proceeding via free nitrenes exhibit higher activation energies, and, above all, positive activation entropies.[8]

The 4*H*-1,2,3-triazole route[8,27] **(10)** runs contrary to chemical intuition, since the bending of an azido group requires a strong force. Moreover, the resulting 4*H*-triazole lacks the advantageous stabilization that a 6π-electron system as in its anion would provide. Therefore, the facile base-catalyzed rearrangement of vinyl azide derivatives[27,28] to triazoles in solution bears no relevance to the gas-phase process. In accordance with the above arguments, MNDO hypersurface studies[29] predict a rather high activation energy of around 230 kJ/mol.[27]

A synchronous process via a three-membered ring supported nitrogen extrusion (11) has been studied as a refinement of the C_2H_3N MNDO hypersurface presented in Figure 4 for the following reasons: upon reinspection of the free nitrene mechanism, i.e., the N_2 expulsion with higher barrier followed by nitrene rearrangement with close-to-zero barrier, a more concerted reaction suggests itself. When both the dihedral angle ∠HCCN and the bond angle ∠CCN are used as reaction coordinates, the activation energy for the synchronous N_2 extrusion plus ring formation is lowered to 138 kJ/mol (Figure 6).

The synchronous process presented in Figure 6 would be in agreement with the negative activation entropies found in the decomposition of substituted vinyl azides,[26] since a geometrically highly strained transition state must be passed through in the course of 2*H*-azirine formation. At the same time, the "neighboring" group effect, which lowers the N_2 extrusion barrier for vinyl azide by over 100 kJ/mol, explains not only its decomposition temperature T_3 (11) lowered by 200 K relative to that of methyl azide[5] but also its instability at room temperature as well as its hazardous explosive properties.

Acknowledgment. This work was made possible by the State of Hesse and the University of Frankfurt, which provided the PE spectrometers and the computer time. We also like to thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous support.

Registry No. Vinyl azide, 7570-25-4; 1,2,3-triazole, 288-36-8; 2*H*-azirine, 157-16-4; ketene imine, 17619-22-6; methyl isocyanide, 593-75-9; aminoacetylene, 52324-04-6; *N*-methylidynemethanaminium hydroxide, inner salt, 61170-69-2; 1*H*-azirine, 157-17-5; vinyl nitrene, 64987-66-2; acetonitrile, 75-05-8; cuprous oxide, 1317-39-1.

(28) Meek, J. S.; Fowler, J. S. *J. Am. Chem. Soc.* **1967**, *89*, 1967; *J. Org. Chem.* **1968**, *33*, 985-987 and literature cited therein.
(29) Kos, A.; Schleyer, P. von R., private communication.

Zwitterionic Bicyclobutane: An Intermediate in the Course of a Nucleophilic Vinylic-like Substitution Reaction on 3-Halobicyclobutanecarbonitrile[1]

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Abstract: In the nucleophilic reaction of the alkoxides MeO^-, EtO^-, *i*-PrO^-, and $CF_3CH_2O^-$ with 3-halobicyclobutanecarbonitrile (**1**-Cl, -Br), the ketal 3,3-dialkoxycyclobutanecarbonitrile (**2**) together with small amounts of the vinylic compound **3** were obtained. Rate constants for the reaction of **1** with MeO^-, EtO^-, and *i*-PrO^- in the parent alcohols were determined at 25 °C. In the reaction of MeO^- in MeOH, the reversible formation of the iminomethoxy compound **4** was also observed. The element effect $k_{Cl/Br} \approx 4$ indicates that in the first step of the reaction the nucleophile cleaves the central bond of **1** rather than the bond to the leaving group. In this step, a cyano-stabilized carbanion is formed on C-1 and a halo ether on C-3 of the molecule. Evidence is presented to show that unlike the addition–elimination mechanism in nucleophilic vinylic substitution reactions, there is no ring closure coupled with the expulsion of the nucleofuge to give the alkoxybicyclobutane **5**. Instead, the halo ether decomposes to give oxocarbenium paired with both the carbanion on C-1 and the halide ion (path b, Scheme I). In the reactions of **1** with $CF_3CH_2O^-$ in *t*-BuOH, the (2,2,2-trifluoroethoxy)carbenium is captured by a trifluoroethoxy ion to give **2** (R = CF_3CH_2) and by *t*-BuOH (which is otherwise unreactive) to give the two cis–trans isomers of the mixed ketal **6**. In these reactions, the less stable isomer **6t** is obtained preferentially over the more stable one **6c**. This behavior is typical in cases where protonation of the cyclobutanic carbanion is the stereochemically controlling step. The ratio **2** (R = CF_3CH_2):**6** is significantly affected by the halogen identity (Cl or Br), whereas there is no element effect on the cis–trans partition of the two isomers of **6**. These last two observations together with analysis of rate constant ratios for similar reactions strongly support a reaction pathway in which the nucleofuge departs to give a zwitterionic intermediate before the carbanion is protonated or nucleophilically displaces the nucleofuge to form the covalent alkoxybicyclobutane **5**. The zwitterionic species is in fact a bicyclobutane derivative in which the central bond is ionic rather than covalent. The origin of the barrier for the transformation of this ionic bond to a covalent one is discussed.

Although formally a single bond, the central bond of bicyclobutane closely resembles a carbon–carbon double bond in its chemical behavior. This is manifested, for example, in its ability to participate in polymerization reactions,[3a,b] to add various electrophiles such as acids and halogens,[3a,b] to trap benzyne intermediates,[3c] and when suitably activated, to undergo nucleophilic addition reactions.[2,4] Nevertheless, to the best of our knowledge it was not reported to undergo a nucleophilic substitution reaction at the bridgehead carbon ("vinylic-like" position) analogously to suitably substituted olefins.[5]

Nucleophilic vinylic substitution reactions are extensively documented in the literature.[5,6] The most common mechanism

(1) Presented in part in the 49th Israel Chemical Society Meeting, Oct 1982. This is part 5 in the series Cyclobutane–Bicyclobutane Systems. For part 4, see: Hoz, S.; Aurbach, D.; Avivi, C. *Tetrahedron Lett.* **1983**, 1639.
(2) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc.* **1980**, *104*, 2340.
(3) (a) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749. (b) Hall, J. K.; Blanchard, E. P.; Cherkofsky, S. C.; Sieja, J. B.; Sheppard, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 110. (c) Pomerantz, M.; Wilke, R. N.; Gruber, G. W.; Roy, U. *Ibid.* **1972**, *94*, 2752.
(4) Hoz, S.; Aurbach, D. *Tetrahedron* **1979**, *35*, 883.
(5) (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (b) Modena, G. *Ibid.* **1971**, *4*, 73.

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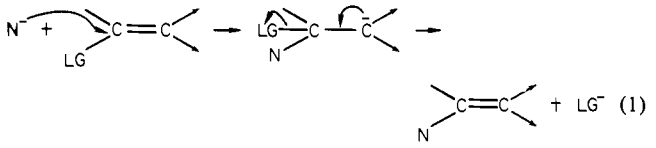
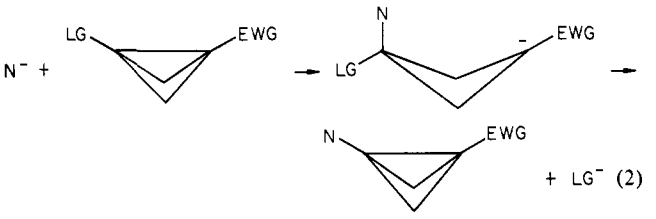
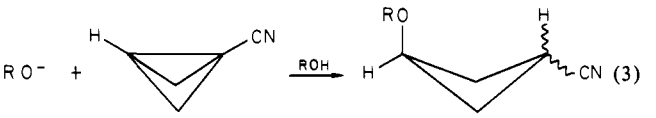
for these reactions is the so called "addition–elimination" mechanism (eq 1).[5,6]



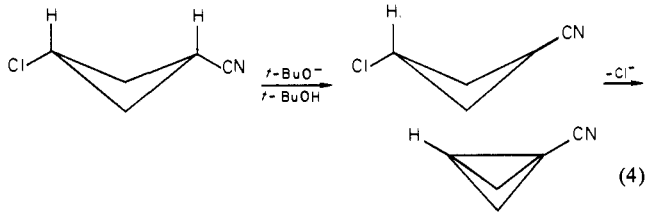
On the basis of the similarity between the π bond of olefins and the central bond of bicyclobutane, one should also expect a properly substituted bicyclobutane to undergo nucleophilic exchange of a leaving group attached to one of the bridgehead carbons according to eq 2.



This mechanism consists of two major steps, the first of which is a nucleophilic cleavage of the central bond in a Michael type reaction and the second one is a nucleophilic ring-closure reaction which is accompanied by expulsion of the leaving group in an E1cB mechanism. These two steps which compose the nucleophilic vinylic-like mechanism are known to operate separately in the cyclo-/bicyclobutane systems. We have previously shown that bicyclobutane, when activated by a cyano group, undergoes facile nucleophilic additions of alkoxides across its central bond (eq 3).[2]

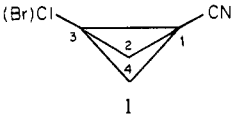


Moreover, in these reactions it competes successfully with analogous olefins such as crotonitrile.[4] We have also shown in a quantitative study that the expulsion of chloride ion from 3-chlorocyclobutanecarbonitrile 1-anion is as rapid as the protonation of this carbanion by a solvent molecule (eq 4).[7]



The demonstrated ability of the cyclo-/bicyclobutanic system to participate in the two steps of which the addition–elimination mechanism (eq 2) consists indicates the feasibility of this system to undergo nucleophilic vinylic-like displacement reactions.

In this study we report the reactions of 3-chloro- and 3-bromobicyclobutanecarbonitrile (**1**-Cl, -Br) with alkoxides as nucleophiles in various solvents.



1

In spite of the close similarity between bicyclobutane and olefins and in spite of the existing precedents for each of the elementary steps, the rather large distance between positions 1 and 3 and the need for ring and carbanion inversion before eliminating the leaving group channel the reactions into a different and rather unexpected course.

(6) Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1.

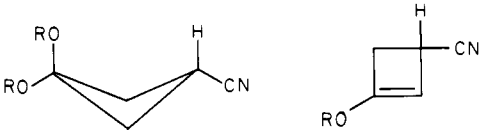
Table I. Second-Order Rate Constants and Element Effects for the Reactions of 1-Cl and 1-Br with Alkoxide in the Parent Alcohol[a]

substrate[b]	alkoxide[c]	$10^4 k_1$, M^{-1} s^{-1}	k_{Cl}/k_{Br}
1-Cl	MeONa	4.03 ± 0.47	3.7
1-Br		1.1 ± 0.09	
1-Cl	EtONa	2.46 ± 0.2	4.7
1-Br		0.52 ± 0.04	
1-Cl	*i*-PrONa	4.5 ± 0.5[d]	1.8
1-Br		2.5[e]	

[a] At 25 °C. [b] Concentration 0.1–0.01 M. [c] Concentration 0.4–0.1 M. [d] Average of two experiments. [e] Single experiment.

Results

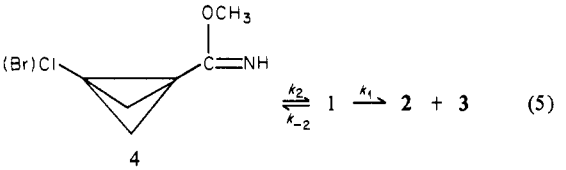
The major products of the reaction of **1** with the alkoxides CH_3O^-, $CH_3CH_2O^-$, $(CH_3)_2CHO^-$, and $CF_3CH_2O^-$ are the 3,3-dialkoxy ketals **2**, which were accompanied by various amounts



2 **3**

(0–20%) of olefinic products **3**. The amounts of **3** obtained in the reaction were found to depend on the individual reaction conditions and were usually larger for **1**-Cl than for **1**-Br. The kinetics of the reaction of **1**-Cl and **1**-Br with the first three alkoxides in the parent alcohols were studied at 25 °C. The reactions were followed by gas chromatography after separation of aliquots by ether extraction from an aqueous solution.

Reaction of 1-Cl and 1-Br with CH_3O^- in CH_3OH. This reaction exhibits unusual behavior in that the fastest step in this system is neither the formation of **2** nor of **3** but rather the reversible formation of the iminomethoxy compound **4** (eq 5).



4 (5)

By use of the following set of equations (eq 6–8), the experimental data were analyzed by a computer simulation technique similar to that previously described.[7] The rate constants k_1, k_2, and k_{-2} are 4.0×10^{-4}, 14.5×10^{-4}, and 3.8×10^{-4} M^{-1} s^{-1} for **1**-Cl and 1.0×10^{-4}, 15.1×10^{-4}, and 2.9×10^{-4} M^{-1} s^{-1} for **1**-Br. In all the reactions of **1**-Cl with CH_3O^- in CH_3OH, 4–5% of the olefinic compound **3** was obtained. The amount of this product dropped to 0–2% for **1**-Br.

$$\Delta[\mathbf{2}]/\Delta t = k_1[\mathbf{1}] \quad (6)$$

$$\Delta[\mathbf{1}]/\Delta t = k_{-2}[\mathbf{4}] - (k_2 + k_1)[\mathbf{1}] \quad (7)$$

$$\Delta[\mathbf{4}]/\Delta t = k_2[\mathbf{1}] - k_{-2}[\mathbf{4}] \quad (8)$$

Reactions of 1-Cl with CH_3O^- in Aprotic Solvents. The reactions were carried out in THF and dimethoxyethane at 25 °C. In both cases the reaction mixtures were heterogeneous due to the low solubility of CH_3ONa in these solvents. The major product was again the ketal **2**. There was no indication of any appreciable formation of **4**, and there was an increase in the amount of **3** (ca. 12%) obtained.

Reactions of 1-Cl and 1-Br with $CH_3CH_2O^-$ in CH_3CH_2OH. The reactions are second order overall, first order in the substrate **1** and first order in the alkoxide. The major product was the ketal **2**, which was accompanied by 4–6% of **3** (not isolated, identified only by GC-MS). No appearance of an iminoalkoxy (**4**) intermediate was detected. The kinetic data for these reactions are given in Table I.

(7) Hoz, S.; Albeck, M.; Livneh, M. *J. Am. Chem. Soc.* **1979**, *101*, 2475.

Table II. Product Distribution in the Reactions of 1-Cl and 1-Br with $CF_3CH_2O^-$ in *t*-BuOH-CF_3CH_2OH[a]

substrate	[1]	$[CF_3CH_2O^-]$	$[CF_3CH_2OH]$	% reaction	% 3 (R = CF_3CH_2)	[2 (R = CF_3CH_2)] / (6c + 6t)	[6t] / [6c]
1-Cl	0.04	0.15	0.15	96	44	2.06	1.6
1-Br	0.025	0.15	0.15	85	34	4.03	1.4
1-Cl	0.04	0.1	0.15	95	42	2.45	1.45
1-Br	0.025	0.1	0.15	72	32	4.23	1.56
1-Cl	0.025	0.045	0.805	49	20	4.36	1.44
1-Cl	0.025	0.135	0.715	89	24	4.1	1.9

[a] At 30 °C.

Reaction of 1-Cl and 1-Br with *i*-PrO⁻ in *i*-PrOH. Reaction products are the ketal **2** and the vinylic compound **3** obtained in 10–13% from **1**-Cl and only 0–5% from **1**-Br. Rate constants obtained for ketal formation are of low accuracy and can serve only as a rough means for comparison purposes. In the presence of an equivalent amount of 18-crown-6 ether, the reaction rates increased for both **1**-Cl and **1**-Br by ca. 6-fold. The kinetic data are given in Table I.

Reactions of 1-Cl with *t*-BuO⁻ in *t*-BuOH. In 0.1 M *t*-BuO^- at 30 °C, the reaction is relatively very slow. None of the "normal" products were obtained. Instead, a single product (suspected to be 3-chlorobicyclobutanecarboxamide) formed and then disappeared. Catalytic hydrogenation of the reaction mixture gave carboxamidocyclobutane as the main product.

Reactions of 1-Cl with $CF_3CH_2O^-$ in *i*-PrOH in the Presence of CF_3CH_2OH. In addition to **2** and **3** wherein R = CF_3CH_2, two geometrical isomers of a mixed ketal where one of the alcohol groups was CF_3CH_2O and the other *i*-PrO were obtained. Isomerization experiments in *i*-PrO^-–*i*-PrOH showed that the equilibrium constant for these two isomers is 1.7. The more stable isomer is probably the one having the trifluoroethoxy and the cyano groups trans to each other. Nevertheless, under the reaction conditions the unstable isomer was obtained in a higher proportion. The isomer ratio remained constant for several days under the reaction conditions. In the presence of 0.2 M $CF_3CH_2O^-$ in CF_3CH_2OH:*i*-PrOH 1:1 (v/v) the percentages of the products **2**:**3**:stable isomer:less stable isomer of the mixed ketal were 72:10:8:10, respectively. When the amount of CF_3CH_2OH in the solvent was reduced to 0.1 M, the percentages were 17:22:24:37, respectively. It is important to note that no **3**, R = *i*-Pr, and no **2**, R = *i*-Pr, were obtained.

Reactions of 1-Cl and 1-Br with $CF_3CH_2O^-$ in *t*-BuOH in the Presence of CF_3CH_2OH. The general picture resembled very much that of the reaction of **1** with the same nucleophile in *i*-PrOH. Again neither **2** nor **3** with R = *t*-Bu were obtained. The formation of the less stable isomer of the mixed ketal is preferred under the reaction conditions. Isomerization experiments in *t*-BuOH–t-BuO^- gave a $K = 2.6$ for the two isomers of the mixed ketals. In Table II the ratios of the various reaction products are given for two pairs of reactions of **1**-Cl and **1**-Br.

In general, the ratio of **3** (R = CF_3CH_2) to the rest of the products ranges from 0.3 to 0.8. This ratio is smaller by about 30% in the reactions of **1**-Br as compared to those of **1**-Cl.

Inspection of Table II reveals the major following features: (a) As can be seen from the reaction percentage, the reactions of **1**-Cl are faster than those of **1**-Br. (b) There is a relatively large element effect on the ratio of the bis(trifluoroethoxy) ketal to the total of the mixed ketals. (c) There is no element effect on the stereodistribution of the two isomers of the mixed ketals. (d) The ratio **2** (R = CF_3CH_2)/**6** is insensitive to the nucleophile $CF_3CH_2O^-$ concentration and remains constant (within experimental error) in spite of a 3-fold change in its concentration when the total concentration $[CF_3CH_2O^-] + [CF_3CH_2OH]$ remains constant (last two rows of Table II).

Discussion

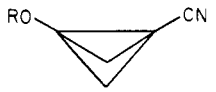
In analogy with the addition–elimination mechanism which prevails in nucleophilic vinylic substitution reactions,[5] a conceivable mechanism for the halide displacement from **1** is a two-step mechanism as depicted in eq 2. In recent years, some doubt has been cast on the generality of this stepwise mechanism in vinylic systems;[5a,8] in an alternative concerted mechansim suggested, bond formation and leaving group departure merge into a single transition state.[9,10] The major probe for distinguishing between these two mechanisms is the element effect k_{Br}/k_{Cl}.[5a] In system **1**, substitution of Cl by Br reduced the rate constants by ca. 4-fold. This was found for MeO^-–MeOH, EtO^-–EtOH, and *i*-PrO^-–*i*-PrOH (Table I). The reaction of $CF_3CH_2O^-$ in *t*-BuOH was also found to be somewhat slower when bromide instead of chloride was the nucleofuge. These observations rule out the likelihood for a direct displacement of the nucleofuge and indicate that the nucleophilic cleavage of the central bicyclic bond is the rate-limiting step. Additional evidence for preferred ring cleavage is provided by the reaction of **1**-Cl with CN^- in MeOH. In this reaction the central bond is cleaved to give 3-chloro-3-cyanocyclobutanecarbonitrile, after protonation, as one of the reaction products.[11] This also demonstrates that in these reactions the nucleophilic attack is coupled with ring opening rather than with a cleavage of the bond to the leaving group.

The preference of nucleophilic ring opening to direct displacement of the nucleofuge probably stems from two sources. The first one emerges from the unique geometry of the molecule. The bridgehead carbon of bicyclobutane has inverted geometry.[12] Approach of the nucleophile from the "exposed" side of the bridgehead carbon produces the "anti geometry" needed for cleavage of the central bond. However, this direction of approach entails a front side attack on the C–halogen bond, which is obviously less favored for direct nucleophilic displacements. The second reason for this preference lies in the strain associated with the central bond. There is strong evidence that olefins activated by strongly electron-withdrawing groups (pK_a of H–C (activating group) ranging from 10 to 20) react by the stepwise mechanism rather than by the concerted nucleophilic displacement.[5a] Since the pK_a of CH_3CN is ca. 25,[13] the cyano group only activated the central bond of **1** slightly. However, ca. 40 Kcal/mol are released upon going from bicyclobutane to cyclobutane.[14] This is equivalent to more than 20 pK_a units at room temperature thus rendering the activating power of the entire system (ring and cyano group) equivalent to that of so-called highly activating groups. Therefore, as in vinylic reactions, these factors should channel the reaction into the stepwise mechanism. Thus both experimental observations and theoretical grounds support the assumption that in the first step of the reaction the central bond of **1** is cleaved while the nucleofuge remains bonded to the bridgehead carbon.

Mechanism of Ketal Formation. In the previous section we showed that the first step of the reaction is as depicted in eq 2. Completion of this stage of the reaction as described by the second

(8) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.
(9) Maffeo, C. V.; Marches, G.; Naso, F.; Ronzini, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 92.
(10) Dodd, D.; Johnson, M. D.; Meeks, B. S.; Titonmarsh, D. M.; Doung, K. N. V.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1261.
(11) Hoz, S.; Aurbach, D., unpublished results. In this reaction, which was performed under codnitions similar to those reported in this paper, the products were: 3,3-dimethoxycyclobutanecarbonitrile (ca. 4.0%), 1,3-dicyanobicyclobutane (ca. 20%), and 3-chloro-3-cyanocyclobutanecarbonitrile (ca. 40%).
(12) Cox, K. W.; Harmony, M. D.; Nelson, G.; Wiberg, K. B. *J. Chem. Phys.* **1969**, *50*, 1976.
(13) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.
(14) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.

step of this equation leads to the formation of 3-alkoxybicyclobutanecarbonitrile (**5**). Then ketal formation can formally be



5

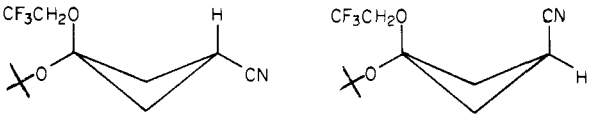
viewed as addition of alcohol across the central bond. However, one should note the following points: First, no **5** was ever found in the course of the reactions. This holds for reactions carried out with excess of alkoxide compared to **1**, as well as for experiments in which the concentration of **1** was higher than that of the nucleophile. Second, replacement of halide by alkoxide in nucleophilic vinylic substitution reactions considerably reduces the reactivity toward further nucleophilic attacks.[15] The same conclusion can be also reached from a comparison of rate constants for nucleophilic attack on activated aromatic compounds.[16] Third, if **5** is indeed the precursor of **2**, then one should expect product distribution to be unaffected by the identity of the leaving group. Yet it is clearly shown in Table II that there is a large element effect on the product distribution. Thus it is quite obvious that the alkoxybicyclo compound **5** is not an intermediate lying on the reaction pathway.

An alternative mechanism that circumvents the intermediacy of **5** involves an oxocarbenium ion as shown in Scheme I. This oxocarbenium ion can either be formed after protonation on C-1 (path a) or prior to it (path b). In order to prove the intermediacy of the oxocarbenium ion (without, at this stage, relating to the exact order of the reaction steps), we carried out trapping experiments in mixed alcohols. The key experiment involves reaction with $CF_3CH_2O^-$ in *t*-BuOH which gives the mixed ketal. We have already shown that, compared to other alkoxides, *t*-BuO^- reacts with **1**-Cl very slowly. Moreover, the main product in the reaction with *t*-BuO^- is the corresponding amide rather than the expected ketal. However, in the reaction of **1** with $CF_3CH_2O^-$ in *t*-BuOH there is practically no *t*-BuO^- present. (The possibility of *t*-BuO^- being present was further reduced by adding small amounts of trifluoroethanol to the reaction mixture—see Table II). Furthermore, even in the reaction of $CF_3CH_2O^-$ in the more acidic *i*-PrOH in which the mixed ketals were also obtained, neither **2** (R = *i*-Pr) nor **3** (R = *i*-Pr) were observed, although *i*-PrO^- itself can react as a nucleophile toward **1**-Cl. Thus it is obvious that the incorporation of *t*-BuO into the mixed ketal must result from a reaction between a *t*-BuOH molecule and a highly reactive intermediate. We believe that the only plausible intermediate for this reaction is an oxocarbenium ion as shown in Scheme I.

The formation of the vinylic product **3** is also consistent with this oxocarbenium intermediate. Under these mild conditions no other bicyclobtuane is known to rearrange to give an olefin having structure **3**. Its formation is therefore best interpreted as loss of a proton from the intermediate oxocarbenium ion by an E1 mechanism.

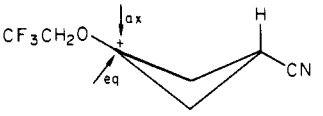
The Stereochemistry of the Reaction. Unlike the reactions that result in the formation of a ketal with two identical alkoxy groups, reactions in which mixed ketals are formed are useful probes for gaining a deeper insight into the reaction mechanism since they give rise to two geometrical isomers. If the two alkoxy groups differ significantly in their steric requirements, then the two isomers will also differ in their stability. In general, in 1,3-disubstituted cyclobutanes, the bulkier substituents prefer to adopt equatorial positions.[17] Therefore the more stable isomer of 3-(2,2,2-trifluoroethoxy)-3-*tert*-butoxy ketal **6** will probably be that in which the CN and *t*-BuO groups are cis to one another (**6c**) (and in the equatorial conformation). In the less stable isomer (**6t**), these groups will be in a trans configuration.

In those reactions in which these products are obtained, it is the less stable isomer that is preferentially obtained (Table II).



6c 6t

This preference for the formation of the less stable isomer in the kinetically controlled reactions is typical of carbanion protonation which determines the stereochemistry of the reaction. This was first pointed out by Zimmerman, who recognized it as being steric in nature.[18] We have recently shown that equatorial approach of the proton donor is also the preferred one in the protonation of 1-cyclobutanecarbonitrile carbanions and probably for the same reason.[2,7] This strongly suggests that the preferred formation of **6t** is due to protonation being the stereochemistry-determining step. This step must therefore be the last step of the reaction, as is shown in path b of Scheme I. If protonation of the carbanion occurred prior to incorporation of the *t*-BuOH into the molecule, then this latter step would be the one that governs the stereochemistry. However, for the very same reason that requires the preferred equatorial approach of a proton donor to the carbanion, equatorial approach of the bulky *t*-BuOH to the hypothetical intermediate **7** will be very much more favored than the axial



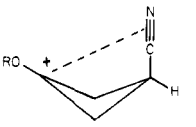
7

approach. Equatorial approach of *t*-BuOH, contrary to the experimental observation of this study, would lead to the preferred formation of **6c** rather than **6t**.[19,20]

The element effect on product distribution in the reaction of **1** with $CF_3CH_2O^-$ in *t*-BuOH also strongly supports our presumption that it is indeed pathway b of Scheme I that properly describes the actual reaction mechanism. As can be seen from Table II, the identity of the halogen affects the ratio **2** (R = CF_3CH_2)/**6**. This element effect apparently results from ion pairing between the halide and the oxocarbenium ion. The assumed intermediacy of ion pairs also derives support from the fact that the fraction of olefin **3** in the product was found to be a function of the halogen atom in **1**. This fraction increases in the order Cl > Br. The same phenomenon was reported by Bunnett et al.[21] for the solvolysis of 2-halo-2,3,3-trimethylbutanes where the reaction is known to proceed via ion pairs.

(15) Scotti, F.; Frazza, E. J. *J. Org. Chem.* **1964**, 29, 1800. Soulen, R. L.; Clifford, D. B.; Crim, F. F.; Johnston, J. A. *Ibid.* **1971**, *36*, 3386.
(16) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
(17) Moriarty, R. M. *Top. Stereochem.* **1974**, *8*, 271.

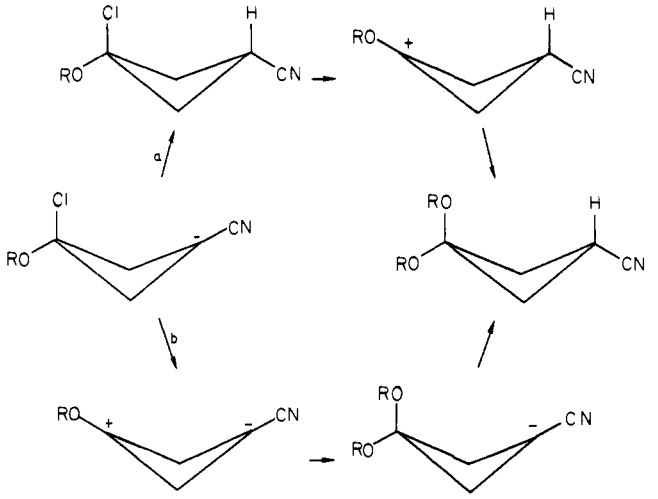
(18) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549. Zimmerman, H. E.; Nevis, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559. Zimerman, H. E.; Mariano, P. S. *Ibid.* **1968**, *90*, 6091.
(19) It should be noted that equatorial approach to the other conformer of **7**, in which CN adopts an axial position, will lead to the less stable isomer. However, the incipient interaction between the CN and the trifluoroethoxy group will raise the energy of this transition state, and therefore the former process is favored.
(20) In principle, cyclic structures such as **8** in which the π system of the



8

cyano group serves to stabilize the oxocarbenium ion can be invokved. However, in another study, (Hoz, S.; Aurbach, D., unpublished results) the possible intermediacy of the bridged cation having the structure of **8** (PhS instead of RO) is excluded. In this study **1**-Cl reacted with PhS^- in MeOH and the less stable isomer was also preferentially obtained although the "initiating" nucleophile PhS^- is bulkier than MeO^-. An additional argument against the inclusion of **8** in the reaction scheme can be obtained from solvolytic studies of 1-ethoxy- and 1-phenyl-3-tosylcyclobutane. Regarding the interactions between positions 1 and 3 it was concluded that "no important π interaction with phenyl or the ethoxy is possible" (Wiberg, K. B.; Nelson, G. L. *Tetrahedron Lett.* **1969**, 4383). The intermediacy of **8** is of a very low probability since the cyano group when compared to the latter two substituents is a much poorer π donor.
(21) Bunnett, J. F.; Eck, D. L. *J. Org. Chem.* **1971**, *36*, 897.

Scheme I



Oddly enough, while the ratio **2** (R = CF_3CH_2)/**6** is dependent upon the halogen identity, the isomeric ratio **6c**/**6t** is not. The stereochemistry of the product must be determined by the last step of the reaction which "locks" the configuration. Since it is highly likely that the paired halide ion, which determines the identity of the entering nucleophile, will also be able to affect the direction of the nucleophile's approach (**6c** and **6t** are obtained in comparable yields, therefore tiny structural changes will have a relatively large effect on their ratio), the fact that it does not clearly indicates that the step in which it is determined whether *t*-BuO or CF_3CH_2O will be incorporated into the oxocarbenium does not determine the stereochemistry of the mixed ketal. Thus, the element effect on the stereochemistry and on the product distribution is consistent with path b of Scheme I. On the other hand, if the reaction proceeds along path a, then entrapment of the second alkoxide group is the step that determines both the product distribution and the stereochemistry of the mixed ketal. Paradoxically, while both are determined in the very same step, product distribution is sensitive to the identity of the halogen whereas the stereochemistry of the mixed ketal is not. Such an unreasonable outcome would lend very low plausibility to path a, of Scheme I.[22]

So far two pieces of evidence have been presented in favor of path b. One based on similar isomeric distribution in the mixed ketal and protonation reactions of cyclobutyl carbanions and the other on the dichotomous behavior of the element effect on the composition and stereochemical distribution of the products in the reaction of **1** with $CF_3CH_2O^-$ in *t*-BuOH.

The last piece of evidence for the existence of a zwitterionic intermediate on the reaction pathway is obtained by comparing the 1,3-elimination and protonation rate constants for the derivatives of cyclobutylcarbonitrile 1-anion. The carbanion of 3-chlorocyclobutanecarbonitrile γ-eliminates Cl^- at the same rate that it incorporates $^3H^+$. When **1**-Cl reacts with CN^- in MeOH,

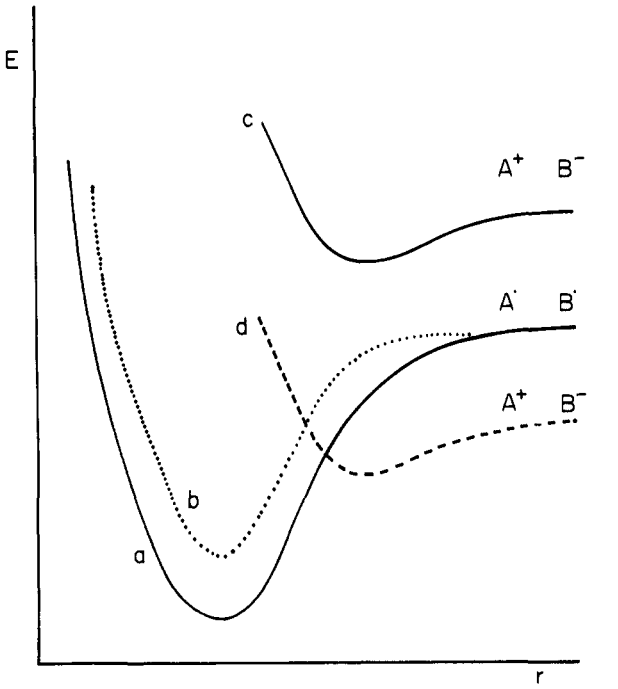


Figure 1. Variation of potential energy (E) as a function of the distance (r). (a) Radical–covalent curve; (b) radical–covalent curve for cyclobicyclobutane system; (c) ionic curve in the gas phase; (d) ionic curve in solution.

the expected 1,3-dicyanobicyclobutane is obtained along with 1,3-dicyano-3-chlorocyclobutanecarbonitrile.[11] Thus, in both systems, protonation of the carbanion and γ-elimination are of comparable rates. Expulsion of chloride from an intermediate in which the geminal group is an alkoxide, as in our case, is expected to be very much faster than from an intermediate in which the geminal group is CN or H. Yet contrary to this, no alkoxybicyclobutane, the expected product of this reaction, is formed in these reactions. Therefore one must conclude that another process takes place at a rate faster than that of the ring-closure reaction (and thus is also faster than protonation on C-1). *This process must be "uncoupled" expulsion of* the *halide ion, which leads directly to the zwitterionic intermediate* shown in Scheme I. This intermediate, as indicated by the stereochemical course of the reaction, first undergoes nucleophilic addition of an alcohol molecule and then protonation at the anionic center C-1.

The Nature of the Zwitterionic Intermediate. In the previous section, we have shown that there is high probability for the existence of a unique cyclobutanic zwitterionic intermediate on the reaction pathway. Attention should be drawn especially to two points of primary importance. The first is the unexpected failure of the intermediate to collapse to the covalent compound **5**, and the second is that, in spite the expected extremely short lifetime of the carbanion on C-1, an oxocarbenium ion on C-3 is both formed and annihilated before the carbanion is protonated. The protonation rate on C-1 is expected to be very fast and probably to approach the diffusion-control region.[23] Yet as we have noted above protonation is *not* the immediate step following carbanion formation.

In order to shed some light on this peculiar moiety, it is worthwhile to use concepts generally associated with ion pairs and ionic bonds.

Covalent bonds are usually shorter than ionic ones.[24] Two hypothetical Morse curves for the ionic and covalent bonds are

(22) An alternative explanation for path a can be advanced by assuming an additional step in which the oxocarbenium ion pairs dissociate into free ions. Both, the free and the paired oxocarbenium ions incorporate alcohol molecules. The free ions will incorporate *t*-BuOH leading to the mixed ketal and therefore its stereodistribution should be independent of the nucleofuge identity, whereas the paired oxocarbenium will react *exclusively* with $CF_3CH_2O^-(H)$. The element effect results from the differnet proportions of paired and free ions obtained from **1**-Cl and **1**-Br. The following two arguments suggest low probability for this mechanism. (a) The insensitivity of the isomeric distribution to the halogen atom dictates that *t*-BuOH will react almost exclusively with the free ions. Such selectivity, however, is not expected since, as can be inferred from the last two rows of Table II, the oxocarbenium ion does not distinguish between $CF_3CH_2O^-$ and CF_3CH_2OH and therefore it is highly likely that *t*-BuOH will also react to an applicable extent with the paired oxocarbenium ion leading to element effect on the stereodistribution as well. (b) As was explained previously, if the reaction proceeds along path a, the stereochemistry of the product is expected to differ from the one observed. Thus path a can be safely ruled out even in its modified form. Moreover, the other arguments presented in the text are consistent with path b and not with a.

(23) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829; **1972**, *94*, 2647.

(24) This is nicely exemplified by the alkali metal halides, where the monovalent ionic and covalent radii are known (Sargent-Welch; table of periodic properties of the elements) except for the fluoride whose ionic radius is uniquely small. See also: Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY, 1972; Chapter 13.

depicted in Figure 1. Transfer to solvent will affect mainly the ionic curve and would probably drastically lower it below the covalent one. Inspection of the two curves in solution shows that *in order for the ionic bond to collapse to a covalent one, the system must go over a barrier whose height is determined by the point of intersection of the two curves.* This in fact is a suitable model for the general description of intimate ion pairs. There are, however, two distinct differences between ion pairs in general and the zwitterionic intermediate at hand. In the cyclobutane, the ion pairs are confined in a single molecule possessing a relatively high rigidity, and thus the two charged units can not diffuse from each other. On the other hand, the barrier for collapse of the zwitterionic intermediate will be even higher since as strain is introduced into the system in the process of shortening the C-1–C-3 distance, the energy of the covalent curve in the bonding zone increases (dotted curve in Figure 1) as does the intersection point, giving rise to an even higher barrier. Thus, one can in fact regard alkoxybicyclobutane **5** as an intermediate in the mechanism of the reaction, provided that *the line connecting carbon atoms 1 and 3 is taken as symbolizing an ionic rather than a covalent bond.* Collapse to the covalent structure can not be a spontaneous process due to the energy barrier separating the two bicyclobutanic species. In addition, the carbanion on C-1, once incorporated into the ionic bond, would not be expected to undergo a diffusion-controlled protonation since its reactivity is largely moderated by its positively charged counterpart.

Experimental Section

General. H NMR spectra were recorded on Varian HA-100 and EM 360A spectrometers. The ^{13}C spectra were taken with a Varian CFT-20 spectrometer. Mass spectra were taken with a Finnigan 4000 mass spectrometer (EI, CI, CH_4). For analytical purposes a Packard Model 878 (FI detector) gas chromatograph was used whereas for preparative separation a Varian 920 gas Chromatograph (TC detector) was used. In both cases the column was of 5–10% XE60 on Chromosorb W acid-washed 60–80 mesh.

Reactants and Products: Preparation and Purification. 3-Chlorobicyclobutanecarbonitrile (1-Cl) was prepared according to published procedure.[2b] The 3-bromo derivative 1-Br was prepared in 60% VPC yield by reacting 1.7 g of 1-Cl with bromide ions in a 50 mL of DMF solution saturated with KBr at 30 °C for 3 weeks. The reaction mixture was extracted with ether, washed with water, and dried over $MgSO_4$. The product 1-Br was obtained by preparative separation on VPC after evaporation of the ether. The product, which decomposed slowly at room temperature, was stored at −78 °C: H NMR ($CDCl_3$) δ 1.85 (s, 2 H), 2.55 (s, 2 H); mass spectrum (EI), *m/e* 157, 159, 78, 51; IR (neat) showed CN absorption at 2220 cm^{-1}.

General Procedure for Preparation of 3,3-Dialkoxycyclobutanecarbonitrile (2, R = Me, Et, *i*-Pr). To a solution of 0.2 M alkoxide in the parent alcohol at room temperature 1 was added up to a concentration of 0.15 M. The reactions were followed by VPC. After completion, the mixtures were dissolved in ether, washed with water and dried over $MgSO_4$. The ether was evaporated and the products were purified by preparative VPC. VPC yields were 90–98%. For **2** (R = Me): H NMR ($CDCl_3$) δ 2.3–2.8 (m, 5 H), 3.15 (s, 3 H), 3.2 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ 13.38 (d, CCN), 37.23 (t, CH_2), 48.71 (q, CH_3O); mass spectrum (EI), *m/e* 141, 136, 110, 96, 78. Anal. C, H, N. For **2** (R = Et): H NMR ($CDCl_3$) δ 1.2 (two t, 6 H), 2.3–2.9 (m, 5 H), 3.45 (two q, 4 H); mass spectrum (EI), *m/e* 169, 154, 140, 124, 123, 95. Anal. C, H, N. For *2* (R = *i*-Pr): H NMR ($CDCl_3$) δ 1.25 (m, 12 H), 2.4–2.9 (m, 5 H), 3.8–4.2 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.64 (d, CCN), 23.83, 24.09 (d, CH_3), 40.00 (t, CH), 65.70 (d, CHO); mass spectrum (CI), *m/e* 198, 156, 145, 138, 114, 103, 96, 85, 82. Anal. C, H, N. In these reactions, the cyclobutene **3** was obtained in a very low yield. Somewhat higher yields were obtained by performing the reaction in THF saturated with the desired alkoxide. After 3–4 weeks at 30 °C about 10–20% of the cyclobutene **3** was obtained. For **3** (R = Me): H NMR δ ($CDCl_3$) 3.0 (m, 3 H), 3.6 (s, 3 H), 4.5 (d, 1 H), mass spectrum (EI), *m/e* 109, 97, 66, 52. **3** (R = Et) was not isolated: mass spectrum (EI, by VPC-MS), *m/e* 123, 118, 78. For **3** (R = *i*-Pr): H NMR δ ($CDCl_3$) 1.3 (m, 6 H), 2.95 (m, 2 H), 3.2 (m, 1 H), 4.3 (m, 1 H), 4.5 (d, 1 H); mass spectrum (EI) m/e 137, 95, 78, 67, 52, 51, 43. In order to isolate **4** (Cl or Br), the reaction of 1 with MeO^- in MeOH was quenched with water when 4 reached its maximum concentration, (60%) after work up as previously described, the product was isolated by preparative VPC. 4-Cl: H NMR δ ($CDCl_3$) 1.6 (m, 2 H), 2.5 (m, 2 H), 3.8 (s, 3 H); IR, broad peak at 1620 cm^{-1}; mass spectrum (CI), *m/e* 148, 146, 147, 145, 132, 130, 116, 114, 115, 113, 110. The analogous bromo compound, **4**-Br, was not isolated: mass spectrum (EI, by VPC-MS), *m/e* 191, 189, 190, 188, 159, 157, 110, 78.

Reactions of 1 with $CF_3CH_2O^-$ in *t*-BuOH. To a 0.1 M solution of *t*-BuO^- in 80 mL of *t*-BuOH 0.9 mL (12 mmol) of CF_3CH_2OH and about 4.8 mmol of 1 were added. VPC analysis after 24 h at 40 °C showed that 1 had reacted completely to give about 55% **2** (R = CF_3CH_2), 25% **3** (R = CF_3CH_2), 10% **6t**, and 5% **6c**. Compound **2** (R = CF_3CH_2) was not prepared by a reaction of $CF_3CH_2O^-$ with 1 in the parent alcohol since in this solvent the reaction was much slower. Spectral data for **2** (R = CF_3CH_2): H NMR δ ($CDCl_3$) 2.4–2.8 (m, 5 H), 3.8 (q, 4 H); IR (neat) 2220 cm^{-1}; mass spectrum (CI), *m/e* 278, 257, 196, 178. Anal. C, H, N, F. **3** (R = CF_3CH_2): H NMR δ ($CDCl_3$) 3.0 (m, 2 H), 3.2 (m, 1 H), 4.15 (q, 2 H), 4.65 (m, 1 H); mass spectrum (CI), *m/e* 178, 150. Anal. C, H, N, F. Upon heating (110–130 °C in the gas chromatograph) **3** (R = CF_3CH_2) apparently gave the electrocyclic ring-opening product 1-cyano-3-(2,2,2-trifluoroethoxy)butadiene: H NMR δ ($CDCl_3$) 4.15 (q, 2 H), 4.6 (m, 2 H), 5.8 (d, 1 H), 6.8 (d, 1 H); IR (neat) 2215 cm^{-1}; molecular weight by mass spectrum 177; mass spectrum (CI), *m/e* 178, 157, 150, 131, 83. **6t** (less stable isomer): H NMR δ ($CDCl_3$) 1.25 (s, 9 H), 2.6–2.9 (m, 5 H), 3.75 (q, 2 H); mass spectrum (CI), *m/e* 252, 246, 224, 195, 178, 152. Anal. C, H, N, F. **6c** (more stable isomer): H NMR δ ($CDCl_3$) 1.3 (s, 9 H), 2.6–2.9 (m, 5 H), 3.8 (q, 2 H); mass spectrum identical with that of **6t**.

The mixed ketals, *cis*- and *trans*-3-isopropoxy-3-(2,2,2-trifluoroethoxy)cyclobutanecarbonitrile were obtained analogously by using *i*-PrOH instead of *t*-BuOH as solvent. The two isomers were obtained in almost equivlaent amounts. H NMR of the more stable isomer δ ($CDCl_3$) 1.2 (d, 6 H), 2.4–2.8 (m, 5 H), 3.75 (q, 2 H), 3.95 (m, 1 H). Anal. C, H, N, F. Mass spectrum (CI) of both isomers, *m/e* 238, 196, 178, 138. The less stable isomer could not be obtained in its pure form since in the preparative VPC procedure it was always contaminated with relatively large quantities of **2** (R = CF_3CH_2).

Isomerization Experiments. Equilibrium constants for the mixed ketals (2,2,2-trifluoroethoxy)isopropoxy- and (2,2,2-trifluoroethoxy)-*tert*-butoxycyclobutanecarbonitrile were measured in *i*-PrOH and *t*-BuOH, respectively, at 25 °C. In each experiment the two isomers (about 0.1 M) were individually equilibrated with the pertinent alkoxide (about 0.05 M solution) until a constant isomeric ratio (VPC) was obtained.

Reaction of *t*-BuO^- with 1-Cl. A *t*-BuOH solution 0.1 M in *t*-BuO^- and 0.09 M in 1-Cl was incubated at 30 °C for 24 h. In the course of the reaction an intermediate product, which is suspected to be 3-chlorocarboxamidobicyclobutane, formed and then disappeared. Catalytic hydrogenation (H_2/Pd) of the reaction mixture gave as main product carboxamidocyclobutane: H NMR δ ($CDCl_3$) 1.7–2.7 (m, 6 H), 2.8–3.3 (m, 1 H), 5.3–6.5 (m, 2 H); IR (neat) broad absorption centered at 3200 (NH_2) and 1620 cm^{-1} (C=O); mass spectrum (CI), *m/e* 100, 63, 82, 72.

Kinetic Procedure. Stock solutions of the substrates containing biphenyl as an internal standard were prepared and mixed at the reaction temperature with appropriate volumes of alkoxide–alcohol solutions. Samples of ca. 0.1 mL were periodically removed, quenched with water, extracted with ether, and analyzed by VPC. Response ratios were periodically determined. In a few cases it was found that the substrate reacted very fast in the alcohol stock solution. The solutions were found to be acidic, and the reactions were tentatively assumed to result from catalytic amount of impurities inducing autocatalytic acidic addition of alcohol across the central bond of 1 to give **2**. (Kinetic experiments were not performed with these solutions.) Products as well as isomeric distributions remained constant under the reaction conditions.

Acknowledgment. Helpful discussions with Professor W. P. Jencks and Dr. S. S. Shaik are gratefully acknowledged.

Registry No. 1-Cl, 23745-75-7; 1-Br, 87712-20-7; **2** (R = Me), 87712-21-8; **2** (R = CF_3CH_2), 87712-23-0; **3** (R = Me), 87712-22-9; **3** (R = CF_6CH_2), 87712-24-1.