is an iododiol ester intermediate in the methanolysis reaction that regioselectively forms the observed epoxide. We previously have observed similar selectivities in related 2-iodo 1,3-diols,[3a] attributable to cis epoxides forming more slowly than trans.

(27) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(28) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Ibid.* **1983**, *24*, 3947. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(29) For an interesting recent study of osmylation that supports a *late* transition state, see: Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094.

(30) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

Estimation of Inner Shell Marcus Terms for Amino Nitrogen Compounds by Molecular Orbital Calculations

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Contribution from the S. M. McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received June 4, 1986*

Abstract: The rate constant k_{et} for electron transfer between the unsaturated bridgehead diazosesquibicyclo[2.2.2]octane (**1**) and $\mathbf{1}^+(NO_3^-)$ in CD_3CN was determined by proton NMR line broadening measurements to be 1.3×10^4 M^{-1} s^{-1} at 23.5 °C, with activation parameters $\Delta H^{\ddagger}_{et} = 7.2_0$ kcal/mol and $\Delta S^{\ddagger}_{et} = -15._4$ cal mol^{-1} K^{-1}. k_{et} for its saturated analogue $\mathbf{2},\mathbf{2}^+(NO_3^-)$ is 7.0×10^2 (23.0 °C, CD_3CN), while that for $\mathbf{2}^+(PF_6^-)$,$\mathbf{2}^{2+}(PF_6^-)_2$ is 2.1×10^4 (24.1 °C, CD_3CN), with activation parameters $\Delta H^{\ddagger}_{et} = 8.4_7$ kcal/mol and $\Delta S^{\ddagger}_{et} = -10.3$ cal mol^{-1} K^{-1}. Because k_{et} for *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (**3**),$\mathbf{3}^+(ClO_4^-)$ in CH_3CN at 20 °C is 1.7×10^6 times that quoted above for $\mathbf{2},\mathbf{2}^+$, the inner shell Marcus term must dominate the et barrier for the hydrazine case. The Dewar group AM1 semiempirical MO calculation method successfully predicts this effect. These calculations also indicate that the inner shell term for **3** is far larger than previously accepted.

Lone pair-lone pair interactions cause tetraalkylhydrazines (R_4N_2) to undergo especially large geometry changes upon electron loss.[1] The nitrogens of neutral R_4N_2 are strongly pyramidal, and there is a rather weak electronic preference for the lone pairs to be perpendicular (lone pair-lone pair dihedral angle θ = 90°). The cation radical $R_4N_2^+$ has much flatter nitrogen atoms and a strong preference for coplanar lone pair axes (θ = 0 and 180°). The unpaired electron is in the π^* orbital of the π-rich orbital hybrid predominately centered at the two nitrogen atoms, a situation described as a "three-electron π bond". Electron loss from R_4N_2 may be thought of as producing half a π bond between the nitrogens, which is the source of the large geometry change.

(1) (a) Nelsen, S. F. *Acc. Chem. Res.* **1981**, *14*, 131. (b) Nelsen, S. F. *Molecular Structures and Energetics*; Liebman, J. F., Greenburg, A., Eds.; VCH Publishers: Deerfield Beach, FL, 1986, Vol. 3, Chapter 1, p 1.

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