Atomic Motions and Protonation Stereochemistry in Nucleophilic Additions to Bicyclobutanes[1]

Shmaryahu Hoz,* Carmela Azran, and Ariel Sella

Contribution from the Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel 52900

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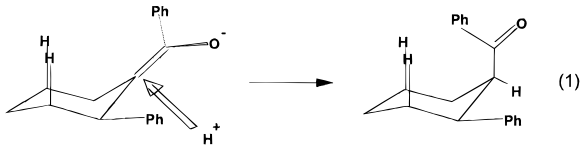
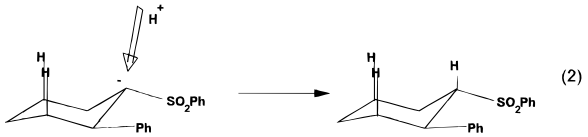
Abstract: Several nucleophilic reactions on bicyclobutanes activated at the bridgehead carbon by electron withdrawing groups (SO_2Ph, CO_2Me, COPh, and CN) were performed in MeOH. In all cases, the *less* stable 1,3-disubstituted cyclobutanes isomer was preferentially obtained (compared to the equilibrium ratio). The results for the two charge localizing groups CN and SO_2Ph oppose the existing knowledge regarding the protonation stereochemistry of such carbanions. *Ab initio* calculations (6-31G*) have shown that as the nucleophile approaches the bicyclobutane, the bridgehead activating group moves inward toward an axial position. With a charge localizing group (CN and S(H)-SO_2) the carbanion remains pyramidal, whereas with C(H)═O as an activating group, the carbanion is nearly planar. It is suggested therefore that under conditions where the carbanion undergoes rapid protonation, it is trapped in its initial pyramidal geometry. Whereas, in cases where the lifetime of the carbanion is long enough to allow appreciable equilibration, protonation may result in a different product distribution. This hypothesis was tested by slowing down the protonation rates. As a result, the *more* stable isomer was indeed preferentially obtained.

As early as 1954, Zimmerman had shown that protonation of enolates in cyclic systems, such as 1-benzoyl-2-phenylcyclohexane (eq 1) and the corresponding nitronate, takes place from the least hindered equatorial side to give preferentially the thermodynamically *less* stable isomer.[2]



(1)

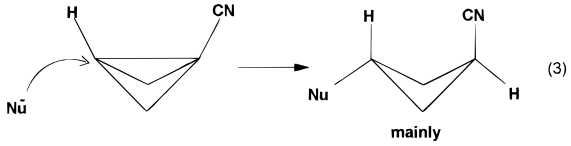
Since then, this phenomenon has been demonstrated many times in similar systems.[3] On the other hand, in the case of the analogous sulfone activated system, the *more* stable isomer is preferentially obtained (eq 2).[4]



(2)

Based on the above discrepancy, Zimmerman suggested that differentiation should be made between electron withdrawing groups (EWG), which delocalize the charge away from the carbon (e.g., carbonyl and nitro groups) and groups which stabilize the negative charge by exerting mainly an inductive effect (e.g., sulfone).[3] When the EWG is a charge delocalizing one, the carbanion will be nearly planar at the transition state. In contrast, in the case of a localizing EWG, the geometry around the carbon carrying the negative charge will be pyramidal, and the EWG may assume either an axial or an equatorial position at the transition state. Due to the 1,3-diaxial interactions the EWG will prefer an equatorial position. Therefore, protonation will take place preferentially from the axial direction, leading to the formation of the more stable isomer. In the case of a transition state with a nearly planar carbanion (EWG = NO_2, RC═O, etc.), 1,3-diaxial interactions with the EWG are absent. Hence, the proton donor will approach the carbanion from the less hindered equatorial side, pushing the EWG to the axial position and ultimately leading to the preferential formation of the less stable isomer.

In contradistinction to the behavior of the sulfonyl group in the system studied by Zimmerman, in the cyclobutyl carbanion generated by nucleophilic attack on bicyclobutane, CN, which is also a localizing EWG,[5] induces mainly equatorial protonation to give preferentially the less stable isomer (eq 3).[6,7]



(3)

In the present work it was established that CN is not unique in this sense and that the sulfonyl group also exhibits, in the cyclobutane system, a behavior similar to that of delocalizing EWGs. Thus, both the cyano and the sulfone groups in cyclobutane show preference for equatorial protonation from the less hindered (equatorial) side in an apparent violation of

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) Presented in part at the Swedish-Israeli Symposium on New Trends in Organic Chemistry; Stockholm, August 14, 1994.

(2) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, 79, 6554. Zimmerman, H. E.; Thomas, E. N. *J. Am. Chem. Soc.* **1957**, 79, 6559.

(3) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263.

(4) Zimmerman, H. E.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1958**, *80*, 3060.

(5) Bell, R. P. In The Proton In Chemistry; Chapman and Hall: London, 1973; Chapter 10. Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326. Fujio, M.; McIver, R. T., Jr.; Taft, R. W. *J. Am. Chem. Soc.* **1981**, *103*, 4017. Hibbert, F. In The Chemistry of Functional Groups, Supplement C; Patai, S., Ed.; Wiley: New York, 1982; Chapter 17. Lien, M. H.; Hopkinson, A. C.; McKinney, M. A. *J. Mol. Struct. Theochem.* **1983**, *105*, 37. Delbeck, F. *J. Org. Chem.* **1984**, *49*, 4838. Abbotto. A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 444, 449.

(6) In nucleophilic attacks on bicyclobutane, the nucleophile always approaches the molecule from the equatorial direction. For a review of the chemistry of bicyclobutane, see: Hoz, S. In The Chemistry of the Cyclopropyl Group; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 19.

(7) In 1,3-disubstituted cyclobutane, cis substitution is more stable, since the two bulky substituents can simultaneously adopt the cis diequatorial geometry. Moriarty, R. M. *Top. Stereochem.* **1974,** *8,* 271.

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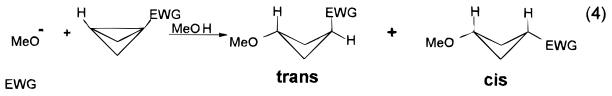
the rule suggested by Zimmerman. Using a combination of computational and experimental techniques, this paper will show that the origin of the deviation of the cyclobutane system from the general pattern outlined by Zimmerman stems from concerted atomic (or group) motions in the course of nucleophilic attacks on bicyclobutane.

Results (Experimental)

Reactions with MeO^- in MeOH. The stereochemistry of the addition of MeO^- in MeOH to the first three substrates in eq 4 was determined at several temperatures under kinetic and thermodynamic control conditions.



EWG	trans	cis
SO_2Tol	**1 s**	**2 s**
COPh	**1 k**	**2 k**
CO_2Me	**1 e**	**2 e**
CN	**1 n**	**2 n**

The reactions of the sulfone (**1s**) and the ketone (**1k**) gave a quantitative yield of a mixture of cis and trans addition products. The ester (**1e**) gave the two isomers of the addition product, which, at high conversion percentages, were accompanied by some unidentified compounds. Therefore, for the reaction of **1e**, product distribution was determined from the first 30% of the reaction, where no side products were observed.

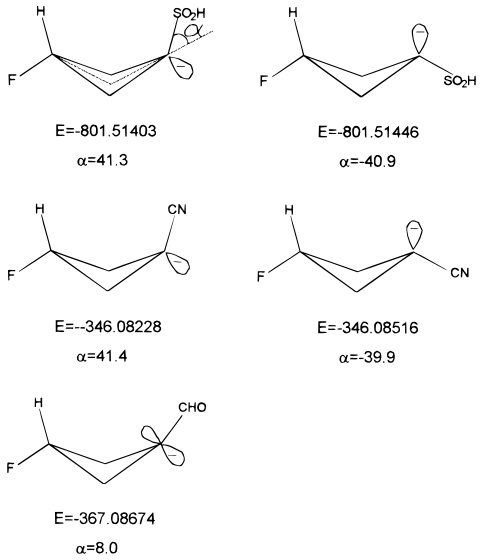
Throughout the course of the reaction of the sulfone derivative **1s**, the ratio of cis/trans isomers in the product **2s** remains constant (0.13 ± 0.01) at 60 °C. Incubation of the product mixture for 14 days with 0.675 M MeO^- at 60 °C raised this ratio to ca. 0.5. A stable equilibrium composition in which the cis/trans ratio was found to be 1.29 ± 0.06 was achieved only in *t*-BuO^-/*t*-BuOH.

Equilibration of the product stereoisomers was fast, compared to the addition rate for the two carbonyl derivatives **1e** and **1k**. In both cases, the kinetic controlled ratio was determined by an extrapolation to $t = 0$. For **2e,** the cis/trans ratio at $t = 0$ at 60 °C was 0.85 ± 0.1, and the ratio leveled off at a value of 2.2 ± 0.1. For **2k**, the ratios at $t = 0$ were 1.5 and 2.0 (± 0.1) at 0 °C and 25 °C, respectively. The final equilibrium ratios were 3.55 and 2.9 (± 0.05) at 0 °C and 25 °C, respectively. Depicted in Table 1 are some of these results, along with the previously reported data for the cyano activated system **1n**.[8] The data show that in all cases there is a preference to produce more of the less stable isomer, compared to the thermodynamic ratio. This is much more pronounced for the localizing groups (CN and SO_2Ph) than for the carbonyl derivative (COPh and COOMe).

The reactions of bicyclobutyl phenylsulfone (**1s′**) and **1n** with PhS^- and $PhSe^-$ as nucleophiles were studied at room temperature in DME (dimethoxyethane) solutions. To these solutions, variable amounts of MeOH or trifluoroethanol (TFE) were added. The reactions went to completion in a matter of seconds (or less) in pure DME. The presence of alcohol slowed the reaction rates with both nucleophiles. For example, in pure MeOH with PhS^- as the nucleophile, a 90% conversion were obtained only after 10 min. The percent of the trans isomer (i.e., equatorial protonation) was determined as a function of the alcohol concentration. As can be seen from the data in Table 2, the addition of alcohol induced an increase in the fraction of the trans isomer.

(8) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc.* **1980**, *102*, 2340.

Chart 1[a]



[a] Energies in au and α in deg.

The cis and trans isomers of the reaction adducts **(3s′** and **3n** for the PhS adducts and **4s′** and **4n** for the PhSe adducts) were equilibrated in *t*-BuOH−*t*-BuO^-. The equilibrium ratios were 1.24 for **3s′**, 1.23 for **4s′**, 1.65 for **3n,** and 1.51 for **4n,** in favor of the cis isomer. For the new compounds, the structural (cis−trans) assignment was based on the equilibrium ratio, as well as on the NMR data.[9]

Computational Results and Discussion

All calculations were performed at the 6-31G* level using Gaussian 92.[10] Although, in the experimental studies, MeO^-, PhS^- and $PhSe^-$ were employed as nucleophiles, for obvious reasons, F^- was used as the nucleophile in the computational work.

Since the stereochemistry of the products is determined by protonation of the carbanion, the first step was to compute the optimal geometry of the CN, SO_2H, and CHO activated fluorocyclobutyl carbanions.

Puckered 3-fluorocyclobutyl rings with a pyramidal carbanion can exist as four possible isomers (with F and EWG being axial−axial, equatorial−equatorial; axial−equatorial, and equatorial−axial). However, attempts to optimize structures with F at an axial position ended in a ring flip, which relocated the F atom at an equatorial position.

At the optimized geometry, the CHO activated carbanion was found to be essentially planar. For the CN and SO_2H activated systems, two stationary structures were obtained, and in both cases the more stable geometry was the one in which the activating group assumed an equatorial position.

Chart 1 shows the calculated pyramidality (α) of the corresponding model compounds (the pyramidality is defined as the angle formed between the C1−C2−C4 plane and the C1−EWG bond vector).

Examination of the data in Table 1 shows that the essentially planar carbonyl activated systems, **1e** and **1k**, have shown, in

(9) The hydrogens on the 1 and 3 carbons are shifted to lower fields when they are cis to an electronegative groups. Hoz, S.; Livneh, M.; Cohen, D. *J. Org. Chem.* **1986**, *51*, 4537 (see also ref 16 below and references cited therein).

(10) Gaussian 92, Revision C.; Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gassian, Inc.: Pittsburgh, PA, 1992.

Table 1. Kinetic and Thermodynamic Cis/Trans Ratio for the Reaction of **1** with MeO^- in MeOH

	cis/trans ratio		
reactant	kinetic	thermodynamic	rel ratio
1s	0.13 ± 0.01[a]	1.3 ± 0.06[b]	10.0
1e	0.85 ± 0.1[c]	2.2 ± 0.1[c]	2.6
1k	1.5 ± 0.1[d]	3.55 ± 0.05[d]	2.4
	2.0 ± 0.1[e]	2.9 ± 0.05[e]	1.5
1n[f]	0.28	2.1	7.2

[a] In the range of 60 °C. [b] In *t*-BuOH. [c] At 60 °C. [d] At 0 °C. [e] At 25 °C. [f] Data from ref 8.

agreement with the data obtained by Zimmerman, a small preference to give more of the less stable isomer compared with the thermodynamic distribution. The cyano and sulfone derivatives, which are much more pyramidal, display a much higher preference in the same direction.

The results of the latter systems cannot be predicted on the basis of Zimmerman's rules. In the cyclohexyl system, the average ratio was ca. 3, in favor of the thermodynamically *more* stable isomer, whereas, in the reactions in MeOH (this study), the *less* stable isomer was preferentially obtained in ratios ranging from 8 to 3.5 (Tables 1 and 2).

One could have argued that for the CN and SO_2 cyclobutane derivatives, product distribution is determined, as in the case of enolate (and nitronate), by the differential ease of protonation on the two faces of the carbanion. The differences between the two faces in the sp^3 hybridized carbanions are more pronounced than in the case of sp^2 carbanions. Therefore, an equatorial approach will be even more preferred over the axial one than in the nearly planar C═O activated carbanion. This explanation can, however, be ruled out because first, as was pointed out by Zimmerman, placing the large bulk of the sulfonyl group in the transition state at the axial position and the proton donor at an equatorial one is energetically less favored. Second, since the sulfonyl group is much bigger than the cyano group, one would have expected much more equatorial protonation in the case of the cyano derivative. Yet, as can be seen from Table 1, the fraction of the equatorial protonation (trans isomer) is much larger for the sulfonyl group.

The most plausible explanation is that the nucleophilic attack on the cyano and sulfone activated bicyclobutanes produces the carbanions in a pyramidal geometry which places the EWG at the axial position. Protonation by the solvent (MeOH), to a large extent, traps the carbanions before they undergo complete equilibration by pyramidal inversion.

In order to determine that, indeed, the initial geometry in which the carbanions are formed is such that the EWG is in an axial position, F^- was located at various distances along the line of attack, and the motion of the central atom in the activating groups was followed as a function of the F^- approach. In order to avoid ion−dipole complexes, where the nucleophile is

Table 2. Percents of 2-Trans (Equatorial Protonation) as a Function of [ROH] in the Reaction of **1s** and **1n**

	percent of the trans isomer							
substrate	**1s′**					**1n**		
nucleophile	PhSe		PhS			PhSe		PhS
ROH	MeOH	TFE	MeOH	TFE		MeOH	TFE	MeOH
[ROH], M					[ROH], M			
0.01	32.5	32.5	30.9	30.9	0.01	48.7	48.7	47.0
0.035	32.4		30.8		0.045		48.8	
0.084	32.6		31		0.097		48.8	
0.134	33.3		31.6		0.149		49.0	
0.158	34.5		32.2		0.164	48.8		
0.257	35.8		32.9		0.184		49.7	
0.288		37.7		39.2	0.219		50.3	
0.405	37.7		34.1		0.257	48.9		
0.504	38.5		35.1		0.319	49.0		
0.566		42.6		43.5	0.319			47.2
0.844		45.5		45.5	0.358		51.4	
0.998	41.7		39.2		0.412	48.9		
1.492			43.5		0.504	49.7		
1.678		53.5		53.5	0.628	50.5		
1.986	48.8		46.5		0.69	50.5		
2.79		65.5			0.705		54.5	
2.79				60.8	0.936			47.3
3.962	57.4		54.5		1.226		57.4	
4.736		73.8		70.6	1.245	51.7		
5.938	62.3		60.8		2.171	53.1		50.7
6.96		84.7		81.5	2.443		61.1	
7.914			64.9		4.333	57.0		55.1
8.902	68.3				4.354		67.1	
9.462		92.5		89.9	7.111			58.9
11.866			71	95.1	7.42	60.0		
12.242		95.4			8.176		78.9	
12.36	73.3				10.435		86.1	
14.83			74.4		10.508			62.4
16.312	78.3				10.816	64.0		
18.157			77.5		12.694		91.3	
19.77	81.1				13.595			65.5
21.252			81.1		14.511	67.0		
23.228	83.8				16.991			68.6
24.71			82.9		18.525	71.0		
					20.696			72.3
					23.166	74.8		
					24.71			74.8

Table 3. Energies and Structural Parameters as a Function of F^- Approach to Activated Bicyclobutanes[a]

C−F distance, Å	pyramidality, α	bridge bond length, Å	energy, au
	EWG=**SO_2H**		
∝	10.0	1.47	−702.27121
2.5	14.0	1.517	−801.46691
2.2	22.0	1.606	−801.46692
2	33.0	1.742	−801.46628
1.8	41.5	1.914	−801.47186
1.7	43.1	1.985	−801.47726
1.6	43.8	2.041	−801.48271
1.394	41.3	2.112	−801.51403
	EWG=**CN**		
∝	9.7	1.478	−246.61423
2.5	12.2	1.522	−346.05158
2.2	17.2	1.581	−346.04836
2	25.3	1.703	−346.04481
1.8	42.6	1.886	−346.04622
1.7	44.9	1.962	−346.04958
1.6	45.6	2.022	−346.05323
1.401	41.4	2.104	−346.08228
	EWG=**CHO**		
∝	14.7	1.494	−267.61045
2.5	20.8	1.565	−367.04337
2.2	25.4	1.637	−367.04195
2	29.4	1.703	−367.04123
1.8	27.0	1.89	−367.04564
1.7	21.3	1.96	−367.05059
1.6	14.4	2.013	−367.05579
1.397	8.0	2.075	−367.08674

[a] The data for C−F distance = ∝ relates to the unpreturbed substrate.

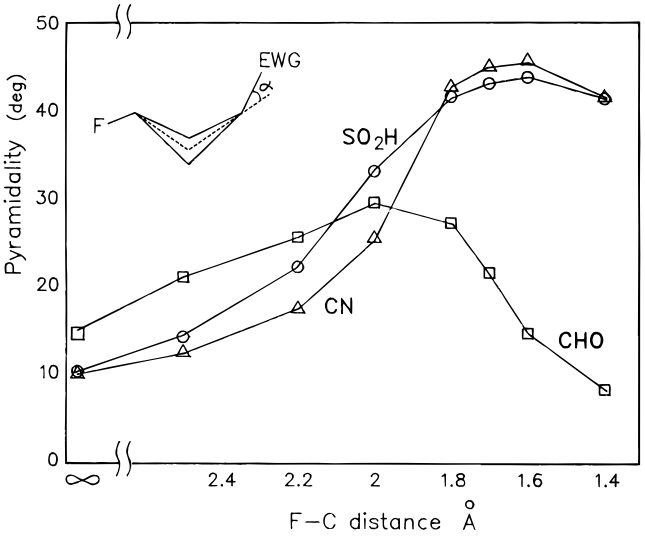


Figure 1. Pyramidality as a function of the C−F distance.

attached to the bridgehead hydrogen, the fluoride ion approach was restricted to a line forming the same F−C3−H angle which is formed at the transition state for the nucleophilic attack (80°). The C−F distance was gradually varied from 2.5 Å to the final geometry of the adduct (ca. 1.4 Å), and the rest of the molecule was fully optimized at each point. The results given in Table 3 and Figure 1 show the bridge bond length and the pyramidality as a function of the C−F distance for the three substituents. The results show that, as the fluoride ion approaches the molecule, the central bond is lengthened and the activating group moves inward, increasing the pyramidality. This motion produces an intermediate structure (at a C−F distance of ca. 1.75 Å for CN and SO_2H and 2 Å for the CHO derivative) at which the degree of pyramidality reaches a maximum. The activating group then oscillates back, relaxing to the stable carbanion geometry, which is pyramidal for CN and SO_2 and nearly planar for the CHO derivative.

The oscillation phenomenon, that is, an inward motion followed by an outward one as the bridge bond is further stretched, was previously suggested based on X-ray data and observed by STO-3G computations.[11] It was found computationally also for the radical cation of bicyclobutane.[12] The present finding, being the third example of the oscillation phenomenon, seems to suggest that stretching of the central bond of bicyclobutane, regardless of the charge or multiplicity, results in the oscillation phenomenon. For obvious reasons, it is expected that the amplitude of the inward motion will be much smaller for the carbonyl substituent than for the two charge "localizing" substituents, CN and $S(H)O_2$, and that its maximum will be reached earlier. These expectations are fully born out, as can be seen from Figure 1.

The above computational results show that *the carbanion is initially formed in the geometry which will yield the less stable trans isomer by equatorial protonation*. Thus, *the observed product distribution may result from a partially successful trapping of the carbanions in their pyramidal geometry, reflecting the fact that in the initially formed carbanion, the EWG, due to the inward motion, assumes an axial position.*

The proposed model can be experimentally tested in the following way. If, indeed, the carbanion is trapped in the reactions in MeOH in its initial conformation, then slowing down the protonation rate will enable equilibration by inversion of the carbanion. The proton donor will then trap the equilibrated carbanion, giving a product mixture in which the percent of the product derived from the equatorial protonation will decrease with the protonation rate. The results will thus resemble those obtained by Zimmerman for the cyclohexylsulfone system in the sense that the more stable product will be preferentially obtained. This was achieved by carrying out the reactions in an inert solvent (DME). Because of the insolubility of MeO^- in this medium, PhS^- and $PhSe^-$ were used as nucleophiles. As in the Zimmerman study, the more stable isomer was indeed obtained in (a ca. two - fold) excess over the less stable one. The protonating agent in this case is probably the solvent itself, because adding large excess of MeOD after 1 min. did not result in deuterium incorporation into the product.

In the next step, increasing amounts of the proton donor-MeOH or trifluoroethanol (TFE) were added to the reaction mixture. According to Scheme 1 (using $PhSe^-$ as a nucleophile and the CN derivative as an example), it is clear that as the protonation rate is enhanced, more of the trans isomer will be obtained. The results given in Table 2 and Figures 2−4 show that, indeed, when protonation rate is enhanced, either by increasing the concentration of the proton donor or by using a stronger acid (TFE), the fraction of the equatorial protonation is increased and then levels off. As expected, a sharper rise is obtained for the stronger acid TFE (Table 2 and Figures 2−4).

Summary and Conclusions

A carbanion in a cyclic system may have either a planar or a pyramidal geometry at the transition state of a protonation reaction. Zimmerman has shown that, in the case of a planar geometry, the proton donor will prefer to approach the molecule

(11) Paddon-Row, M. N.; Houk, K. N.; Dowd, P.; Garner, P.; Schappert, R. *Tetrahedron Lett.* **1981,** *22*, 4799. Irngartinger, H.; Lukas, K. L. *Angew. Chem., Int. Ed. Engl.* **1979**, 18, 694.

(12) Hoz, S.; Basch, H.; Goldberg, M.; *J. Am. Chem. Soc.* **1992**, *114*, 4364.

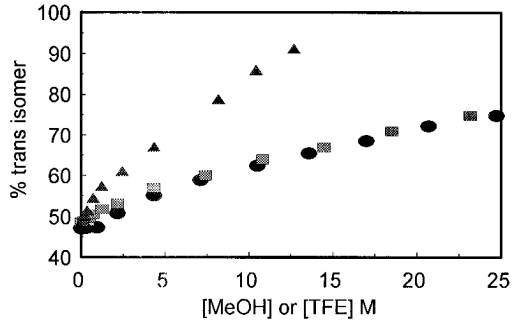


Figure 2. The % of the trans isomer in the reaction of **1n** with PhS^- ●, $PhSe^-$ ■ in MeOH, and $PhSe^-$ in TFE ▲.

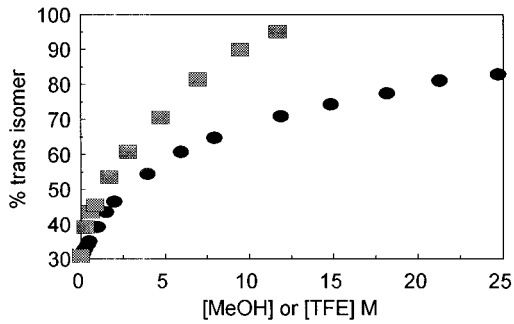


Figure 3. The % of the trans isomer in the reaction of **1s** with PhS^- in MeOH ●, and in TFE ■.

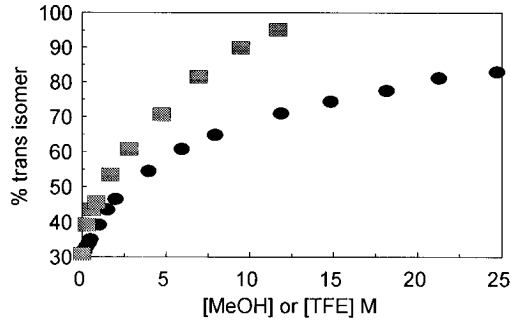
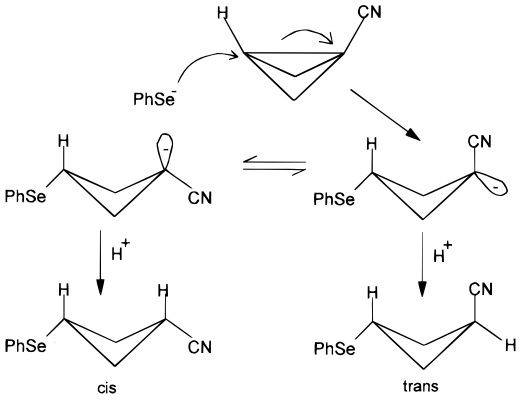


Figure 4. The % of the trans isomer in the reaction of **1s** with $PhSe^-$ in MeOH ●, and in TFE ■.

Scheme 1



from the less hindered equatorial direction, whereas, in the pyramidal geometry case, the favored approach will be from the axial one. In contradistinction to these rules, pyramidal carbanions obtained via the route shown in eq 4 all show disposition toward equatorial protonation. Moreover, this preference is, by far, more pronounced than that for the planar carbanions. We have shown that this behavior is unique to the bicyclobutane−cyclobutane system in fast protonating media. This uniqueness stems from the coupling between two motions, the elongation of the central bond in the course of the nucleophilic attack, and an inward motion of the bridgehead substituents. When protonation is fast enough, the majority of the carbanions are trapped in their incipient geometry before an appreciable inversion can take place, giving the less stable isomer preferentially. For obvious reasons, this phenomenon should be more pronounced with the pyramidal (CN and SO_2R stabilized) carbanions than with the planar (RC═O stabilized) ones. Slowing down the protonation rate, by using only small amounts of proton donor in DME, brought back the adherence to the Zimmerman rule.

Experimental Section

General Methods. NMR spectra were recorded on a Bruker AM-300 spectrometer and measured in $CDCl_3$ solution. Mass spectra were taken with a Finnigan 4021 mass spectrometer. For analytical purposes, a Packard Model 878 (FI detector) gas chromatograph was used, whereas for preparative separations a Varian 920 gas chromatograph (TC detector) was used.

Reactants and Products. 1s and **1s′** were obtained from Prof. Y. Gaoni and are known in the literature.[14] Methylbicyclobutanecarboxylate (**1e**) was prepared according to a literature procedure,[15] with the difference that the two-step hydrolysis of the nitrile function and esterification of the resulting acid derivative were combined into a single step, according to the following procedure: a heterogeneous mixture of 2.8 g (0.024 mol) of 3-chlorobicyclobutanecarbonitrile and 21 mL of conccentrated HCl were vigorously stirred under gentle reflux for 1 h. MeOH (40 mL) was added, and the solution was refluxed for 22 h. The reaction mixture was treated with methylene chloride and aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered, and evaporated, yielding 3.53 g (95% yield) of yellow liquid composed mainly of the two isomers of methyl 3-chlorocyclobutanecarboxylate. The mixture was then subjected to elimination, and the product, methyl bicyclobutanecarboxylate, was kept in ethereal solution at −25 °C. Before each experiment, the product was separated and purified by preparative gas chromatography (5% XE 60 on Chromosorb W, 50 °C). Bicyclobutyl phenylketone (**1k**) was prepared according to literature procedure[16] and purified by preparative GC (0.5% XE 60 on Chromosorb W, nonacid washed, 95 °C).

The methoxy adducts of the three substrates were prepared according to published procedures. The two isomers of 3-methoxycyclobutyl *p*-tolylsulfone (**2s**)[14] were separated on a GC column (0.5% XE 60 on Chromosorb W, nonacid washed, 170°). The two isomers of methyl 3-methoxycyclobutylcarboxylate (**2e**) were separated, and their geometry was assigned by Razin et. al.[17] The two isomers of 3-methoxycyclobutyl phenylketone (**2k**)[16] were obtained as a mixture after column chromatography with methylenechloride.

Bicyclobutanecarbonitrile (**1n**) was prepared according to published procedure.[17]

The thiophenoxide adducts (**3s** and **3n**) and the phenylselenolate adducts (**4s** and **4n**) were prepared in the following procedure, which was used also for the studies of the effect of added alcohols to the DME solution. The substrate (3−4) mg was dissolved in 0.35−0.75 mL of DME or DME−alcohol mixture. To this, 50−150 μL of a nucleophile stock solution were injected to give a reaction mixture with

(13) A referee had suggested an alternative explanation for the observed stereochemistry at high proton donor concentration. According to this explanation, at high MeOH concentration, the reaction is concerted, and no free carbanion is formed under these conditions. We believe that this suggestion can be safely ruled out on the basis of microscopic reversibility since all the 1,3-elimination reactions in the cyclobutane bicyclobutane system are known to be stepwise (see ref 6 above). Moreover, to the best of our knowledge, there is no single reported case of a concerted 1,3-elimination reaction. The reversal must therefore also be a stepwise reaction.

(14) Gaoni, Y.; Tomazic, A. *J. Org. Chem.* **1985**, *109*, 2948.
(15) Hall, H. K., Jr.; Smith, C. D.; Blanchard, E. P., Jr.; Cherkofsky, C. S.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 121.
(16) Azran, C.; Hoz, S. *Tetrahedron* **1995**, *51*, 11421.
(17) Razin, V. V.; Eremenko, M. V.; Ogloblin, K. A.; *Z. Org. Khim.* **1977**, *13*, 1003.

a total volume of 0.5−0.8 mL, with substrate and nucleophile concentrations in the ranges of 0.03−0.05 M and 0.06−0.1 M, respectively. The reaction mixtures were allowed to stand at room temperature for periods of minutes to 2 h (In general, the reactions were slower with PhS^- as nucleophile and in the presence of large concentrations of alcohol.) The reaction mixtures were quenched with 2 mL of CH_2Cl_2, followed by 2 mL of water. The aqueous phase was washed with three portions of 3 mL of CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and evaporated. In all cases, the isolated yield (based on weighing and NMR determination against internal standard ($CHBr_3$)) was between 90 and 100%.

3s cis: ^{1}H NMR, δ 2.6 (t, 4H, CH2), 3.67 (tt, 1H, HC-SPh), 3.68 (tt, 1H, HC-SO2Ph), 7.2−7.35 (m, 5H), 7.45−7.7 (m, 3H), 7.84 (m, 2H). *m*/*e* (CI-NH3) 322.1, 278.1, 256.1.

3s trans: ^{1}H NMR, δ 2.29 (m, 2H, CH2), 3.03 (m, 2H, CH2), 3.93 (dtt, 1H, HC-SO2Ph), 4.05 (dtt, 1H, HC-SPh), 7.2−7.35 (m, 5H), 7.5−7.7 (m, 3H), 7.88 (m, 2H). *m*/*e* (CI-NH3) 322.1, 278.1, 256.1.

Satisfactory C, H, S analyses were obtained for the two isomers.

4s cis: ^{1}H NMR, δ 2.52−2.75 (m, 4H, CH2), 3.69 (tt, 1H, HC-SO2Ph), 3.73 (tt, 1H, HC-SePh), 7.22−7.38 (m, 5H), 7.5−7.67 (m, 3H), 7.8 (m, 2H). *m*/*e* (CI-NH3) 372.1, 370.1, 368.1, 367.1, 366.1, 364.1, 223.1, 206.1, 204.5.

4s trans: ^{1}H NMR, δ 2.35 (m, 2H, CH2), 3.07 (m, 2H, CH2), 3.88 (dtt, 1H, HC-SO2Ph), 4.1 (dtt, 1H, HC-SePh), 7.22−7.38 (m, 5H), 7.5−7.67 (m, 3H), 7.85 (m, 2H). *m*/*e* (CI-NH3) 372.1, 370.1, 368.1, 367.1, 366.1, 364.1, 223.1, 206.1, 204.5.

Satisfactory C, H, S, Se analyses were obtained for the two isomers.

3n cis: ^{1}H NMR, δ 2.44 (m, 2H, CH2), 2.82 (m, 2H, CH2), 3.01 (tt, 1H, HC-CN), 3.77 (tt, 1H, HC-SPh), 7.21−7.35 (m, 5H). *m*/*e* (CI-NH3) 207.0, 204.5, 189.0, 136.0, 134.0.

3n trans: ^{1}H NMR, δ 2.44 (m, 2H, CH2), 2.82 (m, 2H, CH2), 3.29 (dtt, 1H, HC-CN), 4.07 (dtt, 1H, HC-SPh), 7.21−7.35 (m, 5H). *m*/*e* (CI-NH3) 207.0, 204.5, 189.0, 136.0, 134.0.

Satisfactory C, H, N analysis was obtained for the two isomers.

4n cis: ^{1}H NMR, δ 2.49 (m, 2H, CH2), 2.83 (m, 2H, CH2), 3.01 (tt, 1H, HC-CN), 3.85 (tt, 1H, HC-SePh), 7.3 (m, 3H), 7.48 (m, 2H). *m*/*e* (DCI-NH3) 255.1, 253.1, 251.1, 250.1, 248.1, 237.0, 184.0.

4n trans: ^{1}H NMR, δ 2.49 (m, 2H, CH2), 2.83 (m, 2H, CH2), 3.25 (dtt, 1H, HC-CN), 4.12 (dtt, 1H, HC-SePh), 7.3 (m, 3H), 7.48 (m, 2H). *m*/*e* (DCI-NH3) 255.1, 253.1, 251.1, 250.1, 248.1, 237.0, 184.0.

Satisfactory C, H, N analyses were obtained for the two isomers.

Equilibration of 3 and 4. The adducts (10−17 mg) were dissolved in 1 mL of *t*-BuOH. Added to this were 23 mg of *tert*-butoxide to give a solution with a base concentration of 0.2 M and a substrate concentration in the range 0.03−0.075 M. The reaction mixtures of the CN derivatives were examined after 80 and 160 min, and those of the sulfone derivatives were examined after 24 and 48 h. In both cases, the ratio remained constant for the two reaction times.

General Procedure for the Reaction of MeO^- with 1. Solutions of MeONa in MeOH were prepared from Na and MeOH under nitrogen. Solutions at the appropriate concentration were incubated in a temperature bath. These were either added to the substrate (**1s**) placed in the temperature bath, or a 5 μL methylenechloride solution of the substrate (**1k**) was injected into 2 mL of the methoxide solution at the appropriate concentration. In some cases (**1e)**, a weighed amount of the substrate was directly injected into the methoxide solution. In several runs, fluorene or naphthalene were added to the reaction mixture as an internal standard. Aliquots of 0.2 −0.25 mL were periodically removed. The reactions of **1s** and **1k** were quenched by aqueous NaCl solution and extracted with ether. The total volume of the ether and the water was 1.5 mL. In the case of **1e**, quenching was done with AcOH. Care was taken to assure that the quenched solutions were neutral, since under either basic or acidic conditions the composition of the samples did not remain constant over several days. A 2% XE-60 on Chromosorb W column was used for the GC analysis of the reactions of **1e**, whereas a 0.5% XE-60 on Chromosorb W (non-acid washed) column was used for the GC analysis of the reactions of **1s** and **1k**. A similar procedure was used in the isomerization experiments.

Supporting Information Available: Gaussian archive records for the geometry optimized molecules, their fluoride adducts, and transition states for inversion of the carbanions. (4 pages). See any current masthead page for ordering information.

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(18) Blanchard E. P.; Cairncross, A. *J. Am. Chem. Soc.* **1966,** *88*, 487. Hall, H. K., Jr.; Blanchard, E. P. Jr.; Cherkofsky, C. S.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 110. Dietz, P.; Szeimies, G. *Chem. Ber.* **1980**, *113*, 398. Hall, H. K., Jr.; Smith, C. D.; Blanchard, E. P., Jr.; Cherkofsky, C. S.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 121.