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Published on Web 11/21/2002

Could Ionic γ-Elimination Be Concerted: Clocking the Internal Displacement Across a Cyclobutane Ring

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Received September 23, 2002

Abstract: Carbanion **1**, obtained by a nucleophilic attack of $PhSe^-$ on 3-chlorobicyclobutane-carbonitrile in DME undergoes both protonation and elimination as shown in eq 1. Alcohols of increasing acidity in the following order: *t*-BuOH, *i*-PrOH, MeOH, trifluoroethanol (TFE), and hexafluoro2-propanol (HFIP) were used as proton donors. An Eigen-type plot of the log of the product ratio (protonation/elimination) vs the pK_a of the alcohols, levels off for the two most acidic alcohols, TFE and HFIP which react at a diffusion-controlled rate. The partitioning of the products between protonation and elimination enables, therefore, the determination of the rate constant for the internal elimination as $\sim 3 \times 10^{10}$ s^{-1}. Ab initio calculations at the B3LYP/6-31G* level show that the elimination from a model carbanion (**4**, eq 4) occurs in a barrierless process. Simulation of the experimental reaction by including solvation effects using the Onsager model, shows that using the dielectric constant of DME (7.2) stabilizes, as expected, the carbanion and prevents a spontaneous elimination. In the absence of solvation effects, using Me^- as a base, a complete elimination of HCl (proton removal and leaving-group expulsion) took place from 3-chlorocyclobutanecarbonitrile in a barrierless process without the formation of any discrete intermediate.

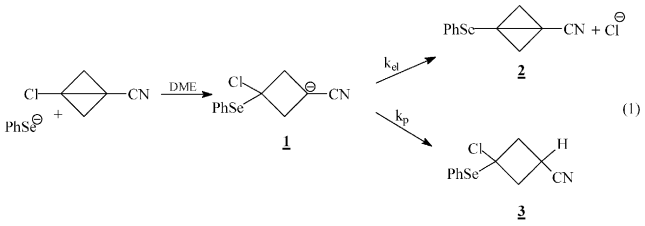
Introduction

While in the majority of cases, base promoted β-eliminations are concerted,[1] to the best of our knowledge there is not a single report of a concerted γ-elimination reaction. Clearly, the proximity of the nucleophilic and electrophilic centers in β-elimination is the reason for the rarity of the stepwise E1cB mechanism[1,2] in such reactions. Since the distance between the reacting centers in γ-elimination is, on one hand, larger than that in β-elimination but, on the other hand, smaller than for S_N2 reactions, the relevant question would be: can one engineer a system appropriate for γ-elimination having a distance short enough to promote concertedness?

In this contribution we focus on the formation of bicyclobutane[3] by bridging across a cyclobutane ring: a case in which the two reaction centers are forced to be relatively close to each other (2.2 Å) in the ground state (in contrast to ca. 2.6 Å in the open chain-propane analogue). Starting with a carbanionic intermediate, as in the E1cB mechanism, our results suggest that, under appropriate conditions, the formation of bicyclobutane could occur via a concerted γ-elimination reaction.

Results and Discussion.

We generated the cyclobutane embedded carbanion **1** by nucleophilic attack of phenylselenolate ($PhSe^-$) on 3-chlorobicyclobutanecarbonitrile (eq 1). In preliminary experiments it was



(1)

found that the elimination of Cl^- to form **2** (eq 1) was accompanied by small amounts (ca. 1%) of the protonation of **1** to yield **3**, probably by adventitious water present in the solvent (DME) indicating that the elimination step is not spontaneous but has a measurable barrier. We were therefore interested in determining the lifetime of the carbanionic intermediate **1** which reacts internally to give the bicyclobutane unit. The partitioning of the reaction between the two products paved the way for a clocking experiment[4] in which the rate constant for the elimination could be determined. This approach was attempted previously in a similar case by Jencks et al. who tried to measure the rate constant for the elimination of a thiolate

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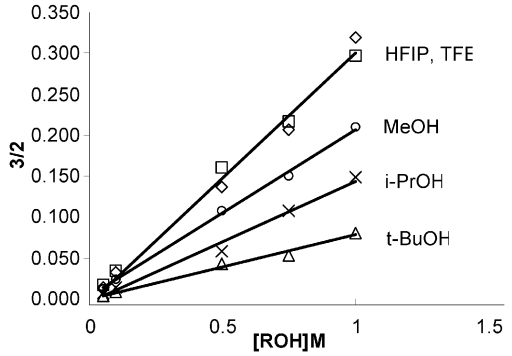

Figure 1. A plot of the protonation/elimination ratio vs alcohol concentration.

Table 1. Percent **3** as a Function of Alcohol Concentration

[ROH]M	HFIP	TFE	MeOH	*i*-PrOH	*t*-BuOH
0.05	1.3 ± 0.3	1.6 ± 0.1	1.2 ± 0.0	0.6 ± 0.2	0.3 ±0.3
0.10	3.2 ± 0.8	3.3 ± 0.5	2.4 ± 0.0	1.4 ± 0.2	0.9 ± 0.0
0.50	12 ± 0.4	13.8 ± 0.4	9.7 ± 0.5	5.5 ± 0.4	4.1 ± 0.5
0.75	17.1 ± 0.6	17.8 ± 1.2	13 ± 1.3	9.7 ± 10.7	5.1 ± 0.3
1.00	24.2 ± 0.8	22.9 ± 1.8	17.3 ± 0.5	12.9 ± 0.1	7.5 ± 0.4

anion from the carbanion shown in eq 2.[5] However, this attempt

(2)

failed because the carbanion underwent protonation in water at the rate of dielectric relaxation ($\sim 10^{11}$ s^{-1}). In our study which was conducted in DME we employed as proton donors, a series of alcohols of increasing acidity in the following order: *t*-BuOH, *i*-PrOH, MeOH, trifluoroethanol (TFE), and hexafluoro2-propanol (HFIP). The product ratio **3**/**2** was determined as a function of the proton donor concentration for all five alcohols in the range of 0.05−1 M. The background protonation due to traces of water in the solvent amounted to ∼1% and was deducted from the values obtained in each experiment. The data are presented in Table 1.

Assuming first-order kinetics in the intermediate carbanion (**1**) for the elimination reaction, and overall second-order kinetics, first-order in **1**, and first-order in the alcohol for the protonation reaction, the ratio of the products **3**/**2** should be linearly correlated to the alcohol concentration as shown in eq 3.

$$\frac{[\mathbf{3}]}{[\mathbf{2}]} = \frac{k_p[\mathbf{1}]\,[ROH]}{k_{el}[\mathbf{1}]} = \frac{k_p}{k_{el}}\,[ROH] \qquad (3)$$

This was indeed observed and is graphically demonstrated in Figure 1. The ratios k_p/k_{el} derived from the slopes are given in Table 2.

To determine the rate constant for the elimination step, the clock—the competing protonation reaction—had to be calibrated. This was done using a variation of the Eigen plot[6] namely, a plot of log k_p/k_{el} vs ΔpK_a (the pK_a difference between the proton donor and acceptor). In the absence of pK_a values in DME for the alcohols at hand and for the conjugate acid of **1,** use was

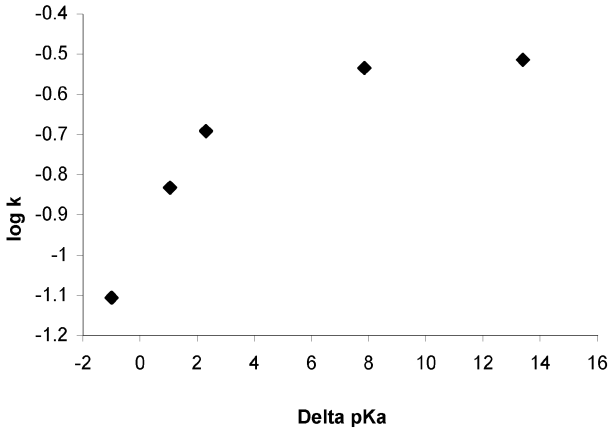

Figure 2. Eigen-type plot of log k_p/k_{el} vs ΔpK_a.

Table 2. k_p/k_{el} and pKa Values in DMSO for the Various Alcohols

ROH	k_p/k_{el}	pK_a
HFIP	0.306	17.90
TFE	0.292	23.45
MeOH	0.203	29.00
i-PrOH	0.147	30.25
t-BuOH	0.078	32.30

made of the pK_a values in DMSO[7] for the alcohols and of acetonitrile as a model for **1** (Figure 2).

In an Eigen plot for normal acids and bases, the slope at endothermic proton-transfer region is 1, and it levels off to zero at the diffusion-controlled limit for exothermic reactions. Localized carbanions behave very much like normal acids, and literature data indeed suggest[8] that cyano-stabilized carbanions are highly localized on carbon.[8,9]

As can be seen from the Eigen plot in Figure 2, leveling off takes place for the two acidic proton donors TFE and HFIP, implying that k_p has reached the diffusion-controlled limit. Since for these two alcohols $k_p/k_{el} \approx 0.3$ and since k_p was found to be diffusion-controlled (1×10^{10} M^{-1} s^{-1}), k_{el} will be slightly higher (ca. 3×10^{10} s^{-1}). *This value is below the vibrational rate limit (*$\sim 10^{13} s^{-1}$*) required for a concerted mechanism and indicates that the elimination reaction in this case is stepwise although with a very short-lived carbanionic intermediate.*

Using Gaussian 98 at the B3LYP/6-31G* level[10,11] we have computed the model reaction shown in eq 4. Starting with the optimal geometry for the neutral (protonated **4**), the carbanionic

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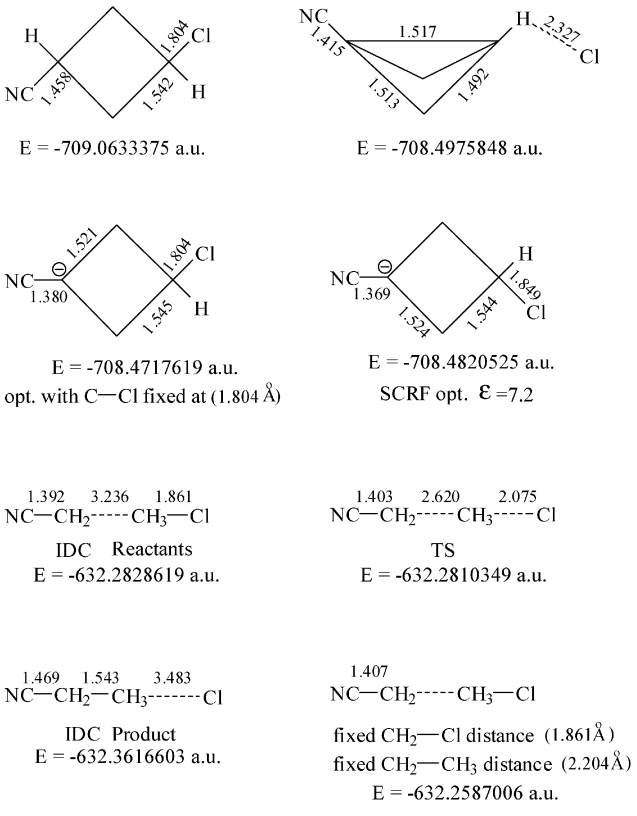
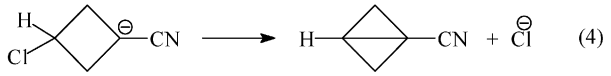
Chart 1.[a]



[a] All lengths are given in Å.

species **4** collapsed in a barrierless motion to the bicyclic product. Thus, the ab initio calculations reveal that the rate of



(4)

4

internal displacement is at the vibrational level. Energies and major geometrical parameters are given in Chart 1.

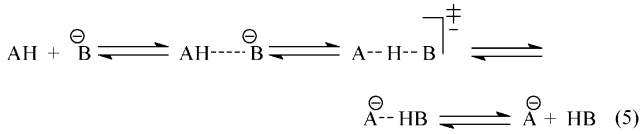
The small discrepancy between the vibrational rate predicted for the elimination step by the ab initio calculations and the experimentally observed discrete lifetime of the carbanionic intermediate ($\sim$ 1.5 orders of magnitude below the vibrational rate) can be attributed to several factors. The first one is solvation, which may stabilize the ground state of the reacting carbanion. Indeed, re-optimization of **4** using the SCRF method for the Onsager model[12] with $\epsilon = 7.2$ gave a stable geometry (see Chart 1 for data) which did not collapse to the product.

In addition, there are essential conformational changes which must be considered.

The carbanion formed in the nucleophilic step is not in the appropriate geometry for the expulsion step.[13] The ab initio calculations show that the carbanionic center is pyramidal (dihedral angle defined as the angle between the atom bonded to the anionic carbon = 153°. The carbanion geometry was optimized while fixing the C−Cl bond length at its length in the neutral molecule 1.804 Å) which is in line with the charge being localized on the carbon. The calculations also show that the cyclobutane ring is puckered. On the bases of "microscopic reversibility", *the carbanion is formed in a geometry suitable to reverse the reaction and displace the nucleophile—PhSe. For it to expel the chloride from an equatorial position, both ring flip and carbanion inversion would have to take place*[13] (Scheme 1). These processes can also contribute to the nonspontaneous decay of the carbanion to the products.

Another point which is of interest is the exothermicity of the reaction. Computational results relating to the gas phase show that the reaction is exothermic by 16 kcal/mol. The experimentally observed low barrier suggests that the reaction in DME is also exothermic. On the other hand, the strain energy of cyclobutane is about 27 kcal/mol, whereas that of bicyclobutane is ca. 66 kcal/mol.[3,14] Thus, the strain energy alone should contribute ca. 40 kcal/mol to the endothermicity of the reaction. It would seem that shifting the negative charge from the carbon to the chlorine contributes significantly more than the increase in ring strain energy. (The exothermicity of the strainless analogue—see eq 6 below—is 50 kcal/mol.)

We have also conducted a short study of the hydrogen−deuterium kinetic isotope effect for two of the alcohols; MeOH(D) and *t*-BuOH(D). Within experimental error, the same product partitioning, (i.e., **3/2)** was obtained with the deuterated alcohols as with the undeuterated ones. Since the elimination rate constant is independent of the alcohol, the kinetic hydrogen−deuterium isotope effect (k_H/k_D) for these two alcohols is 1 ± 0.1. This result strongly supports the notion that cyano stabilized acids, although being carbon acids, behave as normal acids[8,9] from the point of view of the Eigen mechanism. According to this mechanism,[15] proton-transfer reaction takes place in a series of steps. The first one is hydrogen bond formation which is followed by the actual proton-transfer step to form the hydrogen-bonded complex of the products which then dissociates to the free species (eq 5). In the diffusion-controlled region, the rate-limiting step is the diffusion, and the barrier for the actual proton transfer is lower than that of the diffusion. Using the pK_a values



(5)

in DMSO for our reactions in DME (assuming that a proportional variation takes place upon changing the solvents), suggests that the pK_a of the said cyano carbon acid (31.3 for MeCN) is intermediate between that of MeOH (29.0) and *t*-BuOH (32.3).[7] A nearly isoergic proton transfer would imply a symmetrical transition state where the proton is half transferred and the isotope effect should be in the range of 7−8. Rather than being the result of a very early or very late transition state,[16] the absence of a hydrogen−deuterium isotope effect for these

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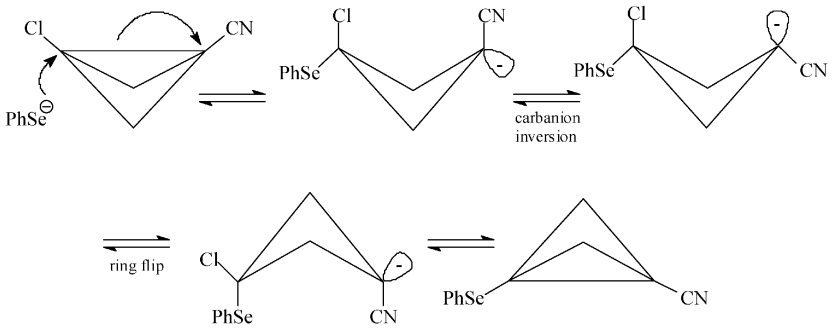
(16) Isaacs, N. S. *Physical Organic Chemistry*; Longman: New York, 1987; Chapter 7.

Scheme 1. Conformational Changes from Nucleophilic Attack to Leaving-Group Expulsion



alcohols must be attributed to the fact that diffusion is largely the rate-controlling step, as in the Eigen mechanism for normal acids and bases. These results are very much in accord with the conclusion reached by Jencks et al. that the solvation shell around a cyano-stabilized carbanion collapses at a dielectric relaxation rate.[5]

How Does Proximity Contribute to Rate Enhancement. Much has been written on the origins of proximity effects,[17] effective molarities,[18] and so forth. In the present discussion we focus only on the enthalpy of the reacting parties at relatively short distances. In the previous discussion we have shown that the carbanion produced in close proximity to the electrophilic center may exhibit a (enthalpically) barrierless reaction, enabling in principle a concerted γ-elimination. Since the nucleophilicity in γ-eliminations is closer in nature to the σ-nucleophilicity of S_N2 reaction than to the π-nucleophilicity of β-elimination, we will focus briefly on the former. In the gas phase, the first step in a S_N2 reaction is the formation of an encounter ion−dipole complex (IDC) between the nucleophile and the substrate. This is followed by the actual displacement step in the course of which the system gravitates to the IDC of the products. The distance between the reactants at the IDC is determined by the point at which the stabilizing ion−dipole interaction balances the interelectronic repulsion. Forcing the nucleophile to further approach the substrate will result in an increase in energy, which contributes much to the height of the barrier. Thus, in the case of **1**, the carbanion may already be in an energetically beneficial position since in its ground state it is formed at a distance shorter than the IDC distance. It should be pointed out that in the formation of any carbanion, interelectronic repulsion is a major cause of destabilization. In the present case, due to its proximity to the electrophilic center, part of the additional cost of bringing the two reacting centers together is avoided since the interelectronic repulsion is already present in the electronic structure of the ground state. Therefore, when compared to the intermolecular reaction, the starting point on the hypothetical reaction profile is not at the bottom of the hill but closer to its peak. This, of course, will lower the activation energy (see Figure 3, point a). Another possibility is that the nucleophilic center is already so close to the electrophilic center that it is located already past the transition state (point b in Figure 3). In this case the system will be going down the hill to the product without a barrier.

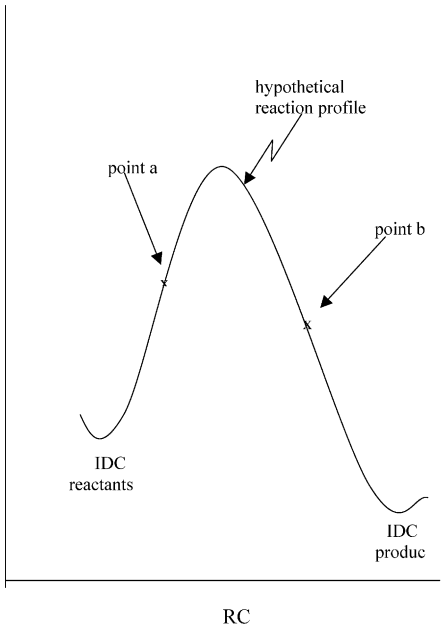
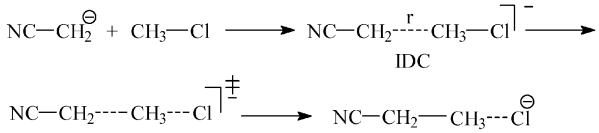


Figure 3. Hypothetical reaction profile for nucleophilic displacement.

To demonstrate these points we have computationally studied the S_N2 analogue of eq 4 by disconnecting the nucleophile from the substrate as shown in eq 6. The geometries and energies of



(6)

the reactant and the product ion−dipole complexes and the transition state were obtained using Gaussian 98[10] at the B3LYP/6-31G* level.[11] The transition state was characterized by frequency analyses. Energies and major geometrical parameters are given in Chart 1.

We have modeled the interelectronic repulsion by determining the increase in energy caused by bringing the nucleophile closer to the substrate from its IDC distance (3.24 Å) to 2.204 Å which is the distance between two opposing carbons in cyclobutane while keeping the C−Cl distance at its IDC value (1.86 Å). The data in Chart 1 show that relative to the energy of the reactants IDC (r = 3.236 Å), bringing the reactants closer induced an energy increase of 15.2 kcal/mol. It is interesting to note that the transition state is achieved at r = 2.62 Å. *This implies that if the potential surface for reaction 6 were a perfect model for the reaction of eq 4, carbanion* ***4*** *may already be on*

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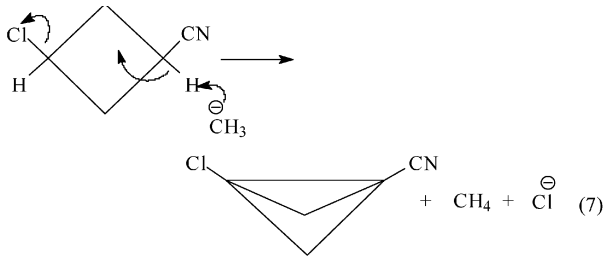
the down-hill slope (Figure 4, point b). It should be emphasized that the profile for the S_N2 reaction (eq 6) is a very crude approximation for the actual profile of any γ- elimination. One obvious difference is that, due to strain energy in the product, the reaction will be less exothermic and according to the Hammond postulate, the transition state will be achieved later. Orbital alignment and other factors will cause the γ-elimination surfaces to differ significantly from the S_N2 reaction, which was used here mainly for illustrative purposes.

Since we have mentioned β-elimination as an example of the proximity effect, we comment briefly on these reactions. It is clear that the high efficiency observed in β-elimination reactions stems from the proximity in the ground state of the nucleophile to the electrophilic center of the substrate. In addition to being entropically favorable this must also engender enthalpic advantage to serve as a rationalization of why concerted β-elimination reactions are so frequently encountered while the E1cB mechanism is only seldom observed. Based on the above model the suggested explanation is as follows: At the reactant ground state in a β-elimination reaction the nucleophilic and the electrophilic centers are separated by a single σ bond only (ca. 1.5 Å). Since a " pure π bond" (without a σ bond) must be longer than a σ bond, it is clear that the hypothetical transition state for the internal π-nucleophilic reaction[19] would be at a larger separation between the nucleophilic and electrophilic centers. Therefore, it is clear that in its ground state, the carbanionic center in β- elimination is located on the reaction coordinate at a distance shorter than that of the hypothetical transition state for the formation of the double bond. As a result, the bonding component becomes dominant, and the system glides down the hill toward the product (Figure 3, point b). Starting from the neutral rather than from a full discrete carbanion, the incipient negative charge developed in the course of the deprotonation in a concerted reaction is sufficient to drive the leaving group out without forming a carbanionic intermediate.

Can γ-Elimination Be Concerted. In the above discussion we have dealt primarily with the ability of a discrete full carbanion to displace a leaving group. The assumption was that if a full carbanion cannot displace the leaving group, the incipient carbanion generated in the course of a deprotonation reaction, for example, will certainly not be able to do it. The above results show that a fully developed carbanion *can* displace the leaving group in a barrierless process. The question then remains: can the displacement merge into a single step with the deprotonation step in which a carbanion is formed? It is clear that the concerted or stepwise nature of the reaction may depend very much on the conditions used to generate the carbanion. For example, low dielectric solvents will promote concertedness more than polar ones since they are less capable of stabilizing the relatively localized charge in the ground state. Using a polar base will also forestall the concerted expulsion of the leaving group, since the deprotonation reaction would most likely result in the formation of a carbanion stabilized by hydrogen bonding to the conjugate acid of the base.[20,21] A nonpolar base such as Me^- may, in theory, conform with the demands of concertedness. (Although it is unlikely to serve successfully in solution since such anions are always ion-paired to a cation and aggregated, the generated carbanion would presumably be similarly stabilized.) Indeed, when we have computationally brought Me^- to a distance of 3.5 Å from the hydrogen α to the cyano group (eq 7), no stable intermediate was obtained, and energy optimization resulted in the barrierless formation of the bicyclobutane derivative. We therefore conclude that under appropriate conditions in systems having the two reacting centers at a distance of 2.2 Å or less (e.g., cyclobutane to give bicyclobutane and 1.1.1-bicyclopentane to give the corresponding propelane), deprotonation and departure of the leaving group may fully merge into a single step.



(7)

Experimental Section

General. NMR spectra were recorded on a 300 MH spectrometer and measured in $CDCl_3$ solution. HPLC analyses were conducted using a Altech Econosil 10 μ, 250 mm long and 4.6 mm in diameter, column with eluent 5% THF in heptane. The same column with a 10-mm diameter was used for preparative separations. All the materials used were analytical grade. MeOH, *t*-BuOH, and *i*-PrOH were dried according to published procedures.[22]

Reactants and Products. 3-Chlorobicyclobutanecarbonitrile was prepared according to literature procedure.[24] The products 3-phenyselenobicyclobutanecarbonitrile (**2**) and 3-chloro-3-phenyselenocyclobutanecarbonitrile (**3**), were purified using the preparative HPLC column (**3** was separated into its 2 stereoisomers **3a** and **3b**[23]).

^{1}H NMR for **2**: δ 7.73 (o) 2H, 7.44 (m) 2H, 7.42 (p) 1H, 2.3 (t, J = 1.5 Hz 2H), 1.67 (t, J = 1.5 Hz 2H); ^{13}CNMR for **2:** δ 134.15 (o), 129.48 (m), 128.53 (p), 126.74 (ip), 118.44 (s), 43.40 (t), 19.51 (s), 1.57 (s). Anal. Calcd for **2** $C_{12}H_{10}NSe$: C, 56.41; H, 3.87; Se, 5.98; N, 33.72. Found C, 56.14; H, 3.94; Se, 5.72; N, 33.70.

^{1}H NMR data for **3a**: δ 7.71 (o) 2H, 7.48−7.36 (m + p) 3H, 3.15 qn under 2,4, 3.10 (m, 4H). ^{13}CNMR data for **3a**: δ 136.1 (o), 129.4 (m), 129.3 (p), 127.46 (ip), 123 (s), 50.8 (s), 46.6 (t), 17.2 (d).

^{1}H NMR data for **3b**: δ 7.72 (o) 2H, 7.48−7.36 (m + p) 3H, 3.45 (qn, J = 10 Hz 1H), 3.08 (m, 4H), ^{13}CNMR data for **3b**: δ 136.6 (o), 129.8 (m), 129.5 (p), 127.46 (ip), 123 (s), 49.3 (s), 46.1 (t), 18.3 (d). Anal. Calcd for **3** $C_{12}H_{11}NSeCl$: C, 48.89; H, 3.70; Se, 5.18: N, 29.26; Cl 12.96. Found C, 48.95; H, 3.64; Se, 5.03: N, 29.25; Cl 12.89.

Reaction Procedure. The reactions of 3-chlorobicyclobutanecarbonitrile with PhSeNa in DME were conducted in a glovebox under nitrogen at room temperature. To 0.95 mL of a solution containing the substrate, 0.05 mL of a solution containing the PhSeNa was added. The final concentrations in the reaction mixture were 0.05 mol of each

(19) Hoz, S.; Gross, Z.; Cohen, D. *J. Org. Chem*. **1985**, *50*, 832.
(20) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc*. **1980**, *102*, 2340.
(21) This is the reason that in our experimental work we produced the carbanion by nucleophilic attack rather than by a deprotonation reaction.
(22) Vogel, A. I. In *Practical Organic Chemistry*; Longmans: London, 1960; p 169.
(23) In the course of nucleophilic attack on bicyclobutane activated by charge localizing group such as CN, the bridgehead activating group moves inward towards an axial position. Under conditions where the carbanion undergoes rapid protonation, it is trapped in its initial pyramidal geometry. In cases where the lifetime of the carbanion is long enough (relatively low concentration of the proton donor) equilibration is possible, and protonation results in the formation of the two stereochemical isomers. See ref 13 for a detailed discussion.
(24) Hall, H. K., Jr.; Blanchard, E. P., Jr.; Cherkofsky, S. C.; Sieja, J. B.; Shepperd, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 121.

of the reactants. In cases where the reaction was conducted in the presence of alcohol, the alcohol was added to the substrate solution prior to the addition of the salt. Immediately upon mixing, precipitation of NaCl was observed. The mixture was taken out of the glovebox and was diluted (1/10) in the eluent solvent of the HPLC. Quantitative analyses were routinely done by HPLC and occasionally also by NMR. Identical results were obtained within experimental error (±3%).

Acknowledgment. We thank Professor M. Sprecher for helpful discussion.

Supporting Information Available: Gaussian archive files for structures appearing in Chart 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028644P