JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 763–773 (1998)

An *ab initio* study of 1-azabicyclo[1.1.0]butyl and isomeric cations

Robert H. Higgins* and Bernice Kidd

Department of Natural Sciences, Fayetteville State University, Fayetteville North Carolina 28301, USA

Received 8 November 1996; revised 17 November 1997; accepted 20 November 1997

ABSTRACT: Solvolysis products of 3-azetidinyl chlorides, tosylates, and mesylates have been interpreted previously to indicate that these reactions proceed by azabicyclo[1.1.0]butyl cationic intermediates. Whether these cations are formed by direct ionization to 3-azetidinyl cations followed by collapse to the bicyclic ion or are formed with anchimeric assistance by the lone pair of electrons on nitrogen is unclear. This investigation was initiated to assess the relative stability of these bicyclic cations and their isomeric 3-azetidinyl and aziridinylmethyl cations. All *ab initio* methods investigated suggest that the bicyclic ions (**1**) are much more stable than the corresponding 3-azetidinyl cations (**3**) and that transition states for conversion of the bicyclic ions to azetidinyl carbocations are not acheivable from the bicyclic ions. Hartree–Fock *ab initio* calculations on *N*-methyl (and *N*,2-dimethyl) bicyclic ions and their isomeric aziridinylmethyl cations (**2**) indicate that the bicyclic ions are significantly more stable than are the isomeric partially ring-opened cations, and that transition states (**4**) for conversion of the bicyclic ions to the corresponding aziridinylmethyl carbocations are probably energetically unattainable. Hartree–Fock theory predicts that the *N*-methyl-2-phenylbicyclic ions are slightly less stable than the resulting aziridinylmethyl cations. Calculations which include electron correlation (MP2) indicate, however, that all bicyclic ions investigated are more stable than any of their isomeric carbocations. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 1-azabicycl[1.1.0]butyl cations; 3-azetidinyl cations; aziridinylmethyl cations; *ab initio*

INTRODUCTION

Although it has been nearly a century since Howard and Markwald[1] first prepared azetidine, the chemistry of azetidines was little investigated, and even less understood, until the late 1960s and early 1970s. For instance, an older review[2] indicates that azetidine is 'instantly decomposed' in hydrochloric acid, while other results[3,4] indicate that azetidines undergo slow ring opening in refluxing hydrochloric acid. Much of the reason for this sparsity of investigation of azetidines was the result of the fact that until the 1960s there were no satisfactory preparative methods for these compounds, particularly those with non-bulky 1-alkyl substituents.[5]

Probably the first general preparative methods, particularly for those with non-bulky 1-alkyl substituents, should be attributed to Testa, Fontanella and co-workers.[3,6–10] It was, however, during the late 1960s and early 1970s that a number of general methods for their preparation were developed. Thus, Wadsworth[11] developed a method for the preparation of alkyl-substituted azetidines by ring closure of γ-haloamines in which the steric bulk of the amino substituent was increased by protective groups. Cromwell's group was successful in the preparation of azetidinyl ketones,[12–16] esters[17–19] and carboxylic acids.[17] It was Gaertner,[20–22] however, who pioneered the chemistry of azetidines with replaceable functional groups[23,24] directly attached to the ring at the 3-position.

Gaertner's preparation of azetidinols, like those of all other methods available at that time, suffered when ring closure was accomplished with small *N*-alkyl substituents.[25] Gaertner speculated that large substituents at the 2-position of 1-(alkylamino)-3-halopropanes should facilitate ring closure to azetidines with the large substituent at the 3-position.[21] Thus, Jenkins and Cale[26] prepared the benzhydryl ethers of 1-methyl- and 1-ethyl-3-azetidinols from the benzhydryl ether of 1,3-dichloropropan-2-ol in excellent yield; Gaj and Moore[27] prepared the methoxymethyl ethers of the 1-methyl- and 1-ethylazetidin-3-ols; and we reported the ring closure of tetrahydropyranyl and trimethylsilyl ethers of 1-(alkylamino)-3-chloro-2-propanols to azetidinols bearing non-bulky 1-alkyl substituents in good to excellent yields.[28–30] While Gaertner's speculation about the steric bulk of the substituent at the 3-position has led to improved methods for the preparation of azetidinols,[26–28] it is questionable whether all, or even any, of the

**Correspondence to:* R. H. Higgins, Department of Natural Sciences, Fayetteville State University, Fayetteville, North Carolina 28301, USA.
E-mail: higgins@chi1.uncfsu.edu
Contract/grant sponsor: National Institutes of Health; *contract grant number:* S06GM08206.
Contract/grant sponsor: North Carolina Biotechnology Center.

 CCC 0894–3230/98/110763–11 $17.50

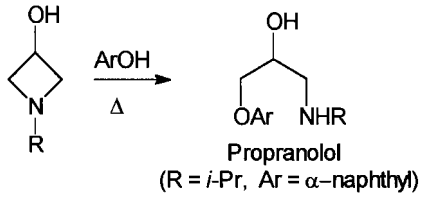


Figure 1. Preparation of aryloxypropanolamines from azetidinols

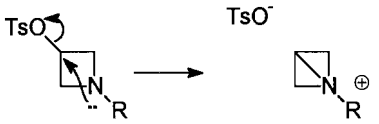


Figure 2. Anchimeric assistance in the solvolyses of azetidinyl tosylates

improvements should be attributed this factor.[29] For example, we have found that 1-methyl- and 1-ethylazetidinyl trimethylsilyl ethers are stable, whereas the corresponding azetidinols undergo spontaneous decomposition on standing overnight. Furthermore, variously substituted 1-benzylazetidin-3-ols undergo spontaneous decomposition to intractable 'gums' on standing. Hence it is unclear whether the failure of Gaertner's method to prepare the 1-methyl- and 1-ethylazetidinols is not due at least partially to decomposition of the azetidinols during preparation and work-up.

Shortly after the appearance of Gaertner's papers, the chemistry of azetidinols became of immense interest. For example, several pharmaceutical companies patented reactions of azetidinols with phenols (see Fig. 1) as a method for the preparation of a number of β-adrenolytic compounds structurally related to propranolol,[31] and experiments in our laboratory indicated that the tosylate of 1-*tert*-butyl-3-azetidinol undergoes methanolysis and first-order reaction with cyanide ion in methanol at the

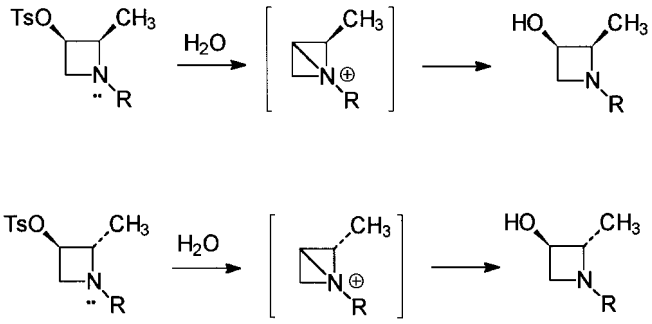


Figure 3. Retention of configurations in the solvolyses of 2-methylazetidinyl tosylates

same rate, suggesting a common intermediate.[32] We suggested that the reaction involved anchimeric assistance with the formation of an intermediate 1-azabicyclo[1.1.0]butyl cation (Fig. 2). Shortly thereafter, we reported retention of configuration in the solvolyses[33] of the *cis*- and *trans*-1-*tert*-butyl-2-methyl-3-azetidinyl tosylates (Fig. 3). At about the same time, Okutani and Masuda[34] observed stereospecific retention and some ring contraction in the solvolyses of mesylates of 1-cyclohexyl-2-phenyl-3-azetidinols (Fig. 4).

Stereospecific retention of configuration and ring contraction to aziridinylmethyl derivatives seemed convincing evidence that bicyclic ions were intermediates for these solvolysis reactions. However, there were some troubling features: ring contraction[34] was observed in the solvolysis of *trans*-1-cyclohexyl-2-phenylazetidinyl mesylate but not in that of the *cis*-isomer, and the Arrhenius plot for the solvolysis of *trans*-1-*tert*-butyl-2-methylazetidinyl tosylate was non-linear even though the reaction appeared to be stereospecific.[33]

As part of our continuing interest in the nucleophilic ring opening of azetidines, particularly with respect to ring opening of azetidinols by phenols to provide aryloxypropanolamines structurally related to proprano-

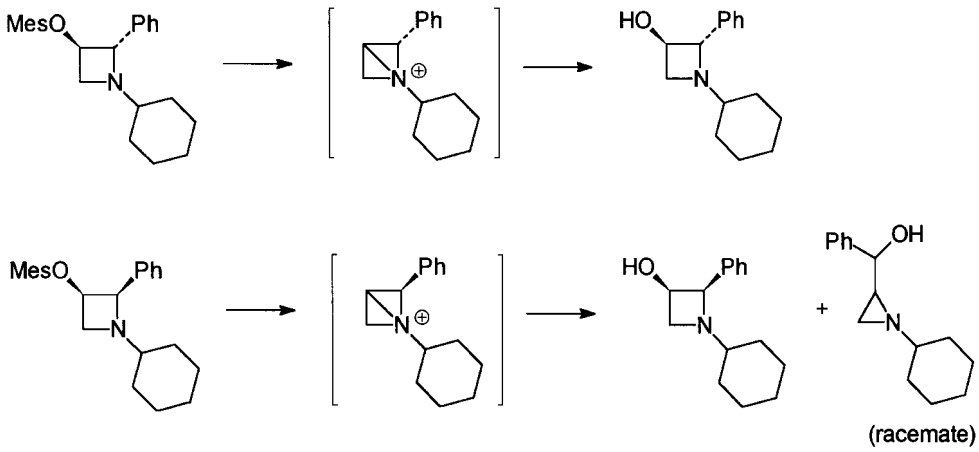


Figure 4. Retention of configurations and ring contraction in the solvolyses of 2-phenylazetidinyl mesylates

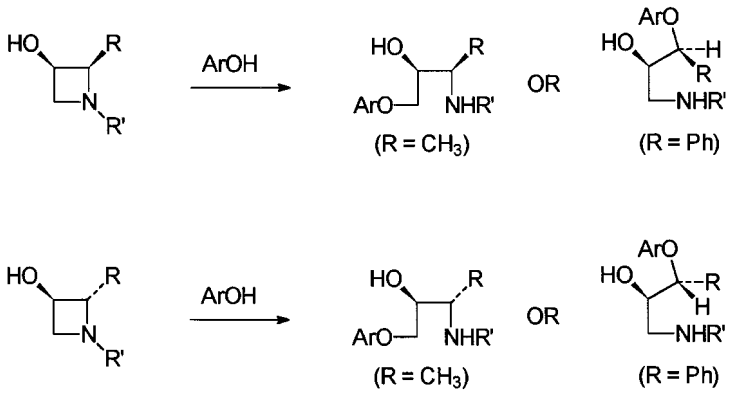
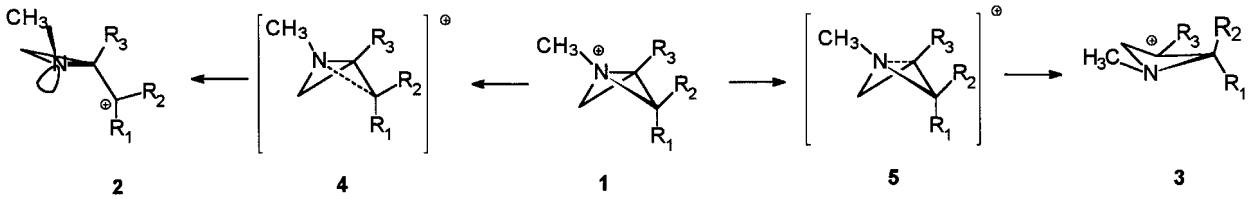


Figure 5. Regiochemical results in the ring openings of 2-methylazetidinols by phenols

lol, we recently reported[35] that the regiochemistry of the ring opening of 2-substituted azetidinols by phenols is dependent on the nature of the substituent. Hence, 2-methylazetidinols undergo nucleophilic attack at the 4-position, whereas 2-phenylazetidinols undergo nucleophilic attack at the 2-position with stereospecific inversion of configuration (Fig. 5). This difference in reactivity was reminiscent of the differences in reactivity of the 2-methyl- and 2-phenyl-1-azabicyclobytyl cations observed earlier.[33,34]

In order to elucidate more fully the nature of factors operative in the nucleophilic ring opening of azetidinium ions, we have initiated a fundamental investigation of these factors. Since our original claims of the existence of azabicyclobutyl cations as intermediates, structural theory has made tremendous progress such that high-level quantum calculations are now available for even moderately sized species. Our initial efforts involved semiempirical MNDO calculations[36] on the possible intermediates: the bicyclic ion **1a** (see Fig. 6), the aziridinylmethyl carbocation, **2a**, the 3-azetidinyl carbocation **3a** and the transition states for their interconversion, **4a** and **5a**, respectively. Later, semiempirical AM1 and PM3 calculations were employed, even though it was known that parameters for all semiempiricial calculations are not very good for small-membered rings (semiempirical calculations are not optimally parameterized for small ring compounds or for transition states).[37,38] The results of these calculations, although computationally cheap and sometimes qualitatively matching experimentally observed phenomena, were often in disagreement with each other. Consequently, our efforts shifted to *ab initio* calculations on these intermediates and transition states. Our reason for including semiempirical results in this report is for comparison purposes, rather than for discrediting these techniques.



	R_1	R_2	R_3
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me
e	Ph	H	H
f	H	Ph	H

Figure 6. Partial ring openings of 1-azabicycl[1.1.0]butyl ions

CALCULATION METHODS

All *ab initio* data presented were obtained by use of Spartan 4.0[39] and were determined using restricted (*i.e.* electron-paired) quantum mechanical calculations. The bicyclic ion was constructed in the Spartan model builder and subjected to one geometry optimization using the builder's minimizer and saved for AM1 optimization. Starting geometries for all other non-transition state structures were obtained starting with the AM1 optimized bicyclic ion (**1**). Structures **2** were obtained by breaking the *N—C-2* bond of **1** followed by deleting the new valences ('atoms') and performing one geometry optimization using the builder's minimizer. Structures **3** were obtained by breaking the *N—C-3* bond of **1** followed by deleting of the new valences and one minimization in the Spartan model builder (C_1 symmetry for all compounds was retained). The results of the AM1 optimizations were employed as input (both 'Wavefunction' and 'Hessian' restart 'dimples' were checked in all post-AM1 calculations) for PM3 calculations and for Hartree–Fock 3–21G(*) calculations, with results of the latter being used as input for HF/6–31G* calculations. On the occasion (**2a**) when the 3–21G basis set failed to optimize to the aziridinylmethyl cation, the AM1 result was employed for 6–31G* calculations. The 6–31G* results were used as input for 6–31G** calculations, the results of which were employed for 6–311G** calculations.

Transition states for the interconversions of **1** and **3** (*i.e.* **5**) by MOPAC AM1 calculations were considerably more difficult to obtain than the transition states **4** for interconversion of **1** and **2**. Transition states **4** were readily obtained by simple path calculations by stretching the *N—C-2* bond of **1** (or contracting this distance in **2**). Similar attempts at finding **5** by simply stretching the *N—C-3* bond of **1** (or decreasing this distance in **3**) provided discontinuous potential energy diagrams.

Saddle-point calculations (for **5**) using points on either side of the discontinuity were unsuccessful. An examination of the geometries before and after the discontinuities indicated that ring inversion, inversion of the nitrogen pyramid and methyl rotation had occurred. MOPAC transition states (**5**) were located by (1) performing grid calculations for each methyl rotamer (the *N—C-3* distance and *N—C-2—C-3—C-4* dihedral were varied), (2) selection of the lower energy for each point in the grid to construct a third potential energy surface (this surface was continuous and possessed a saddle-point), (3) performing a saddle-point calculation by selecting two points on either side of the apparent saddle-point and (4) performing a transition state calculation on the saddle-point geometry. As verification that the correct transition state had been reached, a MOPAC AM1 frequency calculation was performed which provided a single negative frequency. The transition state *z*-matrix was imported into HyperChem,[40] and the negative frequency animated.[41]

Input structures for Spartan transition state calculations were obtained using the transition search tool in its structure editor. The bicyclic ion, **1**, and either the aziridinylmethyl ion, **2**, or the azetidinyl ion, **3**, were used for building the estimated transition state geometries (**4** and **5**, respectively); no energy minimization was performed in the model builder for transition states. The resulting geometry was then subjected to Spartan's transition state search utility (a linear synchronous transient method) at the AM1 level, and vibrational frequencies were calculated. The methods for obtaining MOPAC and Spartan AM1 transition states gave essentially identical structures, energies and vibrations. The AM1 transition states were employed as input (both 'Wavefunction' and 'Hessian' restart 'dimples' were checked in all post-AM1 calculations) for PM3 calculations and for Hartree–Fock 3–21G* calculations, with the results of the latter being used as input for the same hierarchy of calculations as in the optimized structures.

In an attempt to investigate electron correlation effects, the RHF/6–311G** optimized results were used as input for restricted Møller–Plesset (MP2) calculations. Geometry (or transition state) optimizations at the MP2 level were performed (for **1a, 1a′, 3a** and **5a**) by using the HF/6–311** results for MP2/6–31G* optimization followed by optimization of these results at the MP2/6–311G** level; we were unable to obtain the aziridinylmethyl cation (**2a**) by this method. MP2/6–311G** single-point calculations were also performed on the optimized HF/6–311G** structures. Unfortunately, too little machine memory is available to perform calculations on the 2-phenyl ions at this level; thus MP2/6–31** calculations were performed on the HF/6–311G** optimized structures.

RESULTS AND DISCUSSION

1-Methyl rotamers

Two methyl rotamers (**1a** and **1a′**) are possible for **1** (see Fig. 7 and Tables 1 and 2). In view of the uncertainties surrounding semiempirical calculations on small rings,[37,38] *ab initio* calculations on both rotamers were conducted with several basis sets and at both levels of theory. These results are in agreement with those from

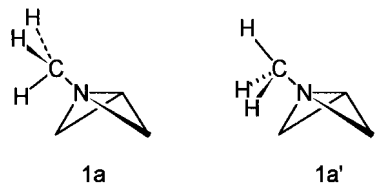


Figure 7. *N*-Methyl rotamers of 1-methyl-1-azabicyclo[1.1.0]butyl ion

Table 1. Optimized Hartree–Fock total energies for **1, 2, 3, 4** and **5**[a]

Compound	AM1[b]	PM3[b]	3–21G	6–31G*	6–31G**	6–311G**
1a	252.5	244.2	−209.07173	−210.26409	−210.27777	−210.31379
1a′	253.0	244.6	−209.06973	−210.26161	−210.27525	−210.31113
1b	242.4	233.3	−247.89934	−249.30655	−249.32339	−249.36578
1c	242.1	232.9	−247.90266	−249.30887	−249.32575	−249.36813
1d	240.4	230.9	−247.90680	−249.31278	−249.32959	−249.37190
1e	273.5	264.4	−437.34977	−439.82089	−439.84174	−439.91537
1f	273.0	263.4	−437.35202	−439.82283	−439.84365	−439.91734
2a	251.4	248.1	—[c]	−210.22866	−210.24227	−210.28064
2b	230.9	228.4	−247.88151	−249.28496	−249.30186	−249.34585
2c	230.5	227.4	−247.88160	−249.28601	−249.30290	−249.34692
2e	250.4	248.6	−437.35506	−439.82612	−439.84667	−439.92035
2f	249.3	245.4	−437.35433	−439.82741	−439.84784	−439.92171
3a	255.0	236.7	−209.02671	−210.21004	−210.22389	−210.26176
3b	248.5	230.3	−247.85706	−249.25489	−249.27190	−249.31611
3c	249.0	231.1	−247.85626	−249.25117	−249.26804	−249.31206
3d	233.5	215.5	−247.87905	−249.27819	−249.29534	−249.33952
4a	270.9	258.0	—[d]	−210.21857	−210.23210	−210.26913
4b	253.0	239.6	−247.87296	−249.27428	−249.29112	−249.33448
4c	252.1	238.4	−247.8778	−249.27864	−249.29552	−249.33883
4e	278.6	265.4	−437.33706	−439.80624	−439.82683	−439.90034
4f	277.2	263.7	−437.34423	−439.81279	−439.83337	−439.90719
5a	267.0	250.7	−209.01622	−210.19972	−210.21324	−210.25083
5b	259.6	242.2	−247.84732	−249.24445	−249.26114	−249.30495
5c	257.7	241.0	−247.84511	−249.24211	−249.25881	−249.30273
5d	247.5	232.0	−247.86977	−249.26844	−249.28540	−249.32931

[a] Calculations not performed on **2d, 3e, 3f, 4d, 5e** and **5f**. Unless indicated otherwise, energy is in hartree. No corrections for zero-point energies were performed.
[b] Calculated heats of formation are in kcal mol^{-1}.
[c] Geometry optimization provided complete ring opening.
[d] Not reported since the incorrect structure was obtained for **2a**.

the semiempirical methods—**1a** appears to be more stable than **1a′**. Indeed, the preference for **1a** increases with larger basis sets and with higher levels of theory. These rotamer energy differences are sufficiently small, however, that corrections for zero-point energies should be examined. Since Spartan (4.0) does not support vibrational analysis at the MP2 level, we ordered a program capable of performing these calculations, the results of which will be given as part of a report dealing with solvent effects on the various ions (**1**–**5**).

Stability of isomeric ions 1a, 2a and 3a

Irrespective of whether **1a** or **1a′** was employed for the starting geometry for setting up the calculations on **2a** and **3a** and the corresponding transitions states, **4a** and **5a**, respectively, the same rotamers for these compounds resulted. No further efforts towards obtaining different rotamers or invertamers were made. Since both AM1 and PM3 are known to overestimate the stability of three-and four-membered rings,[37,38] it is not surprising that these methods overestimate (with respect to all *ab initio* methods used) the relative stability of all derivatives of **2** and **3** investigated when compared with the corresponding bicyclic ions, **1**.

All *ab initio* results predicted **1a** to be much more stable than either of the half-opened cationic species, **2a** and **3a** (see Table 3). Surprisingly, it appears that the primary aziridinylmethyl cation (**2a**) is more stable than is the secondary 3-azetidinyl cation, **3a**. This observation may be the result of hyperconjugative effects[42] by the aziridine ring on the primary carbocation (see below) and/or strain imparted by incorporation of the sp^2 center in the already strained four-membered ring in **3a**.

Further examination of the data in Table 3 with respect to the basis sets and level of theory is instructive. At the Hartree–Fock level, medium- to high-level basis sets (*i.e.* 6–31G* to 6–311G**) provide nearly constant energy differences between all bicyclic ions (**1a**–**f**) and the corresponding isomers of **2** and **3**, although there is a slight tendency for this difference to decrease with larger basis sets. The energy differences obtained with different basis sets are sufficiently small that one wonders whether the costs associated with the larger basis sets were justified. With respect to medium and large basis sets, the small 3–21G basis set tends to underestimate the energy differences between the ring-opened ions (**2** and **3**) and the bicyclic ions. It performs better for differences between aziridinylmethyl cations (**2**) and bicyclic ions (**1**) than for differences between azetidinyl cations (**3**) and the bicyclic ions.

Table 2. Calculated Møller–Plesset (MP2) energies for **1, 2, 3, 4** and **5**[a]

	Optimized		Single-point	
Compound	6–31G*	6–311G**	6–31G**	6–311G**
1a	−210.93521	−211.06084	—	−211.05899
1a′	−210.93263	−211.05820	—	−211.05616
1b	—	—	—	−250.26362
1c	—	—	—	−250.26552
1d	—	—	—	−250.26921
1e	—	—	−441.34193	—
1f	—	—	−441.34336	—
2a	—	—	—	−211.01626
2b	—	—	—	−250.23286
2c	—	—	—	−250.23261
2e	—	—	−441.33239	—
2f	—	—	−441.33172	—
3a	−210.86056	−210.98799	—	−210.98550
3b	—	—	—	−250.19319
3c	—	—	—	−250.18889
3d	—	—	—	−250.21448
4a	—	—	—	−211.00653
4b	—	—	—	−250.22156
4c	—	—	—	−250.22532
4e	—	—	−441.32335	—
4f	—	—	−441.32843	—
5a	−210.85039	−210.97696	—	−210.97759
5b	—	—	—	−250.18539
5c	—	—	—	−250.18162
5d	—	—	—	−250.21049

[a] Calculations not performed on **2d, 3e, 3f, 4d, 5e** and **5f**. All MP2 calculations, regardless of whether optimizations or single-point calculations were performed starting with HF/6–311G** results. Since Spartan 4.0 does not support frequency calculations at the MP2 level, no zero-point corrections were made.

When electron correlation (MP2) is included, the differences between the bicyclic ion and the corresponding derivatives of **2** and **3** are significantly larger than at the Hartree–Fock level, irrespective of whether single-point calculations or optimizations were performed. In view of the much higher *ab initio* energies associated with **2a** and **3a**, it is not surprising that no ring contraction products were observed in the solvolysis of the tosylate of 1-*tert*-butylazetidin-3-ol.[32]

C-2-substituted bicyclic ions (1b, 1c, 1e and 1f)

Two diastereomeric 2-substituted azabicyclic ions are possible, differing in configuration at C-2, either *trans* to the *N*-methyl (pseudoaxial, **1b** and **1e**) or *cis* to it (pseudoequatorial, **1c** and **1f**), (see Fig. 6). All semi-empirical and *ab initio* calculations indicate that pseudoequatorial substituents are more stable than are pseudoaxial ones substituents (see Tables 1, 2 and 4).

Table 3. Calculated energies[a] of **2** and **3** relative to corresponding **1**[b]

	Optimized Hartree–Fock						Optimized MP2		
Compound	AM1	PM3	3–21G	6–31G*	6–31G**	6–311G**	6–31G*	6–311G**	Single-point MP2[c]
2a	−1.09	3.82	—[d]	22.23	22.28	20.80	—[d]	—[d]	26.81
2b	−11.44	−4.91	11.18	13.55	13.51	12.51	—	—	19.30
2c	−11.56	−5.57	13.21	14.35	14.34	13.31	—	—	20.65
2e	−23.07	−15.73	−3.32	−3.28	−3.10	−3.12	—	—	5.99[e]
2f	−23.69	−17.96	−1.45	−2.88	−2.63	−2.74	—	—	7.30[e]
3a	2.52	−7.53	28.25	33.92	33.81	32.65	46.84	45.71	46.12
3b	6.15	−2.92	26.53	32.42	32.31	31.17	—	—	44.20
3c	6.86	−1.82	29.11	36.21	36.21	35.18	—	—	46.89
3d	−6.94	−15.46	17.42	21.70	21.50	20.32	—	—	34.34

[a] Energy differences are in kcal mol^{-1} and are without zero-point corrections.
[b] Calculations not performed on **2d, 3e** and **3f**.
[c] Single-point calculations are with respect to the HF/6–311G** geometry. Unless noted otherwise, these are MP2/6–311G** results.
[d] Incorrect structure obtained on geometry optimization.
[e] MP2/6–31G**//HF/6–311G**.

Table 4. Energy differences between diastereomeric cations[a]

Difference	Optimized Hartree–Fock						Single-point SP MP2[b]
	AM1	PM3	3–21G	6–31G*	6–31G**	6-311G**	
1b–1c	0.3	0.3	2.09	1.46	1.48	1.47	1.19
1e–1f	0.5	0.9	1.41	1.21	1.20	1.23	0.90[c]
2b–2c	0.4	1.0	0.05	0.66	0.65	0.67	−0.16
2e–2f	1.1	3.2	−0.46	0.81	0.74	0.86	−0.42[c]
3b–3c	−0.4	−0.8	−0.50	−2.34	−2.42	−2.54	−2.70
4b–4c	0.9	1.2	3.07	2.74	2.76	2.73	2.36
4e–4f	1.4	1.9	4.50	4.11	4.11	4.30	3.19[c]
5b–5c	1.8	1.3	−1.39	−1.47	−1.46	−1.40	−2.37

[a] Energy differences are in kcal mol^{-1} and without zero-point corrections.
[b] Single-point calculations are with respect to the HF/6–311G** geometry. Unless noted otherwise, these are MP2/6–311G** results.
[c] MP2/6–31G**//HF/6–311G**.

Diastereomeric energy differences calculated by semiempirical methods are substantially smaller than those calculated by all *ab initio* methods, where the Hartree–Fock differences are larger than those calculated by single-point Møller–Plesset theory. While the diastereomeric energy differences are similar in both direction and magnitude to analogous differences in six-membered ring systems,[43] in the absence of zero-point energy calculations, they should probably be viewed with some suspicion (see above).

3-Azetidinyl cations (3a, 3b, 3c and 3d)

Initial ionization of the starting azetidinyl compounds possessing replaceable functional groups at the 3-position could proceed by either of two distinct mechanisms: direct ionization to the 3-azetidinyl cations or anchimeric assistance involving the lone pair of electrons on the nitrogen atom resulting in the bicyclic ions. If initial ionization of the azetidinyl compounds to 3-azetidinyl cations occurs, there are three stereochemical possibilities. If the azetidinyl cations are relatively long-lived, the *cis–trans*-2-substituted compounds should yield the same mixture of *cis–trans*-azetidinols. If the azetidinyl cations are short-lived, one might again expect a *cis–trans* mixture with different ratios of products from the *cis*- and *trans*-2-substituted azetidinyl starting materials as the result of ion-pair formation. The remaining possibility also involves short-lived intermediate azetidinyl cations, which collapse to bicyclic ions before any measurable solvolysis products are formed. The product distribution from the latter azetidinyl cationic mechanism should, like the anchimeric assistance mechanism, yield retention of configuration.

Both the 2-methyl[33] and 2-phenyl[34] compounds yield what appears to be stereospecific retention of configuration. These results require that bicyclic ions, whether formed by anchimeric assistance or by collapse of the 3-azetidinyl cations, are important intermediates in the solvolysis of azetidines with replaceable functional groups in the 3-position. The non-linear Arrhenius plot (obtained in the kinetic investigation of the solvolysis of the tosylate of *trans*-1-*tert*-butyl-2-methylazetidin-3-ol) suggests two competing reactions with differing activation energies leading to the same product.[33] If this interpretation is correct, these differences should be apparent in the initial ionization energies rather than the isomerization calculations presented in this paper. Our *ab initio* investigation of the ionization mechanism is well under way.

Semiempirical methods disagree on the relative stability of **1a–c** and **3a–c** but agree that the 3-methyl-3-azetidinyl cation, **3d**, is more stable than the corresponding bicyclic ion, **1d**. All *ab initio* data (see Tables 1–3) indicate that azetidinyl cations (**3a–d**) are substantially less stable than are the corresponding bicyclic cations. However, these data, particularly when coupled with transition state data (see below), do not unequivocally preclude the competitive solvolytic formation of both **1c** and **3c** and subsequent collapse of **3c** to **1c** before it can react with solvent.

Semiempirical calculations on the 1,3-dimethyl bicyclic and azetidinyl cations (**1d** and **3d**, respectively) suggest that the 3-methyl substituent sufficiently stabilizes **3d** that the reaction could occur without the presence of **1d**, while all *ab initio* calculations (see Tables 1–3) suggest that although **3d** is relatively more stable than is **3a**, it remains much less stable than the bicyclic ion, **1d**. Solvolysis reactions for 3-methylazetidinyl compounds of the type expected to produce these ions are unknown.

All *ab initio* transition state (**5**) energies (Table 5) between **1a–d** and **3a–d** are sufficiently large as to suggest that conversions of **1** to **3** are unlikely. At the same time, these energies are only slightly (5–7 kcal mol^{-1} at the Hartree–Fock level and 2–5 kcal mol^{-1} at the MP2 level, without zero-point corrections, see above) above those of **3**, such that the conversion of **3** to **1** would be extremely likely, particularly since **3**, if formed by direct ionization, would initially possess much excess energy (from achieving the

Table 5. Transition state energies relative to bicyclic ions[a]

	Optimized Hartree–Fock						Optimized MP2		
Compound	AM1	PM3	3–21G	6–31G*	6–31G**	6–311G**	6–31G*	6–311G**	Single-point MP2[b]
4a	18.4	13.8	—[c]	28.56	28.66	28.02	—	—	32.92
4b	10.6	6.4	16.54	20.25	20.24	19.64	—	—	26.39
4c	10.0	5.5	15.56	18.97	18.97	18.38	—	—	24.03
4e	5.1	1.0	7.97	9.20	9.36	9.43	—	—	11.66[d]
4f	4.3	0.3	4.89	6.30	6.45	6.37	—	—	9.37[d]
5a	14.5	6.4	34.83	40.40	40.49	39.51	53.23	52.64	51.08
5b	17.2	9.0	32.64	38.97	39.06	38.17	—	—	49.09
5c	15.6	8.0	36.11	41.89	42.00	41.04	—	—	52.65
5d	7.1	1.3	23.24	27.83	27.73	26.73	—	—	36.85

[a] Energies in kcal mol^{-1} and are without zero-point correction.
[b] Single-point calculations are with respect to the HF/6–311G** geometry. Unless noted otherwise, these are MP2/6–311G** results.
[c] Not reported since **2a** optimization gave incorrect structure.
[d] MP2/6–31G**//HF/6–311G**.

solvolysis transition state). Until our investigation of the mechanistic of ionization is completed, the mechanistic details of bicyclic ion formation must still be considered ambiguous.

In order to verify that the calculated transition states do indeed correspond to **5**, frequency calculations were conducted. As expected, single negative normal vibrational modes (see Table 6) were calculated (Spartan 4.0 does not support vibrational calculations at the MP2 level) and animated. Animation of the negative 'frequency' (which corresponds to vibration along the reaction coordinate) indicated the expected vibration along the *N—C-3* bond with the molecule undergoing concerted ring and nitrogen inversion as this distance increased (see Fig. 8).

Aziridinylmethyl cations (2a, 2b, 2c, 2e and 2f)

No ring-contracted products were observed in the solvolyses of tosylates of 1-*tert*-butyl-3-azetidinol,[32] 1-*tert*-butyl-2-methyl-3-azetidinol (either *cis* or *trans*),[33] or the mesylate of *cis*-1-cyclohexyl-2-phenyl-3-azetidinol,[34] but ring-contracted products were observed in the solvolysis of the mesylate of *trans*-1-cyclohexyl-2-phenyl-3-azetidinol.[34] Ring contraction to aziridinyl compounds requires the existence of **1**, whether formed directly by anchimeric assistance or by collapse of **3** to **1**.

Ring opening of **1b** by rupture of the *N—C-2* bond would yield **2b**, whereas opening of **1c** would yield **2c**. All semiempirical and *ab initio* calculations are in agreement with expectations and predict the stabilizing influence of methyl and, particularly, phenyl substituents on aziridinylmethyl cations (see Table 3 and compare with **2a**). While the semiempirical results suggest that both **2b** and **2c** are more stable than the corresponding bicyclic ions, all *ab initio* results are in agreement with experiment, predicting that the **1b** and **1c** are more stable than **2b** and **2c**.

A recent study[44] on the analogous 2-methyl-l-oxabicyclobutonium ions, 3-oxetanyl cations and one of the possible oxiranylmethyl cations reached the same conclusions that we have drawn, namely, that bicyclic ions are more stable than the exocyclic carbocation(s), and much more stable than the monocyclic four-membered rings bearing carbocationic centers at the 3-position.

Table 6. Imaginary transition state vibrational frequencies[a]

Compound	AM1	PM3	3–21G	6–31G*	6–31G**	6–311G**
4a	−500.76	−445.29	—[b]	−319.46	−320.80	−330.25
4b	−462.26	−326.74	−267.08	−278.93	−285.71	−287.24
4c	−441.47	−280.56	−127.65	−155.71	−155.95	−158.50
4e	−452.08	−236.03	−139.28	−244.36	—[c]	—[c]
4f	−455.93	−217.88	−181.54	−242.53	—[c]	—[c]
5a	−379.30	−295.21	−537.60	−559.35	−564.80	−562.69
5b	−383.36	−302.24	−529.60	−529.27	−533.77	−533.20
5c	−336.64	−275.27	−529.31	−549.28	−554.50	−552.71
5d	−366.46	−332.60	−225.92	−233.35	−234.16	−230.46

[a] All frequencies were obtained from Hartree–Fock calculations and are in cm^{-1}; no scaling was performed.
[b] Not reported since **2a** optimization gave incorrect structure.
[c] Not calculated.

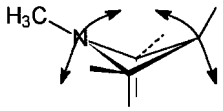


Figure 8. Vibration of the 'imaginary frequency' at the transition state (**5**) between **1** and **3**

The fact that both diastereomeric aziridinyl alcohols were obtained from solvolysis of the *trans*-2-phenyl-3-azetidinyl mesylates seems to point unequivocally to the existence of an aziridinylmethyl carbocationic intermediate for this isomer, while the apparent absence of any aziridinyl products suggests that this is not the case for the *cis*-isomer. Both semiempirical calculations suggest (see Table 3) that **2e** and **2f** are much more stable than are the corresponding **1** isomers, whereas all Hartree–Fock *ab initio* methods predict that both **2e** and **2f** are slightly more stable than the corresponding bicyclic ion. Based solely on the energetics obtained from Hartree–Fock *ab initio* calculations even with large basis sets, significant ring contraction to aziridinyl compounds in the solvolyses[34] of both 2-phenyl mesylates should probably be expected.

Single-point MP2 calculations, however, indicate significantly larger differences between all aziridinylmethyl cations and the corresponding bicyclic cations than at the Hartree–Fock level. Indeed, at the MP2 level all aziridinylmethyl ions were calculated to be less stable than the corresponding bicyclic ions, although the small energy differences between bicyclic ions (**1e** and **1f**) and aziridinylmethyl ions (**2e** and **2f**, respectively) should probably be attainable. On this basis alone, one might expect both 2-phenyl mesylates to yield aziridinyl products.

Both semiempirical and Hartree-Fock *ab initio* calculations indicate that aziridinylmethyl ions **2c** and **2f** are more stable than those from the axial isomers (**2b** and **2e**, respectively). However, MP2 single-point calculations suggest a slight preference for a reversal of stabilities. Whether this is indeed the situation or whether this reversal results from unoptimized calculations, zero-point energy differences and/or solvent effects is currently being investigated.

Transition state (**4**) calculations leading from the bicyclic ions (**1**) to aziridinylmethyl cations (**2**) reflect many of the same effects which were calculated for the aziridinylmethyl cations themselves: *C-2*-methyl and -phenyl substituents produce transition states (and products) which are energetically more favorable than that obtained from **1a** (see Table 5). In agreement with experiment, the transition states for the 2-methyl compounds (**4b** and **4c**) are sufficiently high in energy that one would not expect ring opening of the bicyclic ion. Transition state energies for both 2-phenyl compounds are, however, relatively low in energy (even relative to the bicyclic ions) and might be expected to give some ring contraction to the aziridinylmethyl compounds.

Transition state (**4**) energies for the pseudoaxial substituents are calculated by all methods to be higher than those for pseudoequatorial substituents, as in the bicyclic ions (see Table 4). All methods yield larger differences (between **4** and **1**) in energy between transition states with pseudoequatorial 2-substituents and the corresponding bicyclic ions than with pseudoaxial substituents. Presumably this phenomenon is the result of relief of steric interactions between the *N*-methyl and the *cis* pseudoequatorial 2-substituent. Since these differences are larger with the pseudoequatorial than with pseudoaxial substituents, one is tempted to suggest that the aziridinyl products observed in the solvolysis of the *trans*-2-phenylazetidinyl mesylates result from **1f** (the diastereomer with the lower energy difference). We will later present evidence that **1e** (not **1f**) results from *trans*-2-substitutued azetidinyl compounds by anchimeric assistance. This apparent discrepancy is presumably the result of solvation effects and/or zero-point energy differences and is currently under investigation.

In order to verify that the calculated transition states do indeed correspond to **4**, frequency calculations were conducted. As expected, single negative normal vibrational modes (see Table 6) were calculated (Spartan 4.0 does not support vibrational calculations at the MP2 level) and animated. Animation of the negative 'frequency' indicated the expected vibration along the *N—C-2* bond.

During the analysis of the calculated geometries of the aziridinylmethyl cations, it became apparent that the lengths of some of the bonds varied over a wide range, depending upon the nature of the 2-substituent (see Table 7). Particularly noteworthy are variations within the *N—C-4, C-2—C-3* and *C-3—C-4* bond lengths, which range from about 1.37 to 1.41, 1.35 to 1.45 and 1.53 to 1.71 Å, respectively. The *N—C-4* distance is significantly shorter than the corresponding distance (1.475 Å)[45] in aziridine. Carbon–carbon distances less than 1.40 Å are normally associated with multiple bonding. There are two reasonable explanations.

Table 7. Variation of bond lengths (Å) and angles (°) in aziridinylmethyl cations[a]

Bond	**2a**	**2b**	**2c**	**2e**	**2f**
N—C-4	1.369	1.375	1.375	1.413	1.402
C-2—C-3	1.354	1.384	1.379	1.448	1.435
C-3—C-4	1.713	1.623	1.628	1.526	1.532
C-3—N—C-4	74.44	69.65	69.83	64.64	64.70
N—C-3—C-4	50.35	52.60	52.42	56.78	55.84
N—C-4—C-3	55.21	57.75	57.75	58.58	59.47

[a] The numbering system used is the same as the bicyclic system. All data were obtained by optimizing the geometry employing the HF/6–311G** basis set.

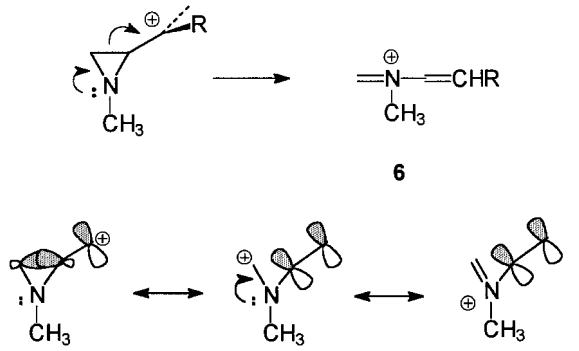


Figure 9. Possible explanations for the abnormal interatomic distance in **2**. The top reaction indicates the structure (**6**) obtained on attempted geometry calculation of **2a** by HF/3–21G(*) and MP2/6–31G* methods. The geometric properties calculated are vastly different from those of **2a**. The bottom scheme represents the hyperconjugative model for stabilization of **2a**

One possible explanation is that the ions are not really the aziridinylmethyl ions at all, but are derivatives of **6**, (see Fig. 9). There are several factors which argue against this. The fact that aziridinylmethyl carbinols were obtained with the mesylate of the *trans*-2-phenylazetidinol is indicative of the aziridinylmethyl cation, at least for this compound. Bond angle data (Table 7) are consistent with **2** and clearly inconsistent with **6**. It should be noted, however, that attempts to optimized **2a** by HF/3–21G* and MP2/6–31G* calculations afforded **6** rather than **2a**.

The other explanation is possibly more controversial and involves hyperconjugation, (see Fig. 9). Aziridinylmethyl cation **2a** is a primary carbocation and must therefore suffer from poor stability. Additional stability can be gained through overlap of its *p*-orbital with the bent *C-3—C-4* bond of the aziridine ring.[42] This would account for the short *N—C-4* and *C-2—C-3* bonds and the long *C-3—C-4* bonds calculated. When substituents are present on *C-2* the stability of the carbocationic center is increased, requiring less contribution from hyperconjugation, accounting for less shortening of the *N—C-4* and *C-2—C-3* bonds and less lengthening of the *C-3—C-4* bonds.

In summary, semiempirical methods often give results which are contradictory to experimental (and *ab initio*) results; however, these methods correctly predict the stabilizing influence of methyl and phenyl substituents on possible carbocationic intermediates and perform well in predicting relative stabilities of diastereomeric ions and for serving as starting geometries for *ab initio* calculations. *Ab initio* results, in agreement with experimental results, predict than 1-azabicyclo[1.1.0]butyl cations are important intermediates formed by solvolyses of azetidinyl compounds possessing a replaceable functional group at the 3-position. These results also indicate that the 3-azetidinyl cations are much less stable than the bicyclic ions and, if directly formed in the ionization step, should rapidly convert to the bicyclic ions. Finally, these results indicate that aziridinylmethyl cations are much more stable than are 3-azetidinyl carbocations and that they are, with the exception of those resulting from ring opening of the 2-phenyl bicyclic ions, sufficiently less stable than the corresponding azabicyclic ions and unlikely to be formed.

Supplementary Material

Spartan ASCII files can be obtained by contacting Robert Higgins.

Acknowledgments

Financial support provided by the National Institutes of Health (Grant No. S06GM08206) and the North Carolina Biotechnology Center is gratefully acknowledged.

REFERENCES

1. C. C. Howard and W. Markwald. *Chem. Ber*. **32,** 2031–2035 (1899).
2. R. M. Acheson. *An Introduction to the Chemistry of Heterocyclic Compounds*, p. 35. Wiley–Interscience, New York (1960).
3. E. Testa, L. Fontanella and V. Aresi. *Liebigs Ann. Chem.* **676,** 151–160 (1964).
4. R. H. Higgins. MS Thesis, Ohio University (1967).
5. A. Bottini and J. D. Roberts. *J. Am. Chem. Soc.* **80,** 5203–5208 (1958).
6. E. Testa, L. Fontanella, G. F. Cristiani and L. Mariani. *Helv. Chim. Acta.* **42,** 4370–4379 (1959).
7. E. Testa, L. Fontanella and G. F. Cristiani. *Liebigs Ann. Chem.* **626,** 114–120 (1959).
8. E. Testa and L. Fontanella. *Liebigs Ann. Chem.* **660,** 118–134 (1962).
9. E. Testa and L. Fontanella. *Liebigs Ann. Chem.* **661,** 187–193 (1963).
10. E. Testa, L. Fontanella and M. Bovara. *Liebigs Ann. Chem.* **671,** 97–106 (1964).
11. D. H. Wadsworth. *J. Org. Chem.* **32,** 1184–1187 (1967).
12. N. H. Cromwell and E. Doomes. *Tetrahedron Lett.* 4037–4042 (1966).
13. E. Doomes and N. H. Cromwell. *J. Org. Chem.* **34,** 310–317 (1969); R. H. Higgins, E. Doomes and N. H. Cromwell. *J. Heterocycl. Chem.* **8,** 1063–1067 (1971).
14. E. Doomes and N. H. Cromwell. *J. Heterocycl. Chem.* **6,** 153–158 (1969).
15. M. C. Eagen, R. H. Higgins and N. H. Cromwell. *J. Heterocycl. Chem.* **8,** 851–853 (1971).
16. R. M. Rodebaugh and N. H. Cromwell. *J. Heterocycl. Chem.* **6,** 439–440 (1969).
17. R. M. Rodebaugh and N. H. Cromwell. *J. Heterocycl. Chem.* **5,** 309–311 (1968).
18. R. M. Rodebaugh and N. H. Cromwell. *J. Heterocycl. Chem.* **6,** 435–437 (1969).
19. R. M. Rodebaugh and N. H. Cromwell. *J. Heterocycli. Chem.* **8,** 19–24 (1971).
20. V. R. Gaertner. *Tetrahedron Lett.* 5919–5922 (1968).
21. V. R. Gaertner. *J. Org. Chem.* **32,** 2972–2976 (1967).
22. V. R. Gaertner. *J. Org. Chem.* **35,** 3952–3959 (1970).
23. T.-Y. Chen, T. Sanjiki, H. Kato and M. Ohta. *Bull. Chem. Soc. Jpn.* **40,** 2401–2404 (1967).

24. R. H. Higgins and N. H. Cromwell. *J. Org. Chem.* **37,** 2918–2920 (1972).
25. W. R. Vaughn, R. S. Klonowski, R. S. McElhinney and B. B. Millward. *J. Org. Chem.* **26,** 138–144 (1961).
26. H. Jenkins and A. D. Cale. *Ger. Offen.* 1 932 219 (1970);*Chem. Abstr.* **72,** 100478s (1970).
27. B. J. Gaj and D. R. Moore. *Tetrahedron Lett.* 2155–2157 (1967).
28. R. H. Higgins, Q. L. Eaton, L. Worth, Jr and M. V. Peterson. *J. Heterocycl. Chem.* **24,** 255–259 (1987).
29. R. H. Higgins. *J. Heterocycl. Chem.* **24,** 1489–1491 (1987).
30. R. H. Higgins, M. R. Watson, W. J. Faircloth, Q. L. Eaton and H. Jenkins, Jr. *J. Heterocycl. Chem.* **25,** 383–387 (1988).
31. Imperical Chemical Industries. *Jpn. Kokai 75* 21 13,*Chem. Abstr.* **86,** P21001m (1977); Laboratorio Martin Cuatress, *Span. Pat.* 453 367; *Chem. Abstr.* **86,** P72437 (1977). H. Tucker. *Br. Pat.* 1 456 525; *Chem. Abstr.* **87,** P5625p (1977).
32. R. H. Higgins, F. M. Behlen, D. F. Eggli, J. H. Kreymborg and N. H. Cromwell. *J. Org. Chem.* **37,** 524– 526 (1972).
33. R. H. Higgins and N. H. Cromwell. *J. Am. Chem. Soc.* **95,** 120– 124 (1973).
34. T. Okutani and K. Masuda. *Chem. Pharm. Bull.* **22,** 1498– 1505 (1974).
35. R. H. Higgins, W. J. Faircloth, R. G. Baughman and Q. L. Eaton. *J. Org. Chem.* **59,** 2172– 2178 (1994).
36. R. H. Higgins and B. Kidd. Paper presented at the 203rd National Meeting of the American Chemical Society, San Francisco, CA, April 1992 (Abstr. No. ORGN 0224).
37. J. J.P. Stewart. in *Reviews in Computational Chemistry*, edited by K. B. Lipkowitz and D. B. Boyd, Vol. 1, Chapt. 2, pp. 68– 73. VCH, New York (1990).
38. M. C. Zerner. in *Reviews in Computational Chemistry*, edited by K. B. Lipkowitz and D. B. Boyd, Vol. 2, Chapt. 8, pp. 342– 347. VCH, New York (1991).
39. *Spartan 4.0.* Wavefunction, Irvine, CA.
40. *HyperChem 4.5.* HyperCube, Waterloo, ON, Canada.
41. R. H. Higgins. *J. Chem. Educ.* **72,** 703– 705 (1995).
42. A. E. Polland, R. C. Badger and N. H. Cromwell. *Tetrahedron Lett.* 4369– 4375 (1965), and references cited therein.
43. E. L. Eliel, S. H. Wilen and L. N. Mander. *Stereochemistry of Organic Compounds*, pp. 690– 700, 740– 754. Wiley– Interscience, New York (1994).
44. M. M. Francl, G. Hansell, B. P. Patel and C. S. Swindell. *J. Am. Chem. Soc.* **112,** 3535– 3539 (1990).
45. W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople. *Ab Initio Molecular Orbital Theory*, p. 169. Wiley-Interscience, New York (1986).

