

Table VI. Analytical HPLC Separations for Propellane Reduction Mixtures

substrate	solvent system			flow, mL/min	retention time, min		
	hexane	EtOAc	<i>i</i> -PrOH		dione	ol	ol
[4.3.3]	57	38	5	1.0	7.6	10.0	13.0
[10.3.3]	75	20	5	0.8	7.1	11.5	13.3
[22.3.3]	85	10	5	1.0	5.1	9.3	10.8

substrate	solvent system		flow, mL/min	retention time, min		
	MeOH	H ₂ O		aa	sa	ss
[4.3.3]	50	50	1.0	15.1	9.2	7.2
[10.3.3]	80	20	1.0	13.6	8.6	7.2
[22.3.3]	95	5	1.0	18.0	11.9	10.1

trans-tert-butylcyclohexanol were 5.4 and 7.0 min, respectively. At 135 °C and a flow of 80 mL/min, the retention times for the axial and equatorial *trans*-1-decalols were 9.5 and 11.1 min, respectively.

VIII. HPLC and TLC Analyses of Propellane Reduction Products. HPLC propellane ketol analyses were performed on a Whatman Partisil 10, 4.6 mm × 25 cm column. Diols were analyzed on an IBM ODS-RP C₁₈ (5 μm) 4.5 mm × 25 cm column. Retention times and separation conditions are recorded in Table VI.

TLC (EtOAc eluent) of the propellane reductions was used to verify the presence or absence of diones, ketols, and diols. The following *R_f* values were found. [4.3.3]: dione, 0.54; ketols, 0.36; aa diol, 0.16; as diol,

0.19; ss diol, 0.26. [10.3.3]: dione, 0.76; ketols 0.55; diols, 0.28. [22.3.3]: dione, 0.82; ketols, 0.64; diols 0.31.

IX. Partition Coefficients of the Reduction Substrates. The partition coefficients (Table III) of the reduction substrates between CTAB micelles and water were measured by HPLC as described by Armstrong.¹⁰ An IBM RP-C₈ (5 μm) 4.5 mm × 25 cm column was used. The void volume of the column (determined with NaI) was 2.16 mL. From the total volume of the column (3.98 mL), the volume of the stationary phase was found to be 1.82 mL. Using [CTAB] = 5, 7.5, and 10 mM, substrate retention volumes were measured and the *K_{MW}* values calculated assuming an aggregation number of CTAB of 100.

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Supplementary Material Available: Tables listing the crystallographic data collection details, data reduction and refinement procedures, bond lengths, bond angles, positional parameters, and thermal parameters of the syn,syn propellane diol (*n* = 8) (6 pages); tables of calculated and observed structure factors (11 pages). Ordering information is given on any current masthead page.

Conversion of Cyclobutane to Bicyclobutane by Base-Catalyzed 1,3-Dehydrohalogenation Reaction: A Mechanistic Study¹

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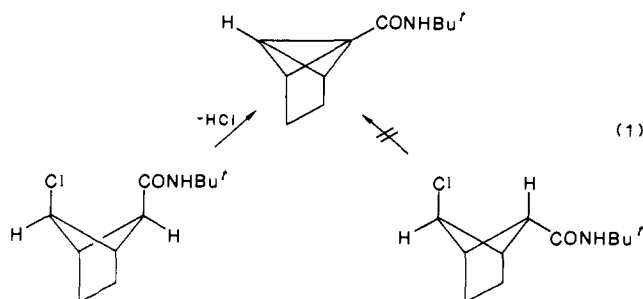
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Abstract: The kinetics of the *t*-BuOK-*t*-BuOH-induced 1,3-dehydrohalogenation of the geometrical isomers of cyclobutanes **2-5** to give the corresponding bicyclobutanes was investigated. Substitution of H by Cl or Me on the carbon bearing the leaving group (substrates **1-3**) caused rate reduction by a factor of 2 only. The cyano-activated substrates with Cl as a leaving group (substrates **1** and **3**) underwent syn-anti isomerization under the reaction conditions. Substrate **2**, which due to local symmetry lacks the geometrical syn and anti isomerism, was found to undergo ³H incorporation during the course of the reaction. In the presence of crown ether, elimination rate constants were significantly enhanced compared to those for isomerization. Negligible isomerization was detected in the reactions of the bromo derivatives **4s** and **4a** as well as in those of the two carbonyl-activated substrates **5a** and **5s**. The effect of added crown ether on the elimination rate constants for the last two substrates was relatively small. The leaving group element effect (*k^{Br}*/*k^{Cl}*) was found to be 71 for the pair **4s**/**3s** and 30 for the pair **4a**/**3a**. On the basis of the analysis of the element effect and supporting data it was concluded that the elimination from the cyano-activated substrates occurs from the hydrogen-bonded carbanion whereas an (E1cB)₁ mechanism was assigned to the reactions of the carbonyl-activated substrates. The results obtained in this study combined with literature data suggest a low probability for a concerted 1,3-elimination reaction in the cyclobutane-bicyclobutane system.

The 1,3-elimination reaction was the key step in the first successful synthesis of bicyclobutane performed by Wiberg et al. about 30 years ago.² In spite of its continually being one of the most useful and popular methods for the preparation of bicyclobutanes,³ this reaction is at best only poorly understood. The stereochemical issue, for example, has been addressed in only three papers, and each of these gave rise to a different conclusion. Thus, Meinwald and co-workers⁴ found that the leaving group (chlorine)

can depart from an *axial* position when the proton assumes an equatorial position (eq 1) whereas the isomer with both the H and the Cl in the axial positions was found to be unreactive.



Several years later, Hall and co-workers⁵ demonstrated in a very

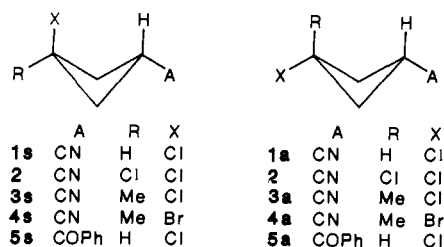
(1) This is part 14 in the series "Cyclobutane-Bicyclobutane System". For part 13, see: Hoz, S.; Basch, H.; Cohen, D. *J. Am. Chem. Soc.*, in press.

(2) Wiberg, K. B.; Ciula, R. P. *J. Am. Chem. Soc.* 1959, 81, 5261.

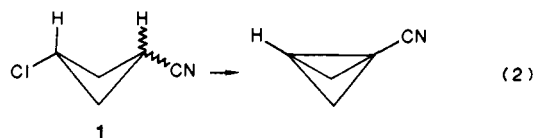
(3) For a comprehensive review on the chemistry of bicyclobutane, see: Hoz, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, in press.

(4) Meinwald, J.; Swithenbank, C.; Lewis, A. *J. Am. Chem. Soc.* 1963, 85, 1880.

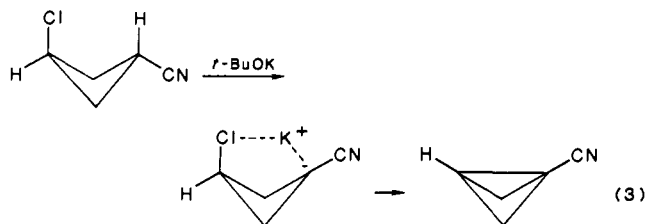
Chart I



elegant experiment using deuterium labeling that in the 1,3 HCl elimination reaction from **1**, the leaving group departs from an equatorial position (eq 2). More recently, we have found⁶ that



in the system studied by Hall and co-workers the syn isomer (throughout this paper syn and anti will refer to the hydrogen and leaving group being eliminated) reacts 15 times faster than the anti isomer under ion-pairing conditions. In the presence of crown ether the reactivity ratio was reduced to 1.56. It was concluded therefore that the metal cation assists the expulsion of the leaving group in a syn-diaxial mode (eq 3).



The contradictory nature of these studies and the absence of basic information in this interesting field prodded us to probe deeper into this useful and important reaction.

Results

The kinetics of the *t*-BuOK-induced 1,3-dehydrohalogenation reactions of substrates **2–5** (Chart I) in *t*-BuOH was followed by gas chromatography. The concentrations of both the base and the substrates were varied in the range 10^{-3} – 10^{-2} M. The reactions were found to be of second-order kinetics, first order in each of the two reactants. The reactions of all substrates except for **2** were followed to completion and gave 100% of the corresponding bicyclobutane. In all cases the reactions were performed under homogeneous conditions (KCl precipitation was observed during the course of the reactions). In each kinetic run at least seven samples of the reaction mixture were periodically removed for GC analysis. The rate constants (k_{el} for the elimination and k_{is} for the isomerization paths) of each reaction are the average of at least five experiments with different concentrations of reactants. However, when the reactions were conducted in the presence of crown ether, the rate constants were usually based on two experiments only. In general, the error in rate constant determination is in the range 2–5%.

Reactions of 2. These reactions were followed up to 50–60% reaction. At higher reaction percentages, the percent of the internal standard in the samples analyzed by GC increases drastically, indicating a loss of material in side reactions. The rate constants $(23.7 \pm 2.5) \times 10^{-3}$ and $(65 \pm 2) \times 10^{-3}$ were determined at two temperatures (30.4 and 50.2 °C, respectively). The activation parameters for this reaction are $\Delta H^\ddagger = 9.3$ kcal/mol and $\Delta S^\ddagger = -21.6$ eu.

Since unlike the other substrates which can undergo syn-anti isomerization, **2** cannot; a measure for the amount of the re-

Table I. Second-Order Rate Constants for the Reaction of Substrates **1–5** with *t*-BuO⁻ in *t*-BuOH at 25 °C

substrate	k_{el} , M ⁻¹ s ⁻¹	k_{is} , M ⁻¹ s ⁻¹	k_{el} , M ⁻¹ s ^{-1 a}
1s	0.027 ^{b,c}	0.025 ^{b,c}	1.31 ^{b,d}
1a	0.0017 ^{b,c}	0.012 ^{b,c}	0.84 ^{b,d}
2	0.0237 ^d		
3s	0.0127	0.0179	1.63
3a	0.0009	0.0176	1.1
4s	0.9		3.95
4a	0.027		2.5
5s	23.9		110
5a	18.5		85.3

^a In the presence of an equivalent amount (to base) of 18-crown-6 ether. ^b Data from ref 6. ^c Calculated from activation parameters. ^d At 30.4 °C.

protonation of the initially formed carbanion was obtained from tritium labeling experiments. These reactions were performed in partly tritiated *t*-BuOH. Quenching the reaction mixture at initial stages after 9% of the elimination products were observed, recovering the unreacted starting material, and analyzing it for ³H showed that the extent of incorporation at this stage was 84%. Similarly, when the reaction was performed in the presence of 18-crown-6 ether in an equivalent amount to the base, at 11% of elimination, 28% incorporation was observed.

Reactions of 3. The reactions of the two isomers of this substrate were conducted at 25 °C. The reactions were followed to completion and quenched samples were found to be stable for several days. In addition to the elimination reaction, syn-anti isomerization was also observed. Rate constants were obtained by the computer simulation technique previously used⁶ to evaluate the rate constant of the reaction of **1**. Addition of equivalent amounts (to base) of crown ether resulted in a large rate enhancement and in a drastic decrease in the extent of the isomerization reaction. Independent of the identity of the starting isomer, the amounts of the isomerization in the course of these reactions were always lower than 2%. Rate constants in the presence and absence of crown ether are given in Table I.

Reactions of 4. The kinetics of these reactions were studied at 25 °C. During the reactions, and independent of the identity of the starting isomer, the extent of the isomerization was always lower than 3%. The reactions were also analyzed in the presence of an equivalent concentration (relative to *t*-BuO⁻) of crown ether. Rate constants for the elimination reactions were calculated neglecting the minute contribution of the isomerization to the overall reaction. The data for the reactions in the presence as well as in the absence of crown ether are given in Table I.

Reactions of 5. These reactions were conducted at 25 °C both in the presence and in the absence of crown ether. Isomerization does not exceed 2%. Second-order rate constants are given in Table I. In addition, the two isomers **5s** and **5a** were prepared labeled with deuterium and the kinetics of their dehydrochlorination reaction was investigated. The hydrogen/deuterium isotope effects (k_H/k_D) were found to be 5.1 and 3.9 for **5s** and **5a**, respectively.

Discussion

Substituent Effect. The most obvious effect of substituents at C(3) is the one probably exerted on the ground-state energy of the starting material. In order to avoid eclipsed interactions in cyclobutane, the cyclic framework undergoes puckering, which differentiates between axial and equatorial positions. The most stable conformation in 1,3-disubstituted cyclobutane is the one that places the largest number of bulky substituents at equatorial positions.⁷ The relative stability of two isomers can be inferred from their equilibrium constant, which in turn can be derived from the ratio of the isomerization rate constants. Thus, **1a** is more stable than **1s** since the former can avoid 1,3-diaxial interaction by simultaneously placing the two bulky substituents CN and Cl at equatorial positions. The addition of a Me group as in **3** removes

(5) Hall, H. K., Jr.; Blanchard, E. P., Jr.; Cherkofsky, C. S.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 110.

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

(7) Moriarty, R. M. *Top. Stereochem.* **1974**, *8*, 271.

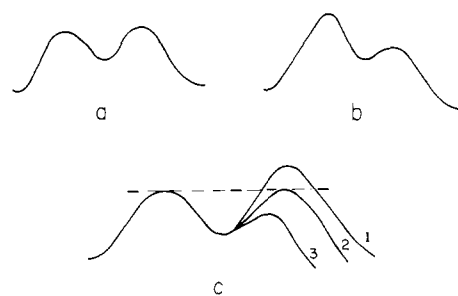


Figure 1. Reaction profiles for an E1cB mechanism involving free carbanions.

this difference between the two isomers, and the equilibrium constant is reduced to unity ($K = 17.9/17.6 = 1.02$).

The effect of substituents on the product stability has been far less studied. To the best of our knowledge, the only study relevant to substituent effect on bicyclobutane itself is an ab initio STO-3G calculation on the stability of bicyclobutane with H, Me, and F as bridgehead substituents.⁸ It was found that these substituents have only a minor effect on the stability of the derived compounds. It seems therefore that neither the ground state of the reactants nor that of the products is drastically affected by substituents at C(3).

Although ground states on both sides of the transition state seem to be almost insensitive to substitution at C(3), the transition state itself may be significantly affected by such a substitution. A typical example is the Favorskii rearrangement in the $\text{PhCH}_2\text{COCHRCl}$ system.⁹ Replacing $\text{R} = \text{H}$ by $\text{R} = \text{Me}$ induced a 220-fold rate enhancement. This was interpreted to be the result of a substantial development of positive charge on C(3) at the transition state.

In the present case the substituent effect on the transition state can be inferred from the data given in Table I. These enable the comparison of the effect of H, Me, and Cl (substrates 1–3) on the reaction rate constants. The presence of two Cl atoms in 2 necessitates the introduction of a statistical correction factor. This factor cannot be 2 since the two chlorines are not identical. However, since in both 1 and 3, the ratio for the elimination reaction between the two isomers in each is ca. 15, one can assume a similar ratio for the two Cl atoms in 2. The rate constants for the syn and anti elimination will therefore be approximately 2.2×10^{-2} and $0.15 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$, respectively. Obviously, the second value is of much lower accuracy. Comparison of the syn elimination rate constant for 2 with that of 1s at the same temperature shows that the second chlorine atom lowers the reactivity by a factor of 2 only. A similar decrease in reactivity is effected also by the replacement of H with Me. Thus it may be concluded that the transition state is balanced in the sense that central bond formation and leaving group departure are highly synchronous and no charge is developed on C(3) at the transition state.

Element Effect and the Nature of the Intermediate. The intermediacy of a reversibly formed carbanion in the course of elimination reactions is generally inferred from hydrogen–deuterium exchange or similar trapping experiments.¹⁰ For substrates 3–5, use has been made of the syn–anti isomerization of the starting isomers as a probe for the formation of carbanions in the course of the reactions. This probe, as we have found in a previous study,⁶ is equivalent to protium exchange in its efficiency. Thus, the isomerization of 1 was shown to be faster for one isomer and slower for the other than the corresponding H–T exchange reactions within a factor of 2.⁶ The similarity in the elimination and isomerization rate constants in the reactions of 1s and 3s indicates that the barriers for the expulsion of the leaving group and reprotonation either to starting material or to its isomer have

nearly the same heights. Such a situation is usually interpreted as a case where the first as well as the second step is rate controlling as shown in Figure 1a. On the other hand, the results for 4s, where isomerization is practically negligible, will by the same reasoning suggest that deprotonation is the rate-determining step and leaving group departure takes place in practically a post-rate-determining step (Figure 1b).

Using the element effect ($k^{\text{Br}}/k^{\text{Cl}}$) we will show in the following discussion that this common analysis for elimination reactions, be they 1,2- or a 1,3-eliminations, is not always correct and in the case at hand happens to be fallacious. For this purpose we will first qualitatively outline the argument. The basic assumption in this argument is that protonation and deprotonation rate constants (k_1 and k_{-1}) are not significantly affected by the identity of the halogen.¹¹ In order to demonstrate the general principle let us assume that the barrier for expulsion of Cl^- in a given elimination reaction is slightly higher than the barrier for the reprotonation of the carbanion as shown in Figure 1c₁. Switching from chloride to bromide as a leaving group will lower the barrier for the expulsion of the leaving group, which in turn effects rate increase and therefore results in an element effect > 1 . The magnitude of the element effect will increase as the barrier for the bromide expulsion decreases. However, when the first and the second transition states will be of the same height (Figure 1c₂), the element effect will level off at its maximum value. A further increase in the rate of the expulsion of the leaving group will only slightly affect the reaction rate since the first step has become rate determining (Figure 1c₃).¹² In case the observed element effect exceeds the maximum value, the assumed mechanism is perforce incorrect.

We will turn now to the case at hand and quantitatively derive, on the basis of the previous assumptions, the expression for the element effect for the pair 3s/4s ($k_{\text{obsd}}^{\text{Br}}/k_{\text{obsd}}^{\text{Cl}} = 71$) in the following way.

The expressions for the rate constants for elimination from the two substrates are

$$k_{\text{obsd}}^{\text{Br}} = \frac{k_1 k_2^{\text{Br}}}{k_{-1} + k_2^{\text{Br}}} \quad (4)$$

$$k_{\text{obsd}}^{\text{Cl}} = \frac{k_1 k_2^{\text{Cl}}}{k_{-1} + k_2^{\text{Cl}}} \quad (5)$$

where k_1 , k_{-1} , and k_2 are the deprotonation, reprotonation, and elimination rate constants, respectively.

To a first approximation k_1 and k_{-1} (proton-transfer steps) are identical for both substrates and are not affected by the identity of the halogen atom.¹¹ The element effect will then be given by

$$\frac{k_{\text{obsd}}^{\text{Br}}}{k_{\text{obsd}}^{\text{Cl}}} = \frac{k_2^{\text{Br}}(k_{-1} + k_2^{\text{Cl}})}{k_2^{\text{Cl}}(k_{-1} + k_2^{\text{Br}})} \quad (6)$$

In the case of 3s, the ratio of the rate constants for the protonation of the assumed intermediate carbanion to give 3a and the elimination from this carbanion (k_2^{Cl}) is $0.0179/0.0127 = 1.4$ (Table I). However, since the protonation rate is likely to be identical on both faces of the carbanion (see Substituent Effect section) a statistical correction factor of 2 must be introduced, giving $k_{-1} = 2.8k_2^{\text{Cl}}$. In addition, $k_2^{\text{Br}} \gg k_{-1}$. The element effect derived in the previous equation will therefore be

$$\text{element effect} = \frac{k_2^{\text{Br}}(2.8k_2^{\text{Cl}} + k_2^{\text{Cl}})}{k_2^{\text{Br}}k_2^{\text{Cl}}} = 3.8 \quad (7)$$

Clearly, this calculated element effect is not in accord with the observed value of 71, indicating that the assumed intermediacy

(8) Dill, J. D.; Greenberg, A.; Liebman, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 6814.

(9) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3370.

(10) (a) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanism of Elimination Reactions*; Wiley: New York, 1973. (b) Bunce, E. *Carbanions: Mechanistic and Isotopic Aspects*; Elsevier: New York, 1975.

(11) Detritiation ($t\text{-BuOK}-t\text{-BuOH}$) to the sulfone in $\text{PhSO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{X}$ is faster for $\text{X} = \text{Br}$ by a factor of 1.5 than for $\text{X} = \text{Cl}$. Issari, B.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1982**, 684.

(12) When the first and second barriers are of the same height, the rate constant will be half of that in which the first step is rate determining. This is because the intermediate in the former case has an equal probability for moving backward and forward.

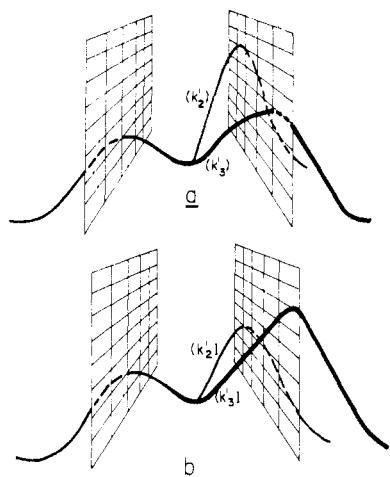
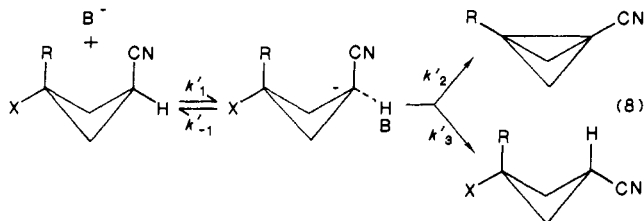


Figure 2. Reaction profiles for an E1cB mechanism involving hydrogen-bonded carbanions.

of a free carbanion is incorrect. We believe that the above treatment is suitable only for cases where the intermediate carbanion is formed or becomes a free, non-hydrogen-bonded carbanion prior to any subsequent processes in the system. When this condition is not fulfilled, namely when elimination and isomerization occur from a hydrogen-bonded carbanion, k_{-1} is the rate constant for the collapse of the internal return complex and is not represented by rates of protium exchange or isomerization reactions. For the case at hand, the reaction scheme must be bifurcated as shown in eq 8. Following the formation of the hydrogen-bonded carbanion,¹³ one path leads to elimination (k'_2) while the second (k'_3) leads to isomerization. The reaction profiles for **3s** and **4s** are shown in parts a and b of Figure 2, respectively.



The general analysis for the element effect in this case is as follows. Assuming a steady state for the internal return complex and the absence of a significant dependence of k'_{-1} and k'_3 on the identity of the halogen, the element effect will be expressed by

$$\text{element effect} = \frac{k'_2{}^{\text{Br}}(k'_{-1} + k'_2{}^{\text{Cl}} + k'_3)}{k'_2{}^{\text{Cl}}(k'_{-1} + k'_2{}^{\text{Br}} + k'_3)} \quad (9)$$

If $k'_{-1} + k'_3$ is larger than k'_2 , then the element effect directly reflects the ratio of the elimination step rate constants ($k'_2{}^{\text{Br}}/k'_2{}^{\text{Cl}}$). If k'_2 is larger than the other two rate constants, then an element effect of 1 will be observed, indicating that the leaving group is expelled at a post-rate-determining step.

In summary, *whenever a hydrogen-bonded carbanion is formed in the course of an E1cB reaction, the absence of protium exchange or isomerization reaction should not be taken as indicative of an (E1cB)₁ mechanism.* The reaction may still be (E1cB)_R ($k'_{-1} > k'_2$) with $k'_2 > k'_3$.

The likelihood for the intermediacy of a hydrogen-bonded carbanion is increased with the degree of negative charge localization on the carbon.¹⁴ In these cases its behavior will

resemble that of a normal acid where the rate-limiting step in deprotonation is the dissociation of the hydrogen-bonded complex.

Further support for the conclusion that for substrates **3** and **4**, expulsion of the leaving group takes place from hydrogen-bonded carbanions, and not from free carbanions which lack all memory of their precursors, can be gained from the differences in the rate constants between the isomers in each pair of substrates (these are in the range 15–30). If a free equilibrating carbanion had been formed, k_2 would be no more dependent on the geometry of the starting material and would be identical for both isomers. The relative elimination rate constants would therefore reflect the differences in the ground-state energies within a pair of isomers, which are very small ($k < 2$; $\Delta G < 0.4$ kcal/mol).

Unlike isotope effects, the element effect cannot be used as an exact quantitative probe for the degree of cleavage of the bond to the leaving group at the transition state.¹⁵ Such a quantification, even if it existed would give an average number which may be too remote from either of the individual values for the two elements. We will therefore not go beyond the conventional statement that the observed element effect indicates an appreciable cleavage of the C–halogen bond at the transition state.

Crown Ether Effect. In a low-polarity medium such as *t*-BuOH, the base (*t*-BuO⁻) is highly paired with the metal cation.¹⁶ Addition of crown ether induces pair separation,¹⁷ which in turn causes an increase in the reactivity of the base. Examination of the data in Table I shows that for substrates **1–5**, elimination rate constants increase from 5- to 1200-fold. The most pronounced effect is on the ratio of elimination to isomerization. In the presence of crown ether the amount of the isomerization products is reduced to nearly zero, implying that pair separation affects the elimination more than the isomerization reaction. This could possibly be explained in the following way. In proton-transfer reactions (isomerization, isoinversion, etc.), the presence of the cation lowers the energy of the ground state but to some extent it also stabilizes the transition state. On the other hand, in elimination reactions, where the negative charge is transferred to the leaving group located remotely relative to the cation, the electrostatic stabilization of the transition state is much less pronounced. Therefore, removing the metal cation from the vicinity of the reaction center will increase to a relatively greater extent the elimination rather than the isomerization rate constant.

We note that the effect of crown ether addition is smaller for the isomers where the hydrogen and the leaving group are located syn rather than anti to each other (substrates **1**, **3**, and **4**). This may be due to an electrostatic assistance for the expulsion of the leaving group as we have previously suggested.⁶

Activating Group Effect. Having studied the effect of the cyano group, we have chosen to examine the reaction of a carbonyl-activated substrate. This choice was made since, unlike the cyano group whose electron-withdrawing effect is largely inductive, negative charge stabilization by the carbonyl group is achieved primarily by a delocalization mechanism.¹⁸ The lower ability of the cyano group to effectively delocalize a neighboring negative charge stems from the fact that the π^* orbital of the CN group is of relatively high energy. Therefore, delocalization of the negative charge into this orbital is energetically unfavorable. On the other hand, the π^* orbital in C=O is of lower energy and, moreover, delocalization of the negative charge onto the oxygen enables the formation of three hydrogen bonds, which further stabilizes the negative charge.

In order to compare the effect of these two activating groups on the reaction mechanism, the reactions of substrates **1** and **5** should be compared. Examination of the available data reveals

(13) In β -elimination reactions this is called (E1cB)_{ip}. See for example: Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 265 and references cited therein. However, in the case where BH is not charged, the intermediate is not an ion pair.

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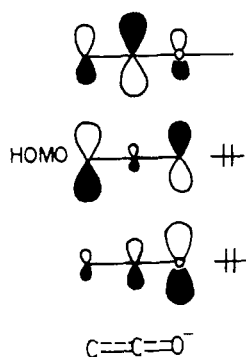
(15) Rappoport, Z., personal communication. See however: Bird, R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1221.

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Scheme I

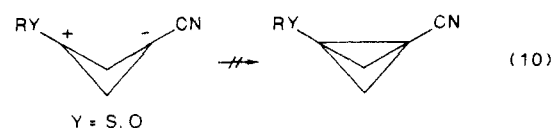


five major differences: (a) while deprotonation of the cyano-activated compounds shows a hydrogen-deuterium isotope effect of 1,¹⁹ an isotope effect of 4 was observed for **5**; (b) while there is a considerable extent of isomerization in **1**, it is practically negligible in the reactions of **5**; (c) rate increase due to addition of crown ether is in the range 50–500-fold for **1** and only 4.6-fold for **5**; (d) the elimination rate constant ratio for the syn-anti pair in **1** is ca. 16, whereas it is only 1.3 for **5**; and finally (e) rate constants for the reactions of **5** are larger than those of **1** by 3–4 orders of magnitude. These results clearly indicate that the elimination mechanisms for the two substrates are substantially different. The hydrogen-deuterium isotope effect and the small amount of isomerization found for **5** indicate that the reaction is either (E1cB)₁ or E2. The crown ether effect points to the former mechanism as the operative mechanism in the case of **5**. As we have shown in the discussion of the crown ether effect, in deprotonation reactions both ground state and transition are electrostatically stabilized by the metal cation (an (E1cB)₁ case); therefore, the crown ether effect will be relatively small. On the other hand, if at the rate-determining transition state, the charge is delocalized onto a remote position (leaving group in the case of an E2 reaction), the transition state will be much less affected by the neighboring cation and a much larger crown ether effect is bound to be observed. Thus, the small rate acceleration observed for **5** is consistent with a mechanism in which charge is not effectively delocalized onto the leaving group at the transition state. The reaction mechanism is therefore either (E1cB)₁ or an E2 mechanism in which the C–Cl bond cleavage has not advanced to a significant extent at the transition state. The likelihood of an E2 mechanism is further reduced if one considers the effect of the stereochemistry of the substrate on the reaction mechanism. It is only reasonable to assume that the rate of a concerted syn elimination in **5s** will be significantly different from the rate of the anti elimination for **5a**. The relatively small differential effect of the two isomers of **5** argues strongly against such concertedness. Thus while the mechanism of the reaction of the cyano-activated substrates was found to be an (E1cB)_R with elimination occurring from the hydrogen-bonded carbanion, the data for the carbonyl-activated substrate indicates a (E1cB)₁ mechanism. Since in this case the rate-limiting step is deprotonation and since carbonyl-activated carbon acids are stronger acids (thermodynamically as well as kinetically) than the corresponding cyano acids,²⁰ it is clear why the rate constants for the elimination from **5** is much larger than those of **1**.

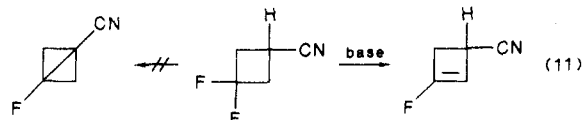
An interesting question, however, is the preference of the carbanion derived from **5** to undergo elimination rather than protonation (isomerization). A possible explanation could be advanced by using the charge vs orbital control theory.²¹ According to this theory, protonation being a charge-controlled reaction is governed by the negative charge density on a given atom. The elimination step, on the other hand, being an orbital-controlled reaction depends on the coefficient on the carbon

at the HOMO level. The schematic diagram (Scheme I) of the MOs of enolate anion shows that the largest coefficient at the HOMO is indeed on C(1).²² However, the negative charge resides mainly on the oxygen of the enolate anion. Thus qualitatively, this electronic configuration does not promote protonation on C(1), whereas it favors the orbital-controlled elimination step.

The last point about which we would like to comment is the stepwise nature of the reaction. To the best of our knowledge there has not been a single case where a 1,3-elimination was reported to be concerted. One could assume that the proximity of the two opposite carbons in cyclobutane provides a substantial deriving force for a concerted reaction. Yet the results of this study seem to indicate that, even in this system, concerted elimination does not occur. Our studies of the ionic bicyclobutane^{23,24} seem also to indicate that the likelihood for a concerted reaction in this system is very low. This conclusion is based on our failure to observe, up to now, a single case where an ionic bicyclobutane collapsed to give a covalent compound (eq 10). In all cases it



was found that the incorporation of the solvent alcohol molecule is faster than the nucleophilic attack on the carbocation across the ring. Therefore it seems that coupling of C–H and C–leaving group cleavage is of small probability. Moreover, in the difluoro compound **6**, although H–D exchange at the position α to the cyano group was observed, the only product obtained under basic conditions was the corresponding olefin²⁵ (eq 11). Apparently



the strain involved in the cross ring bond formation renders a concerted reaction unlikely.

Experimental Section

General. ¹H NMR spectra were recorded on Bruker AM-300 and Varian EM-360A spectrometers and measured in CDCl₃ solution. Mass spectra were taken with a Finnigan 4021 mass spectrometer. Radioactive measurements were carried out on a Tri-Carb 2450 liquid scintillation spectrometer (Packard). 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. In most cases the columns were of 20% XE 60 on Chromosorb W, acid-washed 60–80 mesh.

Reactants and Products. 3,3-Dichlorocyclobutanecarbonitrile (**2**) and the corresponding dehydrohalogenation product 3-chlorobicyclobutanecarbonitrile are known compounds⁵ and were identified by ¹H NMR and mass spectrometry. The procedure for tritiation of **2** is similar to that previously published.⁶ 3-Chloro-3-methylcyclobutanecarbonitrile (**3**) was prepared by slowly bubbling gaseous HCl over a period of 5 h through 3 g of 3-methylenecyclobutanecarbonitrile⁵ (the procedure for the preparation of the analogous bromo derivative (**4**) involved an aqueous solution of HBr; replacing HBr by HCl under these conditions resulted in hydrolysis of the cyano group). Analytical gas chromatography showed the formation of two new compounds. The reaction mixture was treated with water and ether, and the ethereal phase was washed with a 10% NaHCO₃ solution and then with saturated NaCl solution. Drying over MgSO₄ and evaporation gave 4 g of a thick yellow liquid, consisted mainly (80%) of a mixture of the two isomers. The isomers were purified by preparative gas chromatography. **3s**: ¹H NMR δ 1.80 (s, 3 H), 2.65–2.86 (m, 4 H), 3.4 (m, 1 H); *m/e* (EI) 132–130 (1:3 d), 94, 76. Satisfactory C,H,N,Cl analysis was obtained. **3a**: ¹H NMR δ 1.70 (s, 3 H), 2.65–3.05 (m, 5 H); *m/e* (EI) 132–130 (1:3 d), 94, 76, 67. Satisfactory C,H,N,Cl analysis was obtained. 3-Bromo-3-methylbicyclobutanecarbonitrile (**4**) was prepared by hydrobromination of 3-

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methylenebicyclobutanecarbonitrile: 10 g (0.13 mol) of this compound was vigorously stirred with 30 g of HBr (47%) at room temperature for 24 h. The reaction mixture was treated with water and ether, and the ethereal phase was washed with a 10% NaHCO₃ solution, then with water, and finally with a saturated NaCl solution. After drying over MgSO₄ and evaporation, 18 g of a yellow liquid consisting mainly (95%) of the two isomers **4a** and **4s** was obtained. The isomers were purified by preparative gas chromatography. **4s**: ¹H NMR δ 1.95 (s, 3 H), 2.65-2.72, 2.92-3.0 (m, 4 H), 3.4-3.55 (m, 1 H); ¹³C NMR δ 17.5 (CH₃), 33.8 (C-CN), 45.2 (CH₂), 58.4 (C-Br), 121.0 (CN); *m/e* (CI) 174-176, 127, 94. **4a**: ¹H NMR δ 1.90 (s, 3 H), 2.75-2.85, 2.95-3.2 (m, 5 H); ¹³C NMR δ 17.5 (CH₃), 31.9 (C-CN), 45.1 (CH₂), 52.5 (C-Br), 120.5 (CN); *m/e* (CI) 176-174, 94, 72. Satisfactory C,H,N,Br analysis was obtained for the two isomers. The elimination product 3-methylbicyclobutanecarbonitrile is a known compound.²⁶ 3-Chlorobicyclobutyl phenyl ketone (**5**) was prepared from the corresponding alcohol: 7 g (0.06 mol) of thionyl chloride was heated to 55 °C in a round-bottom flask equipped with reflux condenser and a separatory funnel. At this temperature 4.5 g (0.028 mol) of 3-hydroxycyclobutyl phenyl ketone²⁷ with 250 μL of DMF was added over 45 min through the separatory funnel. The reaction mixture was heated to 98 °C with mixing until HCl evolution ceased (2 h). It was then treated with water and CHCl₃, the chloroform layer was separated and washed with water and a 10% NaHCO₃ solution, and the mixture was dried and evaporated, yielding 6 g of red oil. Column chromatography (Kieselgel 60, hexane) of the oil gave (second fraction) 4.2 g (77% yield) of a mixture of the two isomers **5s** and **5a**. The isomers were separated and purified by preparative gas chromatography (0.5% Carbowax 20 M on Chromosorb P at 130 °C). **5s**: ¹H NMR δ 2.65, 2.95 (m, 4 H), 4.25 (p, 1 H), 4.5 (p, 1 H); ¹³C NMR δ 51.0 (t, C-Cl), 36.6 (CH₂), 37.5 (C-CO), 199.6 (CO), 135.1, 128.3, 128.7 (C₆H₅); *m/e* (CI) 195-197, 159, 105. **5a**: ¹H NMR δ 2.65, 2.85 (m, 4 H), 3.8 (p, 1 H), 4.5 (p, 1 H); ¹³C NMR δ 48.3, 37.5, 36.4, 198.1, 135.2, 128.3, 128.7, 135.2 (peak assignment as for **5a**);

m/e (CI) 195-197, 159, 105. Satisfactory C,H analysis was obtained for the two isomers. 3-Chloro-1-deuteriocyclobutyl phenyl ketone was prepared by slow addition of 4 mL of trifluoroacetic anhydride to a cooled mixture of 4 mL of D₂O and 1.5 g (0.008 mol) of **5** (as an isomer mixture). The mixture was vigorously stirred for ca. 20 h at 60 °C under nitrogen, extracted with CH₂Cl₂, and washed with NaHCO₃ solution and water. Drying over MgSO₄ and evaporation of the ether gave 1.5 g of a mixture of the two isomers deuteriated α to the carbonyl group (90% by NMR) together with ca. 15% of an unidentified substance. 1-Bicyclobutyl phenyl ketone was obtained by dehydrochlorination of **5** according to the following procedure. To a 25-mL *t*-BuOH solution of 1 g of **5** (0.0052 mol) were added 5-mL portions of *t*-BuOK-*t*-BuOH solution (0.2 M) until GC analysis indicated that all the starting material had been consumed. At the end, 0.1 g of phenothiazine was added to the reaction mixture, which was then treated with water and ether. The ethereal layer was dried over MgSO₄ and most of the organic solvent was evaporated. The pure product was obtained by preparative gas chromatography (0.5% XE60 non-acid-washed on Chromosorb W, 95 °C). However, most of it decomposes on the column and separation yield is 5-10%: ¹H NMR δ 1.5 (d, 2 H), 2.6 (d, 2 H), 2.2 (m, 1 H), 7.1-8.1 (m, 5 H); *m/e* (EI) 157, 129, 115, 105, 77.

Kinetic Procedure. Stock solutions of the substrates containing biphenyl, naphthalene, or fluorene as internal standards in *t*-BuOH were prepared and mixed with the appropriate aliquots of *t*-BuOK-*t*-BuOH solutions. Crown ether when needed was added to the base stock solutions. Samples of 0.1 mL were periodically removed, quenched by 0.1 mL of water, and analyzed by gas chromatography.

Acknowledgment. Helpful discussions with Professors P. Ahlberg and D. J. McLennan are gratefully acknowledged.

Registry No. **2**, 27744-70-3; **3s**, 110509-57-4; **3a**, 110509-58-5; **4s**, 110509-59-6; **4a**, 110509-60-9; **5s**, 110509-61-0; **5a**, 110509-62-1; 3-methylenebicyclobutanecarbonitrile, 15760-35-7; 3-hydroxycyclobutyl phenyl ketone, 110509-63-2; *cis*-3-chloro-1-deuteriocyclobutyl phenyl ketone, 110509-64-3; *trans*-3-chloro-1-deuteriocyclobutyl phenyl ketone, 110509-65-4; 1-bicyclobutyl phenyl ketone, 24464-69-5.

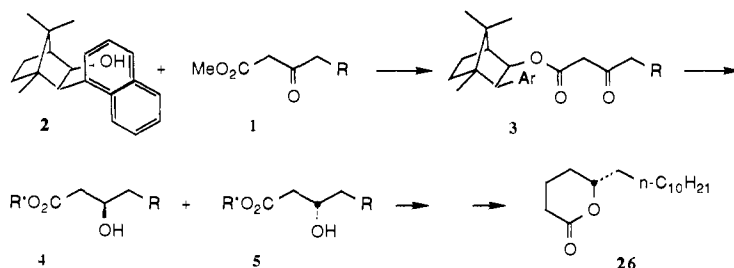
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Enantioselective Construction of Dialkylcarbinols: Synthesis of (-)-5-Hexadecanolide[†]

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Abstract: Alcohol **2** is designed to block one face of the carbonyls in the derived β-keto ester **3**. Hydride reduction can then



proceed either via the transition state in which the carbonyls are syn (ZnCl₂/Zn(BH₄)₂, **4:5** = 92:8) or via the alternative transition state in which the carbonyls are anti (Dibal-BHT, **4:5** = 4:96). Alkyl coupling of the primary tosylate of the 1,3-diol from LiAlH₄ reduction of **5** then opens a general enantioselective route to dialkylcarbinols.

With an increase in the complexity of the targets of natural product synthesis has come an increasing reliance on convergent synthetic design. A requisite for the desired convergence is the availability of synthetic intermediates of high optical purity. Current methods for enantioselective acyclic construction include direct incorporation of naturally derived starting materials,³ en-

antioselective epoxidation of allylic alcohols,⁴ hydride reduction of sterically biased ketones,⁵ and addition of a carbon nucleophile

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[†] Dedicated to Professor Gilbert Stork on the occasion of his 66th birthday.