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Torquoselectivity Studies in the Generation of Azomethine Ylides from Substituted Aziridines

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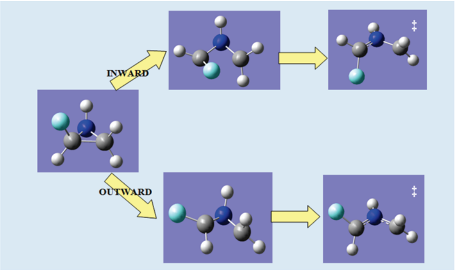

Aziridines are useful precursors to the azomethine ylide family of 1,3-dipoles whose cycloaddition chemistry has been extensively exploited in the synthesis of heterocyclic targets. The torquoselectivity of aziridines that lack a plane of symmetry was investigated as an essential component of the calculation of the overall relative reaction rates and in prediction of the stereochemistry of the 2,3-*trans* compounds in 1,3-dipolar cycloaddition chemistry. It has been found at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level that outward rotation is preferred for electronegative or anionic substituents while electropositive and cationic substituents favor inward rotation. After consideration of frontier molecular orbital theory, inductive, resonance, and electrostatic effects, an explanation of the preferred direction of rotation during ring cleavage that is based on substituent electron-withdrawing ability by means of a polar effect is presented.

Introduction

Aziridines occupy a prominent position in the arsenal of synthetic organic chemistry.[1,2] Their use as sources of azomethine ylides for 1,3-dipolar cycloaddition chemistry to synthesize larger heterocycles is a favored methodology.[3] One drawback to more extensive application of this chemistry is that the temperatures required to rupture the C−C bond of aziridines are too high to avoid disruption of fragile chemical structures generated late in a synthesis or, certainly, to study biological systems. We have been interested in exploring the possibility that substituents might lower the free energy of activation to a point that an azomethine ylide might be formed in good yield under very mild conditions (< 37 °C.)[4] Such a discovery would place 1,3-cycloaddition chemistry using aziridines within the realm of the extremely

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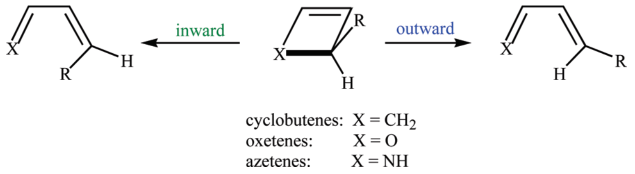
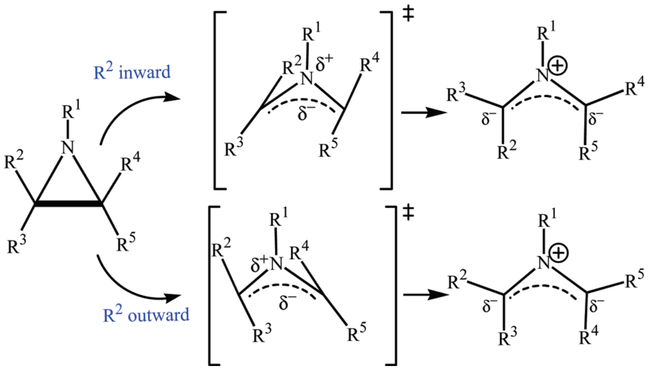
SCHEME 1. Torquoselectivity for Monosubstituted Cyclobutenes and Oxetanes



useful click chemistry[5] that has been extensvely exploited using the reaction of azides with alkenes or alkynes. Azomethine ylide reactions have the advantage of occurring in the absence of potentially deleterious metal ion catalysts.

Aziridines that lack a symmetry plane have two modes of ring cleavage in these conrotatory thermal processes. A torquoselective reaction is one in which a given substituent preferentially rotates inwardly or outwardly with respect to the original molecular plane.[6] While this effect has been extensively investigated for the isoelectronic substituted cyclobutenes,[7] 2-oxetenes,[8] 2-azetines[9] (see Scheme 1), and quite recently for cyclopropyl anions,[10] to the best of our knowledge, a study of torquoselectivity in the cleavage of substituted aziridines has not been reported.[11] A knowledge of the torquoselectivity is essential for calculation of relative rates of reaction as a function of substitution. In addition to its kinetic importance, torquoselectivity has potential stereochemical consequences.[12,3e] For example, under mild conditions such that diastereomeric intermediates do not interconvert, a *trans* symmetrically 2,3-disubstituted aziridine will produce a *cis* azomethine ylide in the rate-determining step (See Scheme 2) that after rapid reaction with a dipolarophile will generate, at temperatures sufficiently low to prevent isomerization to the *trans* intermediate, a *cis* 2,5-disubstituted tetrahydropyrrole. Accordingly, a high level ab initio study of the thermal opening of unsymmetrically substituted aziridines was undertaken. Since the rate of dipole formation is rather unresponsive to changes in solvent,[3e] calculations in the gas phase were deemed sufficient to predict relative reaction rates as a function of substituent. Interestingly, even though chosen primarily for their theoretical value, more than one-quarter of the compounds investigated herein are presently available for laboratory research.[13]

SCHEME 2. Conrotatory Bond Cleavage Modes with Respect to R^2 (and R^5) of a Substituted Aziridine



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Computational Methodology

Ab initio calculations were performed at the MP2(Full)/6-311++G(d,p)// MP2(Full)/6-31+G(d) level by means of the Gaussian 03 suite of programs[14] for determination of energies and the NBO charges[15] (keyword pop = SaveNBOs.)[16] Gas-phase calculations were deemed to be sufficient for calculation of relative energies since calculations using a water solvent model SCI-PCM[17,18]) for aziridine and 2-fluoroaziridine produced only modest changes in relative rates (< 25 kJ/mol). The minor effect of solvent on the rate azomethine ylide formation has also been observed experimentally.[3e] A scaling factor of 0.9646 was used[19] for the thermal correction to the computed energies at a reaction temperature of 298.15 K. Criteria for finding the transition states and ground states were calculation of one and zero imaginary frequencies, respectively. GaussView 3.09[20] was used for animation of the sole imaginary frequency and IRC calculations were used to confirm identification of the transition states. Rate differences between invertomers were found to be insignificant. It was determinined using 2-substituents such as CH_3CO and $OCOCH_3$ with aziridine and oxirane for which conformational isomerism[21] was possible that the energy differences were < 4 kJ/mol. These differences were judged too small to justify the expense of an exhaustive study of ground state and corresponding transition state for all pertinent compounds. Relative reaction rates were obtained from transition-state theory.[22] Electrostatic energies, E_{elst}, in kJ/mol were calculated using a classical relationship[23]

$$E_{\text{elst}} = \frac{(1.39 \times 10^3)(q_{C2})(q_{C3})}{(D_{\text{eff}})(d)} \tag{1}$$

where q_{C2} and q_{C3} are the calculated charges at C_2 and C_3 from the atomic NBO charges with hydrogens summed into the heavy atoms, D_{eff} is the effective dielectric constant, d is the distance between these atoms in angstroms, and E_{elst} is expressed in kJ/mol. For the calculations $D_{\text{eff}} = 1.0$, that of a vacuum, was used.[24] Torquoselectivity was found to be kinetically as opposed to thermodynamically controlled by calculating the free energies of activation for the reverse reactions of the azomethine ylides corresponding to outward and inward rotation and discovering that these quantities were too high to play a role in the determining the preferred reaction course.

Results and Discussion

Since cyclobutenes and cyclopropyl anions are isoelectronic to aziridines, comparisons of these two systems are useful in understanding the factors involved in influencing the torquoselectivity of ring cleavage of the nitrogen heterocycle. For 3-substituted cyclobutenes the possible products of the reaction are *E*- or *Z*-dienes resulting from outward and inward rotation, respectively. For the tetrasubstituted aziridine depicted in Scheme 2 (R^1 = H), "inward" rotation may be defined as movement of the substituent in the direction of the breaking bond. If R_2 and R_5 move "inward" during this conrotatory thermal process, R^3 and R^4 must necessarily move "outward."

The torquoselectivities of a representative number of aziridines, with diverse substituents, are presented in Table 1. In stunning contrast to the findings for 3-substituted cyclobutenes, 2-oxetenes, 2-azetines, and cyclopropyl anions,[7-10] in virtually all cases for aziridines **2**-**33**, outward rotation is preferred for aziridines bearing donor *and* acceptor groups. Calculations for the substituents for which preferential inward rotation is calculated, COOMe and COMe, produce relative rate constants that are close to unity (0.227 and 0.409, respectively.)

Houk[25] rationalized the outward torquoselectivity of donor functionalities for the 3-substituted cyclobutenes in terms of a preference for rotation of a substituent depending on the nature of its interaction with the developing electron density of the HOMO of the cleaving bond, coupled with potential interactions with the LUMO. This concept led to the correct analysis that donor substituents would lead to preferential outward rotation, while acceptors would promote inward rotation.

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(25) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Nakamura, K; Houk, K. N. *J. Org. Chem.* **1994**, *60*, 686. (d) Dolbier, W. R.; Kornoniak, H.; Houk, K. N.; Sheu, D. *Acc. Chem. Res.* **1996**, *29*, 471. (e) Um, J. M.; Xu, H.; Houk, K. N.; Tang, W. *J. Am. Chem. Soc.* **2009**, *131*, 6664. (f) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072. (g) Niwayama, S.; Kallel, E. A.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517. (h) Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813. (i) Houk, K. N. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A., Blechert, S., Eds.; Kluwer Academic Publishers: Dordrecht, 1989. (j) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (k) Yasui, M.; Maruse, Y.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 7246.

TABLE 1. Torquoselectivity in Thermal Cleavage of Substituted 3-Membered Heterocycles

	Substituents	$\Delta G^{\ddagger}{}_{out}{}^{b}$	$\Delta G^{\ddagger}{}_{in}{}^{b}$	k_{out}/k_{in}
aziridines[a]				
1	none	194.6	194.6	1.00E+00
2	2-F	176.7	213.7	3.00×10^{6}
3	2-Cl	168.1	207.8	9.13×10^{6}
4	2-Br	164.8	204.8	1.05×10^{7}
5	2-NH_2	157.7	207.7	5.70×10^{8}
6	2-$NHCOCH_3$	163.8	205.1	1.73×10^{7}
7	2-OH	167.7	216.3	3.27×10^{8}
8	2-OCH_3	160.8	194.7	8.61×10^{5}
9	2-$OCOCH_3$	137.5	185.7	2.81×10^{8}
10	2-vinyl	163.4	195.8	4.61×10^{5}
11	2-ethynyl	162.5	183.8	5.45×10^{3}
12	2-Ph	152.7	182.9	1.95×10^{5}
13	2-(*o*-FC_6H_4)	151.5	203.1	1.12×10^{9}
14	2-CN	167.2	179.3	1.33×10^{2}
15	2-COOMe	186.4	182.7	2.27×10^{-1}
16	2-CHO	167.4	169.2	2.10E+00
17	2-(*E*)-CH=CHCHO	156.0	19.2	2.30×10^{5}
18	2-CH_3CO	161.7	159.5	4.09×10^{-1}
19	2-CF_3	187.0	193.9	1.59×10^{1}
20	2-Me	184.7	206.5	6.57×10^{3}
21	2-*t*-Bu	180.0	199.0	2.12×10^{3}
22	*trans*-2-F, 3-Ph	141.0	203.0	$6.98 \times 10^{1}0$
23	*trans*-2-Cl, 3-Ph	128.8	191.3	$8.69 \times 10^{1}0$
24	*cis*-2-Cl, 3-Ph	146.9	161.0	2.95×10^{2}
25	*trans*-2,3-diF	165.4	248.9	4.14×10^{14}
26	*cis*-2,3-diF	194.3	194.3	1.00E+00
27	*trans*-2,3-diCl	147.1	222.2	1.42×10^{13}
28	*trans*-2,3-diMe	181.2	221.8	1.30×10^{7}
29	*cis*-2,3-diMe	191.0	191.0	1.00E+00
30	*trans*-2,3-diPh	113.4	165.1	1.16×10^{9}
31	*cis*-2,3-diPh	142.3	142.3	1.00E+00
32	*trans*-2,3-diCHO	149.9	123.7	2.59×10^{-5}
33	2-COOH	165.3	170.7	8.96E+00
34	2-COO^-	186.5	229.1	2.88×10^{7}
35	2-$CH{\equiv}C^-$	122.3	178.4	6.58×10^{9}
36	2-NH^-	43.5	75.0	3.29×10^{5}
37	2-$SO_3{}^-$	163.9	196.4	5.02×10^{5}
38	2-SO_3H	181.0	182.9	2.21E+00
39	2-O^-	47.2	90.5	3.83×10^{7}
40	2-S^-	115.6	181.2	2.98×10^{11}
41	2-Li	176.2	133.3	3.09×10^{-8}
42	2-Na	196.6	183.8	5.82×10^{-3}
43	2-BH_2	163.6	97.3	2.44×10^{-12}
44	2-Be^+	111.7	17.8	3.62×10^{-17}
45	2-$NH_3{}^+$	186.9	198.3	9.67×10^{1}
46	2-SiH_3	182.3	182.3	1.00E+00
47	2-$Si(CH_3)_3$	184.1	184.3	1.09E+00
phosphiranes				
48	none	271.5	271.5	1.00E+00
49	$2F^-$	257.3	282.1	2.18×10^{4}
50	2-$OCOCH_3$	251.0	273.7	9.20×10^{3}
oxiranes				
51	**None**	241.4	241.4	1.00E+00
52	**2F-**	247.8	301.0	2.09×10^{9}
53	**2-$OCOCH_3$**	237.0	279.8	3.13×10^{7}
thiiranes				
54	none	226.8	226.8	1.00E+00
55	2F-thiirane	223.8	259.6	1.90×10^{6}
56	2-$OCOCH_3$	219.9	254.2	1.02×10^{6}

[a] Scheme 2, R1 = H. [b] In kJ/mol. For disubstituted aziridines **22**–**32**, "in" and "out" refer to the rotational mode of the C_2 substituent.

When a comparable analysis is effected for the aziridines, the HOMOs and LUMOs for inward and outward rotation are remarkably similar (see the Supporting Information.) This finding is perhaps not surprising, as the effects of donors and acceptors in the cyclobutene system were found to be too small.[25g] An alternative approach was presented by Inagaki[26] who applied orbital phase theory to the torquoselectivity of cyclobutenes. In this method, a rotational mode is selected on the basis of the electron-donating or electron-withdrawing ability of the σ-orbital of the carbon–substituent bond. Since the vast majority of the neutral substituents in the present study prefer outward rotation, neither of these theoretical treatments is applicable. The introduction of an electronegative nitrogen into the four-electron electrocyclic reaction would be expected to represent a significant perturbation of the carbocyclic systems previously studied.

Since outward rotation brings a substituent closer to the N–H bond, the possibility of hydrogen bonding for hydrogen bond accepting groups was investigated. No evidence based on measured atomic distances was found for the incursion of this effect.

Charge development in the transition state was explored as a possible source of selectivity. In previous studies, it was found that for substitution reactions with a neutral nucleophile, attractive electrostatic energies in the transition state were found to exert significant rate retardation.[16] In these electrocyclic reactions, charge accumulation at the ring carbons could potentially introduce different electrostratic energies into the transition states resulting from the unique rotational modes. Increased relative rates could result from increasing the rate of C–C bond cleavage either by a diminution of attractive energies at the carbon centers should opposite charges develop as the reaction proceeds or from an increase in repulsive energies at these centers resulting from increases in the magnitude of like charges. Substituting the NBO charges in to eq 1, no straightforward correlation could be found between charge development and torquoselectivity (Table 2). For example, for 2-fluoroaziridine, the cleavage reaction results in repulsive energies of 78.4 and 30.1 kJ/mol for the inward and outward conrotatory modes, respectively; if electrostatic energies were the sole determinant of the reaction rate, inward rotation would predominate, contrary to the calculated results.

For a 2-formyl substituent, electrostatic energy calculations for inward and outward rotation result in attractive energies that would have to be overcome in order for the reaction to proceed. Since the attractive energy calculated for inward rotation is 36.1 kJ/mol higher than the alternative, one would incorrectly, based on electrostatic interactions alone, predict the latter to be overwhelmingly preferred. The actual calculated result is that inward and outward rotational modes have similar free energies of activation. Additional examples of the lack of correlation of electrostatic energies and rotational preference may be found in Table 2.

For the overwhelming majority of substituents studied, outward rotation is greatly preferred over inward rotation. Such rotations are free from the through-space interactions that come into play for inward motion. Since this list of substituents contains both electron-releasing and electron-withdrawing substituents via the resonance effect, and since these substituents, regardless of the direction of their resonance effects, lead to faster rates than **1**, it is unlikely that resonance effects are important here. A feature that virtually all the investigated substituents have in common is that they are inductively electron withdrawing.[27] It is reasonable to

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[26] Yasui, M.; Naruse, Y; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 7246.

[27] For an excellent review of substituent constants, see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 185.

TABLE 2. Electrostatic Energies at the Transition States in Corotatory Cleavage Modes for 2-Substituted Aziridines[a–c]

		q					*d*			
compd	substituent	C_2	(H at C_2)	C_3	(H_1 at C_3)	(H_2 at C_3)	(C_2−C_3)	$(E^{c})_{\text{elst}}$ (kJ/mol)	$(E_{\text{out}} - E_{\text{in}})_{\text{elst}}$ (kJ/mol)	$(E - E_{\text{H}})_{\text{elst}}$ (kJ/mol)
1	H	−0.290	0.405	−0.228	0.195	0.218	2.059	14.4	0.0	0.0
2	F out	0.431	0.214	−0.370	0.220	0.220	2.086	30.1	−48.3	15.7
	F in	0.192	0.568	−0.269	0.222	0.203	2.101	78.4	0.0	64.0
3	Cl out	−0.069	0.252	−0.295	0.203	0.217	2.060	15.4	−2.59	1.09
	Cl in	−0.105	0.227	−0.204	0.222	0.204	2.089	18.0	0.0	3.6
4	Br out	−0.184	0.269	−0.385	0.228	0.198	2.057	2.35	−5.14	−12.0
	Br in	−0.186	0.232	−0.185	0.224	0.206	2.089	7.49	0.00	−6.86
16	CHO out	−0.279	0.231	−0.038	0.205	0.235	2.065	−13.0	36.1	−27.3
	CHO in	−0.357	0.229	0.097	0.229	0.235	2.034	−49.0	0.0	−63.4
5	NH_2 out	0.275	0.230	−0.489	0.196	0.195	2.102	−32.7	−66.4	−47.1
	NH_2 in	0.124	0.185	−0.252	0.213	0.199	2.040	33.7	0.0	19.3
14	CN out	−0.267	0.249	−0.068	0.206	0.235	2.040	−4.57	−6.80	−18.9
	CN in	−0.239	0.247	−0.038	0.216	0.235	2.057	2.23	0.00	−12.1
10	$CH{=}CH_2$ out	−0.111	0.217	−0.201	0.198	0.224	2.091	15.6	−1.10	1.21
	$CH{=}CH_2$ in	−0.125	0.216	−0.161	0.204	0.227	2.049	16.7	0.0	2.30
6	$NHCOCH_3$ out	0.236	0.235	−0.396	0.200	0.205	2.073	2.84	−17.3	−11.5
	$NHCOCH_3$ in	0.215	0.213	−0.328	0.201	0.200	2.150	20.2	0.0	5.82
12	C_6H_5 out	−0.072	0.222	−0.210	0.199	0.222	2.081	21.1	−0.62	6.78
	C_6H_5 in	0.037	0.218	−0.275	0.201	0.204	2.117	21.8	0.0	7.41
7	OH out	0.395	0.214	−0.462	0.197	0.206	2.097	−23.8	−66.0	−38.2
	OH in	0.293	0.181	−0.281	0.215	0.199	2.073	42.2	0.0	27.9
8	OCH_3 out	0.410	0.215	−0.462	0.197	0.204	2.098	−25.2	−59.4	−39.6
	OCH_3 in	0.323	0.190	−0.306	0.209	0.198	2.109	34.1	0.0	19.8
9	$OCOCH_3$ out	0.296	0.227	−0.293	0.210	0.204	2.041	43.1	0.0	28.7
	$OCOCH_3$ in	0.254	0.209	−0.219	0.222	0.198	2.079	62.2	0.0	47.8

[a] The *q* values are atomic NBO charges. with hydrogens summed into C_2 and C_3. [b] The C_2−C_3 distance in the transition state is provided in Å. [c] For calculation of the electrostatic energies *E* (E_{elst}, see the Computational Methodology section), the charges of the attached hydrogens were summed into C_2 and C_3.

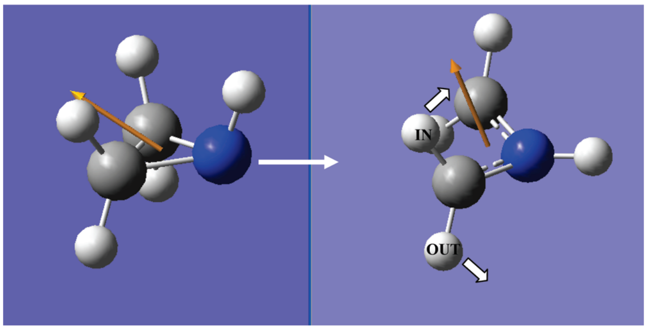

FIGURE 1. Ground state and transition state for **1** with dipole moment directions.

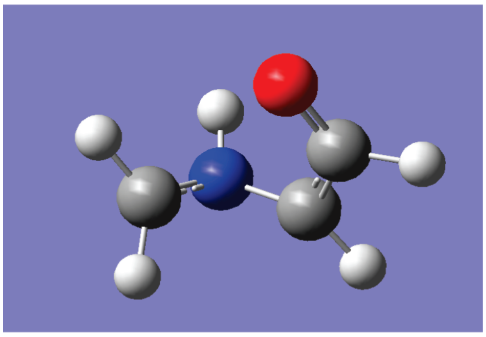

FIGURE 2. Inward transition state for **16**.

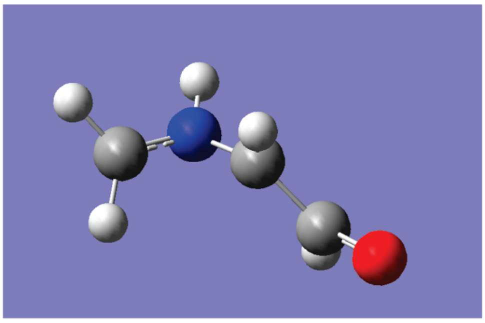

FIGURE 3. Outward transition state for **16**.

propose that the inductive effect is the primary reason for these rate accelerations. Many examples are found in the literature[3] of stabilization of azomethine ylides by means of electron-withdrawing substituents, and in view of the fact that electrocyclic reactions are endothermic, application of the Hammond postulate[28] demands that the transition states for bond cleavage should also be stabilized by electron withdrawal.

A rationalization of the results for substituents[27] using the example of the electron-withdrawing formyl group (**16**) is based on perturbations of the transition state of parent compound **1** by the substituents during the different modes of rotation. The ground state and transition state of **1** are presented along with their dipole moments in Figure 1. The dipole is directed at an upward angle with respect to the plane of the cleaving ring. During inward rotation for **16**, (Figure 2, resulting from counterclockwise rotation), the positively polarized carbon of the carbonyl group is brought toward the negative end of this dipole, stabilizing the transition state. Outward rotation (Figure 3), resulting from clockwise rotation also derives transition-state

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(28) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. (b) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley-Interscience: New York, 1984; p 44.

stabilization, in this case from relief of unfavorable repulsive interactions between the positive end of the ring dipole and the carbonyl carbon. When the electron-withdrawing CHO group is removed from the immediate vicinity of the ring using the (*E*)-CH═CHCHO group of **17**, its stabilizing effect is attenuated and this compound is found to react at only 20 times the rate of the 2-vinyl derivative **10**. Resonance interactions by means of the π system are absent.

For inward rotation, it is obvious that a substituent must encounter the negative end of the dipole of the cleaving aziridine ring. Electron-withdrawing substituents, the halogens, for example, negatively polarize the bond to carbon in this vicinity, giving rise to destabilizing repulsive interactions. When rotation occurs inward, the fluoro group of **13** is directed over the aziridine ring and toward the negative end of its dipole; this repulsive interaction leads to an increase in $\Delta G^{\ddagger}$ of about 21 kJ/mol. Attachment of an acetyl group (**6** and **9**) decreases this effect for amino (**5**) and a hydroxy (**7**) groups, increasing the reaction rate for inward rotation. Steric effects (**20** and **21**) do not play a major role; even the bulky CF_3 group of **19** does not lead to rate retardation relative to **1**. In this case, however, this very polar group may give rise to attractive interactions with the ring, counteracting rate-retarding steric effects.

In outward rotation, electron withdrawal by means of the inductive effect by substituents such as methoxy, methoxycarbonyl, acetyl and acetoxy groups all give rise to calculated accelerated rates relative to **1**. The unsaturated vinyl, acetylenic and phenyl substituents are also electron withdrawing and produce accelerations. Slight accelerations are calculated for the weakly electron-releasing methyl and *tert*-butyl groups. Interestingly, the fluoro group of an *o*-fluorophenyl substituent (**13**) is apparently too far from the reaction center to produce a palpable difference with respect to unsubstituted **12**, in keeping with the expectation that the inductive effect falls off with distance from the reaction center.

Anionic species **36**, **39**, and **40** exhibited tremendous rate enhancements. The transition-state geometries are such that the bonds between carbon and the heteroatom have been shortened to 1.321 and 1.290 for **36**, 1.259 and 1.229 for **39**, and 1.689 and 1.673 Å for **40**, for outward and inward rotation, respectively. These results indicate considerable stabilizing double-bond character in these bonds,[29] although the larger sulfur atom would be expected to be less effective, in accord with the results. Additionally, the negative charge is dispersed over the C−heteroatom bond. Charge dispersal minimizes the repulsive effects that attend inward rotation. When these stabilization mechanisms are unavailable, the inward rotational mode becomes quite unattractive. The high $\Delta G^{\ddagger}$ for inward rotation of carboxylate **35** provides additional support for the rationale given above that invokes the impediments to inward rotation when a substituent without recourse to double bond formation to the attached ring carbon is repelled by the ring dipole in the transition state. The large, diffuse substituent sulfonate **37** has only weak repulsive interactions in the inward mode. An additional example of a group whose negative charge is too far from the aziridine ring dipole to destabilize the inward mode but is able to inductively stabilize the transition state is provided by **35**.

The observation that inward rotation of the anionic species occurs more rapidly than for **1** suggests that strong electron-withdrawing substituents are capable of overcoming the unfavorable electrostatics is illustrated by Figure 2. The effects of anionic substituents on the course of the reactions can be appreciated by comparison with their unionized parent compounds. For example, both rotational modes of alcohol **7** occur considerably slower than those of **39**.

Substituents containing electropositive elements **41**−**45**, with the exception of organosodium compound **42** and ammonium derivative **45**, are also more reactive than **1**. The low electronegativity of Na renders the C−Na bond essentially ionic.[30] The carbanionic center in this molecule has captured maximum electron density and would be predicted to be a poor electron withdrawer. Outward rotation for **42** is thus essentially unaffected relative to **1**. Inward rotation is somewhat favored; however, the bond distance of the sodium−carbon bond, ca. 2.30 Å,[31] suggests that Na is too far from the negative end of the ring dipole to make a significant stabilizing contribution. This conclusion is supported by the impressive preferences for inward rotation of organolithium **41** and borane **43** where considerably shorter bond distances between the ring carbon and the electropositive atom obtain. These smaller substituents are reasonably effective electron-withdrawing groups and are responsible for lowering $\Delta G^{\ddagger}$. On the other hand, the positive charge of salt **45** is not localized, but dispersed over the ammonium hydrogens, making for weak electrostatic interactions that do little to stabilize the inward transition state.

The effect of a fully positive center was explored hypothetically with Be^{+}. This substituent has the advantage of being relatively small and in good position to interact with both transition states. The largest preference for inward rotation was obtained for this derivative supporting the concept of strong stabilizing electrostatic interaction between the cationic center and the dipole of the ring. Outward rotation for this compound is also significantly faster than that of **1**. This demonstrates a reasonable consequence of the powerful electron-withdrawing ability of this cationic center.

The trimethylsilyl group has been reported to have an electron-releasing inductive effect.[32] The magnitude of its effect is critically dependent on the nature of the system under study. In the present conrotatory cleavage of **47** to form an azomethine ylide, this group appears to be no more effective in directing torquoselectivity than the alkyl groups.

Several *trans*-2,3-disubstituted derivatives have been studied. For outward rotation, the stabilizing effect of each substituent combine to decrease $\Delta G^{\ddagger}$. The addition of a second methyl group produces little change; however, the

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(29) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 21.

(30) Benkeser, R. A.; Foster, D. J.; Sauve, D. M. *Chem. Rev.* **1957**, *57*, 867.

(31) Li, B.-Z.; Xin, J.; Ziurys, L. M. *Chem. Phys. Lett.* **1997**, *280*, 513.

(32) See, for example: (a) Bažant, V.; Chavalovský, V.; Rathouský, J. *Organosilicon Compounds*; Academic Press: New York, 1965; Vol. 1, pp 16−17. (b) Olah, G. A.; Doggweiler, H.; Felberg, J. D.; Frohlich, S. *J. Org. Chem.* **1985**, *50*, 4847. (c) Prakash, G. K. S.; Reddy, V. P.; Rasul, G.; Casanova, J.; Olah, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 3076–3078. (d) Katritzky, A. R.; Eabom, C.; Walton, D. R. M.; Topson, R. D. J. *Organomet. Chem.* **1972**, *43*, 131. (e) Yoder, C. H.; Gardner, R. D. *J. Org. Chem.* **1981**, *46*, 64.

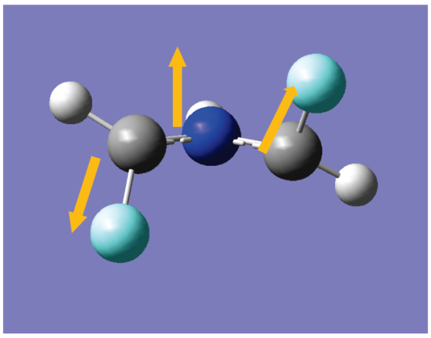

FIGURE 4. Transition state for inward rotation of **25**.

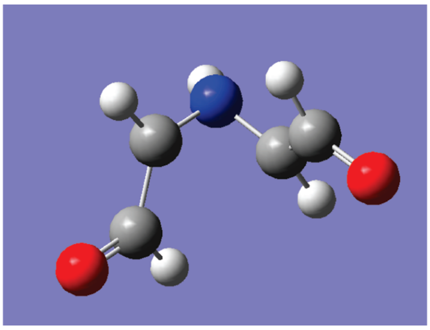

FIGURE 5. Transition state for inward rotation of **32**.

remaining compounds in this group have stabilizing effects that are approximately additive. The *trans* diastereomer has opposing polarities for the bonds between the substituents and the ring carbons. The net dipole tends to generally increase the repulsive interactions involved in inward rotation. This is illustrated for difluoro **25** in Figure 4. The propensity for inward rotation of diformyl derivative **32** appears rather large when compared to monosubstituted **16**.

Inspection of the structure of its transition state (Figure 5) reveals that neither functionality is found in close proximity to the ring dipole, minimizing potential repulsive interactions. This transition state is able to benefit from the electron-withdrawing ability of the carbonyls.

The individual substituents of the *cis*-2,3-disubstituted derivatives necessarily have rotational modes in opposite directions. When the substituents are identical (**26**, **29**, **31**) the calculated values of $\Delta G^{\ddagger}$ are intermediate with respect to those for outward and inward rotation of the corresponding *trans* diastereomer. For unsymmetrical **24** it was of interest to determine which group, chloro or phenyl, rotated preferentially inward; since inward rotation of monochloro compound **3** is 25 kJ/mol less favorable than that of **12**, it was to be expected that its outward would be favored with **24**. Indeed, this is what was calculated.

Table 1 also provides the torquoselectivities of derivatives of phosphirane **48**, oxirane **51**, and thiirane **55**. All torquoselectivities are calculated to be high. The data demonstrate that azomethine ylide formation from aziridine is a considerably more facile process than the corresponding ones for its heterocyclic relatives. In the case of the oxygen heterocycle, it is reasonable to assume that oxygen, due to its high electronegativity, is a reluctant electron pair donor to the four-electron electrocyclic transition state. In spite of the lower electronegativity of the heteroatoms of phosphirane and thiirane, electron donation to the four-electron ring cleavage is less facile than that of aziridine. The electron pairs of the phosphirane and thiirane are found in large $3sp^3$ orbitals that tend to overlap with the cleaving C−C bond less effectively. For each compound, the fluoro and acetoxy derivatives were studied. Substitution of a 2-fluoro group in **1** produced a small rate acceleration for outward rotation, and a significant rate retardation for inward rotation; the reverse was observed for a 2-acetoxy functionality. For phosphirane derivatives **49** and **50**, outward rotation was moderately accelerated, while the rate of inward rotation was somewhat depressed relative to **48**. This finding is in accord with the larger size of the phosphorus atom relative to nitrogen. A similar conclusion can be reached for thiirane **55** and its derivatives. Nakamura and Houk reported that the activation energy for outward rotation of 2-formyloxirane was 11.7 kJ/mol higher than that for inward rotation when calculated at the MP2/6-31G(d) level.[33] Both rotational modes were found to be more favorable than that of **51**. In the present study, it was determined that the fluoro and acetoxy derivatives were less reactive than their parent compound. As expected for the derivatives of **51**, the high electronegativity of oxygen renders the electron-withdrawing effect of a fluoro group modest in outward rotation. Given the large ring dipole of **51** it is not surprising that inward rotation for its derivatives is highly disfavored. In the case of the formyl compound, preference for inward rotation may be determined by a favorable electrostatic attraction between the positively polarized carbon of the carbonyl group for the negative end of the ring dipole, similar to that found in **16**.

Conclusions

Torquoselectivities were determined for a representative number of substituted aziridines that lack a plane of symmetry as an integral component of relative rate determination and prediction of the stereochemical outcomes for thermal cleavage reactions leading to azomethine ylides. Substituents were found to exert a sizable effect on torquoselectivity. Electronegative or anionic functionalities enforce outward rotation, while electropositive or cationic groups dictate inward rotation.

Frontier molecular orbitals and electrostatic, resonance, and inductive effects were considered as possible explanations of the results. The most reasonable rationalization of the results is that electron withdrawal by a substituent stabilizes the transition state of the outwardly rotating mode. In inward rotation, electrostatic attractions or repulsions between the substituent and the ring dipole are predominant. The rates for each mode of rotation relative to **1** were determined.

To gain further insight into the factors that underlie the rate of cleavage of three-membered heterocycles, phosphirane, oxirane, and thiirane derivatives were studied; these heterocycles were found to be less considerably reactive than the corresponding aziridines; it is reasonable to conclude that the higher electronegativity of oxygen makes donation of an electron pair to an electrocyclic reaction a higher energy process for oxiranes, while poor orbital overlap in

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[33] Nakamura, K.; Houk, K. N. *Heterocycles* **1993**, *35*, 631.

the case of phosphorus and sulfur lead to lower reactivity for phosphoranes and thiiranes.

Supporting Information Available: Energies of the reactants, transition states, their Cartesian coordinates, the transition-state unique imaginary frequencies for **1**−**56**, and HOMOs and LUMOs for transition states of representative thermal cleavage reactions. This material is available free of charge via the Internet at http://pubs.acs.org.