Why molecular oxygen could oxidize the carbanions only in the micellar system is of considerable interest. We recently found that the flavin oxidation of nitroalkane carbanions, which does not proceed in nonenzymatic systems unless an electron-deficient isoalloxazine is used,[9] occurs readily with flavins bound to cationic micelles or to cationic polyelectrolytes.[7,8] It was concluded that the reaction is facilitated by the activation of the adsorbed carbanions on the cationic micelles and not by the shift of the redox potential of the flavins.[7,8,33] Therefore, the behavior of molecular oxygen may be described as follows: the carbanion, $R\bar{C}(CN)(OH)$, possesses the more positive redox potential than molecular oxygen being in a simple aqueous medium. In the cationic micellar system the opposite situation becomes true owing to the negative shift of the redox potential of the micelle-bound carbanion. The detailed mechanism of the micellar activation of the carbanion has been discussed elsewhere.[7,8,34]

In conclusion, the present work establishes that the combination of cyanide ion and cationic micelle remarkably facilitates the flavin oxidation of aldehydes and α-keto acids. Also significant is that the pattern of the flavin-mediated reaction is altered readily by changes in the reaction conditions. Although the results of the present study do not stimulate further understanding of the enzymatic mechanism, they do provide useful information concerning the interaction of flavins and carbanions in enzyme and model systems.

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Free, Hydrogen-Bonded, and Cation-Stabilized Carbanions α to a Cyano Group in a Cyclobutane Ring[1]

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Abstract: The carbanion α to the cyano group of 3-alkoxycyclobutanecarbonitrile (**3**) was prepared by three different methods: (a) addition of MeO^- in MeOH and *i*-PrO^- in *i*-PrOH to bicyclobutanecarbonitrile (**2**); (b) deprotonation of the cis and trans isomers of **3** in MeO^--MeOH and in *i*-PrO^--*i*-PrOH in the presence of crown ether; (c) deprotonation of **3** under ion-pairing conditions (*i*-PrONa-*i*-PrOH). The different product distribution (cis-trans ratio) obtained in each case indicates that each method yields a different type of carbanion. In method (a), a "free" carbanion whose inversion rate is faster than the reorganization of the surrounding solvent molecules is obtained. The observed cis-trans ratio of 3.5 reflects the relative ease of protonation of an equatorial position as compared to protonation of an axial one. Method (b) yields a hydrogen-bonded carbanion which exhibits some retention of configuration, while the paired sodium cation in method (c) induces equivalent amounts of retention and inversion. In the latter case, the inversion is accompanied by some isoinversion. A near-unity H/D kinetic isotope effect in the deprotonation reactions points to a preequilibrium formation of the carbanion with the subsequent step being rate limiting. The elimination of HCl from 3-chlorocyclobutanecarbonitrile under non-ion-pairing conditions is intrepreted accordingly as a monomolecular elimination from the hydrogen-bonded conjugated base ($E1cB_{hb}$).

Unless they are heavily substituted by electron-withdrawing groups, carbanions are usually encountered as short-lived intermediates. As the direct observation of a carbanion is rarely feasible, its nature is usually inferred from the rate, type, and

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stereochemistry of the reactions it undergoes.[2] One of the most useful reactions in this respect is the protonation of carbanions. The three major observable stereochemical courses of carbanion protonations are retention, inversion, and isoinversion.[3] The two latter processes differ from each other in the identity of the proton which is finally attached to the inversion product. While in a "simple" inversion this proton originates from the solvent pool, in isoinversion the same proton which is removed from one face of the molecule forms the C–H bond on the other face.

Retention of configuration might be observed in cases where the carbanion is intrinsically asymmetric or when asymmetry is induced on an intrinsically symmetric carbanion by the presence of a cation in close proximity to one of its faces. Since retention is detected by proton exchange, a restrictive condition is that isomerization or the removal of asymmetry in the carbanion will be slower than the rate of protonation by proton donors in the solvent pool. Based on the many observations made mainly by Cram's group, it was concluded that removal of the cation from the vicinity of the carbanion either by means of crown ether or by using a dissociating media will result in racemization rather than retention.[2c] An exception was found in the reaction of 3-chlorocyclobutanecarbonitrile (**1**), which

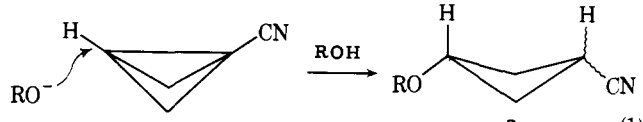
1

contrary to the above generalization exhibits retention in the presence of crown ether and a mixture of retention and inversion under ion-pairing conditions.[1]

In this article we report the generation of 3-alkoxycyclobutanecarbonitrile anion by addition of alkoxide to bicyclobutanecarbonitrile (**2**) and by deprotonation of the cis and trans isomers of 3-alkoxycyclobutanecarbonitrile (**3**) under ion pairing and under dissociating conditions. These three reactions lead formally to the same carbanion. A study of the stereochemistry of its protonation, however, reveals that each of the three reactions generates a different type of carbanion. The mechanism of the reactions, the nature of the various carbanions formed by these reactions, and some general implications are discussed.

Results

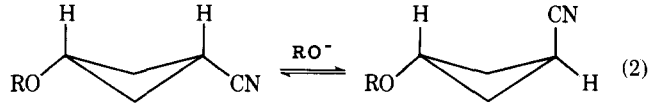
Alkoxide Addition to Bicyclobutanecarbonitrile (2). Reactions of alkoxides in the parent alcohols with **2** (eq 1) were



2 **3** (1)

carried out at 50 °C. Product distribution was followed by VPC. The additions were conducted in three different media: *i*-PrOH–*i*-PrONa, *i*-PrOH–*i*-PrONa–18-crown-6 ether, and MeOH–MeONa. (*t*-BuOH–*t*-BuONa does not add to **2** in the absence of crown ether. With crown ether, isomerization of the product is much faster than addition, thus rendering any intrinsic product distribution studies highly inaccurate.) Slow isomerization of the products was observed in 2-propanol solutions. The initial cis/trans ratio of 3.6 ± 0.2 in *i*-PrOH–*i*-PrONa was changed to 2.85 at 50% and to 2.2 at 85% reaction. In the presence of crown ether, isomerization rates were slowed down relative to addition rates. The initial ratio of 3.5 ± 0.1 dropped at 50% reaction to 3.0 and to 2.85 at 85% reaction. In methanol, the initial ratio of 3.6 ± 0.1 remained practically constant for at least 6 half-lives. The reactions are irreversible and go to completion. Equilibrium constants were obtained by allowing the reaction mixtures to reach a constant cis–trans ratio and from isomerization experiments which were carried out independently (see below). The equilibrium constant for the methoxy adducts (**3**(Me)) in MeOH at 50 °C is 2.1 in favor of the cis isomer. Other equilibrium constants are given in Tables I and III.

Deprotonation of 3-Alkoxycyclobutanecarbonitrile (3). The reactions of **3** (eq 2) under basic conditions were studied mainly



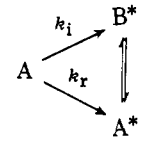
(2)

R = Me: *cis*-**3**(Me) R = Me: *trans*-**3**(Me)
R = *i*-Pr: *cis*-**3**(*i*-Pr) R = *i*-Pr: *trans*-**3**(*i*-Pr)
R = *t*-Bu: *cis*-**3**(*t*-Bu) R = *t*-Bu: *trans*-**3**(*t*-Bu)

with its isopropoxy derivative (**3**(*i*-Pr)); however, in two cases (tritium incorporation and H–D kinetic isotope effect experiments), measurements were taken on the methoxy (**3**(Me)) and *tert*-butoxy (**3**(*t*-Bu)) derivatives instead.

Reactions were carried out at 50 °C under three different reaction conditions: *i*-PrOH–*i*-PrONa, *i*-PrOH–*i*-PrONa–18-crown-6, and MeOH–MeONa. The reactions were pseudo first order with respect to the catalytic concentrations of the base. Isomerization rates were followed by VPC. Analysis of the data by the reversible first-order equation yields the sum of the first-order rate constants in both directions, which in combination with the independently measured equilibrium constant gives the individual isomerization rate constants. While isomerization reactions could be easily followed by VPC analysis, the detection of the reprotonation pathway by which the carbanion reverts to starting material necessitates the use of a labeling technique. Consequently, several reactions were conducted in tritiated alcohol ROH(O-*t*). The amount of ^3H incorporation into the starting material serves as a quantitative probe for analyzing this degenerate process. In the tritiated media, the starting isomer A is irreversibly converted to tritiated A (A*) and to its tritiated isomer B* (Scheme I). The

Scheme I



rate by which A disappears was determined by measuring the incorporated radioactivity into isolated A after ca. 10 and 20% reaction. The observed rate constant equals $k_i + k_r$. Since k_i is already known, k_r can be easily evaluated. Isomerization and retention rate constants are given in Table I. The accuracy of the rate constants measured by VPC is estimated to be ±5% and those based on radioactivity measurements to be ±7%.

In the course of a "regular" isomerization kinetic experiment only a few milligrams of starting isomer are used. However, since the experimental procedure for the tritium incorporation reaction requires that the analyzed isomer be twice separated by VPC and then divided into several weighed portions for the radioactivity measurements, much larger amounts are needed. This is even more critical in experiments designed for the detection of the isoinversion pathways since these reactions were run only to about 20% and the product isomer, which constitutes only one-fifth of the total amount of **3** present in the reaction mixture, was analyzed. As a result only a few experiments of this type were performed. In *i*-PrOH–*i*-PrONa, experiments were not carried out with **3**(*i*-Pr) but with **3**(Me) and **3**(*t*-Bu) instead. The calculated specific activities for complete exchange and the measured values are given in Table II. These values are accurate to about 2–3%.

Measurements of the hydrogen-deuterium isotope effect

Table I. Retention, Isomerization, and Equilibrium Constants for the Reaction of *cis*- and *trans*-**3**(*i*-Pr) at 50 °C

reaction	*i*-PrOH–*i*-PrONa[a]		*i*-PrOH–*i*-PrONa–crown ether[b]		MeOH–MeONa[c]	
	10^4k_i, M^{-1} s^{-1}	10^4k_r, M^{-1} s^{-1}	10^4k_i, M^{-1} s^{-1}	10^4k_r, M^{-1} s^{-1}	10^7k_i, M^{-1} s^{-1}	10^7k_r, M^{-1} s^{-1}
trans → cis	1.46	1.32	7.7	12.3	6.0	15.4
cis → trans	0.7	0.7	3.8	8.5	2.85	8.1
equilibrium constant (cis/trans)	2.1		2.0		2.1	

[a] Alkoxide concentration 0.06–0.27 M. [b] Alkoxide concentration 0.03–0.055 M with an equivalent amount of crown ether. [c] Alkoxide concentration 0.5 M.

Table II. Specific Molar Activity of Product Isomer (10^6 cpm/mol). Theoretical Values Calculated for Complete Exchange and the Observed Values[a]

	i-PrOH–*i*-PrONa		*i*-PrOH–*i*-PrONa–crown ether		MeOH–MeONa	
	calcd	obsd	calcd	obsd	calcd	obsd
cis-**3**(Me) → *trans*-**3**(Me)	420	388 (23)				
cis-**3**(*i*-Pr) → *trans*-**3**(*i*-Pr)			320	311 (22)	345	353 (22)
trans-**3**(*t*-Bu) → *cis*-**3**(*t*-Bu)	380	301 (21)				

[a] Numbers in parentheses denote percent reaction.

in the isomerization reaction were carried out in *i*-PrOH–*i*-PrONa on *cis*- and *trans*-**3**(Me) and -**3**(*t*-Bu) labeled with deuterium at carbon 1. Data were analyzed by the initial-rates method. Each experiment was repeated twice. The isomerization rate constants and kinetic hydrogen–deuterium isotope effect are given in Table III. The estimated error in k_H/k_D is ±0.1.

Conductivity Measurements. In *i*-PrOH, *i*-PrONa exists mainly as ion pairs, while in MeOH, MeONa exists mainly as free ions. This was substantiated by standard conductivity studies. The conductivity of 0.06 M solution of *i*-PrONa in *i*-PrOH was increased from 45 to 900 μS as a result of the addition of an equivalent amount of crown ether (additional amounts of crown ether did not alter the conductivity). In contrast, the addition of crown ether to 0.05 M MeONa in MeOH increased conductivity only by a factor of 1.27, from 2600 to 3300 μS.

Discussion

Additional Reactions. Two types of interactions in cyclobutane determine its stereochemical features.[4] The first is the eclipsed interaction of adjacent substituents which forces the ring out of planarity. Because of this puckering, a substituent on the cyclobutyl ring can assume either an equatorial or an axial position which then induces the second type of interaction between two axial substituents at positions 1 and 3 of the ring. A bulky substituent will preferentially adopt an equatorial position rather than an axial one. In a case where the ring is 1,3-disubstituted, there are two possible geometrical isomers, cis and trans. In general, the cis isomer is somewhat more stable since the two substituents can simultaneously assume an equatorial position, while in the trans isomer one substituent must always be axial. The cis–trans equilibrium constants for compounds **3**(Me, *i*-Pr, *t*-Bu) are about 2. This value is in good agreement with equilibrium constants of 1,3-dihalocyclobutanes.[5] The gradual decrease of K upon going from **3**(*t*-Bu) to **3**(Me) (Tables I and III) is probably caused by the bulkier substituent forcing the molecule out of planarity to a greater extent and thus giving rise to more intensive destabilizing 1,3 (CN,H) interactions in the trans isomer.

The addition of alkoxide to **2** is followed by an isomerization of the product **3**. In the presence of crown ether, the rate of both the addition and the isomerization reaction is markedly increased. However, the results indicate that the alkoxide nucleophilicity is enhanced more than its kinetic basicity. A similar observation was also made by Gokel[6] in several illustrative reactions. Although it can be explained on the grounds of the difference in the steric requirements of the two reactions,[1,7] a somewhat different explanation can be advanced.

Table III. Rate and Equilibirum Constants and Hydrogen–Deuterium Isotope Effects for the Isomerization Reaction of **3**(Me) and **3**(*t*-Bu) in *i*-PrOH–*i*-PrONa at 50 °C

starting isomer	10^4k_i, M^{-1} s^{-1}	K[a]	k_H/k_D
cis-**3**(Me)	1.47	1.84	0.93
trans-**3**(Me)	2.7		1.07
cis-**3**(*t*-Bu)	0.31	2.68	1.16
trans-**3**(*t*-Bu)	0.83		1.17

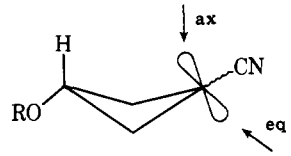
[a] K = [cis]/[trans].

In contrast to nucleophilic reactions, where the charge ends up on a remote leaving group, the cation in close proximity to the base in the deprotonation reaction is capable of stabilizing the product carbanion as well. Removal of the cation from the reaction center by means of crown ether will destabilize both reactants and products in deprotonation reactions. However, in nucleophilic reactions only the reactants are destabilized, leaving the product energy essentially unchanged. This assumption, as to the possible interaction between the paired cation and the negative charge on the reaction product, can be easily verified for the present system by comparing the effect of crown ether on the product distribution of the two reactions. While the cis–trans ratio in the alkoxide addition to **2** is not affected by crown ether, its addition to the reaction mixture of the deprotonation reaction drastically affects the protonation stereochemistry of the carbanion (Table I). If product stability is reflected to some extent at the transition state, then, compared to deprotonation, nucleophilic reactions might benefit more from the addition of crown ether.

It is interesting to note that the obtained cis–trans ratio is insensitive to the size of the nucleophile. The same ratio (within the limits of error) was obtained in the reaction of **2** with MeONa and with *i*-PrONa as well. This supports the conclusion that at the transition state for protonation of **4** the nucleophile assumes the remote equatorial position. It further substantiates an earlier suggestion[1] that the cis isomer in 1,3-disubstituted cyclobutane is obtained by axial protonation whereas equatorial protonation leads to the less stable trans isomer.

Since the removal of the sodium cation from the reaction site did not alter the isomer distribution ratio, the preferred syn addition cannot be attributed to the acidification of the neighboring solvent molecules by the cation. This preferred addition mode probably reflects the relative ease of an equatorial approach as compared with an axial one.[8]

Isomerization Reactions. On the basis of a large body of data



4

in which protonation stereochemistry was studied under ion-pairing as well as dissociating conditions,[3,9] Cram concluded that the presence of a cation at the front face of the carbanion is a necessary condition for a retention mechanism.[2c] Evidently, our results contradict this generalization, since in the presence of the sodium cation the same amounts of retention and inversion are observed, whereas removal of the cation by means of crown ether or by using a dissociating medium such as methanol results in partial retention. Similar results were also obtained in the reaction of **1** with *t*-BuO$^-$ in *t*-BuOH.[1] Since reaction conditions used in these studies are not unusual and were used before in other studies which provided the basis for Cram's rule,[9] it is clear that the exceptional behavior observed in the reactions of **1** and **3** is due to the unique nature of the cyclobutanic carbanion itself. We believe, however, that at this stage a more detailed explanation of this phenomenon would be highly speculative. Moreover, any analysis based only on the three observable modes of reaction, namely, retention, inversion, and isoinversion, is incomplete and must be regarded at best as tentative. The fourth mode which is essential for a complete description of the system is isoretention (analogous to isoinversion), in which the intermediate hydrogen-bonded complex or ion pair reverts to starting material without undergoing hydrogen exchange. Unfortunately, practically nothing is known about the rate and nature of this process in carbon acids.

Although the data in Table II is incomplete, as not all the isomers were investigated, it indicates that, within the limits of error, under non-ion-pairing conditions, inversion is completely accompanied by exchange. It also demonstrates that, if the behavior of **3**(*i*-Pr) is intermediate between those of **3**(Me) and **3**(*t*-Bu), isoinversion is induced by the paired sodium cation. The enhancement of the isoinversion reaction by a gegencation relative to other competing processes was demonstrated by Cram et al.[3] for the reaction of 2-methyl-3,3,3-triphenylpropionitrile in *t*-BuOH–*t*-BuOK. The carbanion derived from **3**(*i*-Pr), having a good site for delocalizing the negative charge by conjugation, fulfills the condition required for the operation of the conducted tour mechanism. However, since, unlike the carbanions studied by Cram's group, this carbanion is intrinsicially nonplanar, the nonstructured mechanism[10] cannot be ruled out. In this mechanism, the original proton attached to the alkoxide molecule coordinated to the sodium cation protonates the carbanion on its other face after rotation within the ion pair. Exchange can take place via protonation by the less acidic bulk molecules, by rotation of the cation which brings another sector of its solvation sphere closer to the protonation site, or by exchange on the cation.

A near-unity hydrogen–deuterium isotope effect was observed for the reaction of **3**(Me) and **3**(*t*-Bu) with *i*-PrONa. This is usually interpreted as an indication for a preequilibrium formation of a carbanion with the subsequent step being rate determining. However, this interpretation might be somewhat ambiguous as small isotope effects might also result from a highly asymmetric transition state.[11] The pK_a of acetonitrile (literature values are 25 in aqueous solution[12] and 31 in Me_2SO[13]) can be used as a rough approximation for the lower limit of the pK_a of **3**. If one assumes that deprotonation of **3** is the rate-determining step, its rate constant will be the sum of the individual rate constants for the isomerization and retention reactions (ca. 10^{-4} M^{-1} s^{-1}). This value, when combined with a pK_a = 25 for **3**, leads to the specific rate of protonation of **4**, which is on the order of 10^{21} M^{-1} s^{-1}. Protonation rates on cyano-stabilized carbanions are on the order of 10^8 M^{-1} s^{-1}.[14] It is possible that proton transfer to **4** is somewhat faster, reaching the diffusion-control limit (10^{10} M^{-1} s^{-1}), as its charge is probably more localized on the carbon atom. Nevertheless, the gap of 11 orders of magnitude between the upper limit for the actual rate of proton transfer to **4** and the calculated value (which represents a lower limit) clearly indicates that carbanion **4** is reversibly formed as a preequilibrium intermediate and not in a rate-determining step. Such a preequilibrium intermediate is usually visualized as a hydrogen-bonded complex in which the carbanion formed is hydrogen bonded to the conjugated acid of the deprotonating base.[11] Similar behavior was observed, for example, in the deprotonation of phenylacetylene,[15a] chloroform,[15b] etc.[11]

Nature of the Intermediate Carbanion 4. In the preceding discussion it was shown that the carbanion derived from the reaction of **3** with alkoxide is hydrogen bonded to the alcohol molecule formed during the course of the deprotonation reaction. This specific bonding clearly introduces an asymmetry in the carbanion. However, it is still questionable whether intrinsically this carbanion acquires a planar symmetric configuration or a pyramidal one. In the addition reaction, the inversion at carbon 3 during the course of the nucleophilic attack requires an equatorial approach of the nucleophile; thus the ionicity developed on carbon 1 at the transition state is trans to the entering nucleophile. Nevertheless protonation of the intermediate carbanion **4** occurs preferentially syn to the entering nucleophile. Again, this can be explained either by assuming a planar configuration at C-1 of **4** which might be "free" or symmetrically solvated or a pyramidal structure with an inversion rate faster than protonation. It is highly unlikely that hydrogen-bond formation in the carbanion is faster than its rate of inversion, since this would require that **4** be trapped mainly as the trans OR,H isomer rather than as the cis.

A difference of 1.9 kcal/mol in strain energy between cyclobutane and methylenecyclobutane[16] indicates that, according to this all-carbon model, the planar configuration is a transition state for inversion of **4**. This model might be somewhat inadequate since the energy gain due to delocalization of the negative charge on the cyano group can exceed the strain energy, thus turning the planar configuration into an intermediate rather than a transition state. Nevertheless, ab initio calculations on $H_2\bar{C}$–CN in which the HCH angle was set to 90° to simulate the cyclobutane ring support the latter assumption, viz., C-1 of carbanion **4** is pyramidal.[17] This necessarily eliminates the possibility of symmetrical solvation of **4** obtained in the addition reaction. One of the most restrictive criteria for the existence of a common intermediate for two different reactions is that identical product distribution is observed in both cases.[18] Clearly, this demand is not met by any of the three carbanion-forming reactions. The alkoxide addition reaction yields mainly the trans isomer, isomerization with *i*-PrONa results in equal amounts of retention and inversion, whereas retention is the main route when the reaction is conducted in MeOH or in *i*-PrOH in the presence of crown ether. This also indicates that the carbanion derived from one isomer differs from that derived from the other. As the base system is highly paired in 2-propanol, one should expect that the carbanion formed by the deprotonation reaction will not resemble the one formed by the alkoxide addition reaction. However, the marked difference in product distribution between the two reactions when the cation was removed from the vicinity of the carbanion, namely, the addition reaction and the deprotonation in the presence of crown ether, can thus be readily explained by assuming that *in the deprotonation reaction the intermediate carbanion is hydrogen bonded to the conjugate acid of the base, whereas the addition reaction*

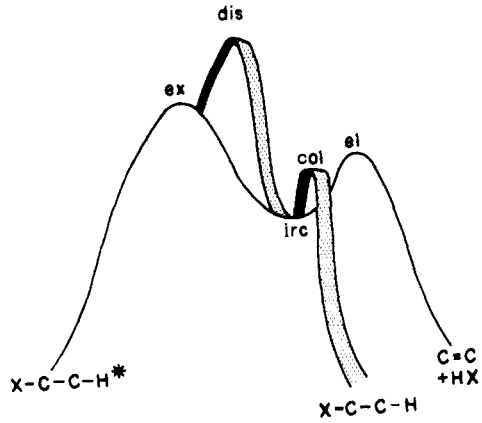
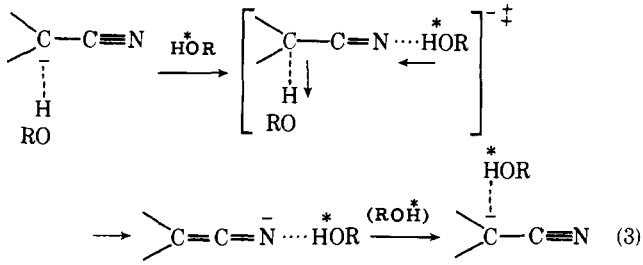


Figure 1. Schematic representation of the reaction profiles for exchange (ex), elimination (el), collapse (col), and dissociation (dis) of the internal return complex (irc).

yields a "free" carbanion whose inversion rate is faster than the reorganization of the surrounding solvent molecules to give the hydrogen-bonded complex. The reactions in methanol, where again non-ion-pairing conditions prevail, exhibit the same behavior and thus should bear the same conclusion, i.e., the carbanion obtained by deprotonation is hydrogen bonded to the methanol molecule formed in this reaction.

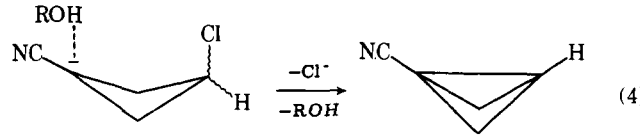
It should be emphasized that, since different product distributions are observed from the two different carbanions, at least a portion of the initially formed hydrogen-bonded carbanions undergo the consecutive reactions without ever being converted to free ions. In other words, isomerization and hydrogen exchange can take place in a series of steps which do not involve the free carbanion as a reaction intermediate. An isomerization mechanism which does not give rise to a "free" carbanion was suggested by Cram et al. and is known as the "conducted tour mechanism".[2a] In this mechanism the proton bonded to one face of the molecule is transferred to its other side by a series of successive steps in which the hydrogen-bond donor migrates from the carbon to the nitrogen and back to the carbon from the opposite direction. Since complete incorporation of the solvent hydrogen into the isomerization product was observed under non-ion-pairing conditions (last two columns of Table II), hydrogen exchange must therefore be faster than the isomerization reaction. This exchange can take place either on the hydrogen-bonded carbon or nitrogen, or in a modified conducted tour mechanism as depicted in eq 3. Al-



(3)

ternatively, a direct inversion through a planar transition state where the carbanion is symmetrically hydrogen bonded on both its faces will also account for complete incorporation.

It was shown that the free carbanion is not an intermediate on the reaction coordinate of the major (and probably the only) pathways for the isomerization and reprotonation of **3** in the presence of crown ether. As the experimental conditions for the base-catalyzed reaction of **1** in the presence of crown ether[1] are very similar to those of **3** in this work (*t*-BuOK-*t*-BuOH instead of *i*-PrONa-*i*-PrOH), it is reasonable to assume that the same conclusion is valid for this system as well. The electrophilic attack of carbon 3 on the hydrogen-bonded carbanion of **1** during the course of the elimination reaction (eq 4) can be described as a monomolecular elimination from a hydrogen-bonded conjugated base ($E1cB_{hb}$).



(4)

Observations made in this study are insufficient to allow a clear-cut decision as to whether the ion-paired carbanion is also hydrogen bonded or not. Thus it is not clear whether hydrogen bonding is also involved in the elimination of HCl from **1** under ion-pairing conditions or if the reaction is of the regular $E1cB_{ip}$[19] type.

The two major variants of the E1cB reactions are the reversible and the irreversible mechanisms.[20] The former is characterized by the reversible formation of a carbanion with leaving-group expulsion in the rate-determining step, whereas in the latter mechanism proton abstraction is rate limiting. One of the most commonly used probes for the detection of the reversible E1cB mechanism is proton exchange in the unreacted starting material. In the *t*-BuOK-catalyzed reaction of **1**, reprotonation, isomerization, and elimination rates are relatively similar to each other. However, in the presence of crown ether, elimination greatly exceeds the rates of the other two processes.[1] This is one of the few examples where the irreversible mechanism was shown to be operative.[21] It should be pointed out that, according to the preceding discussion, the absence of proton exchange in the starting material does not rule out the possibility of a reversible E1cB mechanism since the transition state leading to hydrogen exchange by an electrophilic attack of a proton donor from the solvent on the hydrogen-bonded carbanion might be higher in energy than that of the elimination reaction. The reaction will still be "reversible E1cB" if the barrier for the collapse of the internal return complex is lower than the other barriers (Figure 1).

Experimental Section

General. ^1H NMR spectra were recorded on a Varian HA-100 spectrometer. Mass spectra were taken with a Hitachi/Perkin-Elmer RMU mass spectrometer. Radioactive measurements were carried out on a Tri-Carb 2450 liquid scintillation spectrometer (Packard USA). For analytical purposes, a Packard Model 878 (FI detector) gas chromatograph was used, whereas for the preparative separation of the isomers a Varian 920 gas chromatograph (TC detector) was used. In both cases the columns were of 20% XE60 on Chromosorb W, acid washed, 60-80 mesh. Conductivity was measured by a TH27 conductometer (El Hama, Israel).

Reactants and Products. Preparation and Purification. Bicyclobutanecarbonitrile (**2**) was prepared from allene and acrylonitrile by a published procedure[22] and was purified by preparative VPC. *cis*- and *trans*-3-methoxy- and 3-isopropoxycyclobutanecarbonitrile were synthesized by alkoxide addition to **2** in the appropriate alcohol according to a previously described procedure.[23] For the synthesis of 3-*tert*-butoxycyclobutanecarbonitrile 18-crown-6 ether (purified by the acetonitrile method[2]) in equivalent amount was added to the reaction mixture. The resulting mixture of *cis*- and *trans*-**3**(Bu) (about 90% yield) was separated on a preparative VPC to yield the pure isomers. *cis*-**3**(Bu): NMR ($CDCl_3$) δ 1.2 (9 H, s), 2.1-2.9 (5 H, m), 3.9-4.2 (1 H, m); *m/e* 153 (M^+). Anal. Calcd: C, 70.59; H, 9.80; N, 9.15. Found: C, 70.50; H, 9.92; N, 9.20. *trans*-**3**(Bu): NMR ($CDCl_3$) δ 1.2 (9 H, s), 2.2-2.7 (4 H, m), 2.8-3.0 (1 H, m), 4.3-4.6 (1 H, m); *m/e* 153 (M^+). Anal. Calcd: C, 70.59; H, 9.80; N, 9.15. Found: C, 70.48; H, 9.95; N, 9.20. The 1-deuterio-3-methoxy- and 3-*tert*-butoxycyclobutanecarbonitrile were similarly prepared in the appropriate deuterio alcohol (*O-d*) solvent. In the NMR spectrum, the singlet of the trans isomer at ca. 3 ppm vanished and the two ring methylenes appeared as two distinct doublets around 2.3 and 2.6 ppm. Analytical grade methanol and 2-propanol (Frutarom-Israel) were distilled over sodium. Alkoxide solutions were prepared by dissolving oxide-free sodium in the appropriate alcohol. The alkoxide concentration was titrimetrically determined.

Kinetic Procedure. The addition, isomerization H-D isotope effect measurement, and tritium incorporation reactions were carried out similarly to the previously published procedure[1] with the major exception being that the reaction solution was quenched with dilute acetic acid in alcohol rather than in water.

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Formation Kinetics of an Amino Carboxy Type Merostabilized Free Radical

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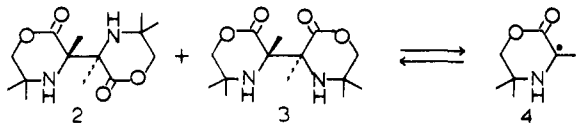
Abstract: The reduction of isatin (**5**) and *N*-methylisatin (**6**) by the merostabilized free radical 3,5,5-trimethyl-2-morpholinon-3-yl (**4**) to isatide (**7**) and *N,N'*-dimethylisatide (**8**) is described. The reaction rates are first order in the meso and *dl* dimers (**2** and **3**) of **4** and zero order in *N*-methylisatin. The rate of reaction is a measure of the rate of bond homolysis of the meso or *dl* dimer. Rate constants and activation parameters are reported. The free energies of activation for homolysis of **2** and **3** in chloroform solvent are 24.6 ± 0.3 and 25.1 ± 0.2 kcal/mol, respectively. The enthalpy of activation for recombination of **4** is estimated at 4-5 kcal/mol. Measured rate constants for bond homolysis were consistent within one standard deviation with the observed kinetics of isomerization of the meso dimer (**2**) to the equilibrium mixture of the meso and *dl* dimers. The activation parameters in part are a measure of the effect of merostabilization on radical stability.

We have reported that the meso and *dl* dimers (**2** and **3**, respectively) resulting from photoreduction of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**) in 2-propanol solvent exist in equilibrium with the unusually persistent carbon free radical, 3,5,5-trimethyl-2-morpholinon-3-yl (**4**).[1,2] The facile bond



2 3 4

homolysis, which has a $\Delta H°$ of 22 ± 1 kcal/mol in chloroform solvent, has been discussed in terms of steric and electronic factors.[2,3] The 3,5,5-trimethyl-2-morpholinon-3-yl radical is one of the simplest examples of a relatively new class of free radicals which are stabilized by dipolar resonance structures[2] and which have been named merostabilized free radicals.[4] The structure and reactivity of **4** are especially significant because of a probable relationship with the pyridinyl radicals, especially the radical of NAD.[5,6]

We have recently described some of the reactivity of 3,5,5-trimethyl-2-morpholinon-3-yl (**4**).[5] Specifically **4** is a mild reducing agent and reacts via the net transfer of a hydrogen atom. The hydrogen-atom transfer most likely occurs by electron transfer followed by rapid proton transfer. Reduction of a variety of functional groups in one-electron steps often with the intermediacy of other persistent free radicals has been achieved. In this context we now report the reactivity of 3,5,5-trimethyl-2-morpholinon-3-yl (**4**) with isatin (**5**) and *N*-methylisatin (**6**) and the application of this reaction to the measurement of the kinetic parameters for the primary bond homolysis of both the meso and *dl* dimers (**2** and **3**) of the morpholinonyl radical **4**.

Results and Discussion

Reactivity of 1 and 2 with Isatin and *N*-Methylisatin. A mixture of the meso and *dl* dimers of 3,5,5-trimethyl-2-morpholinon-3-yl cleanly reacts with isatin (**5**) in degassed dimethyl sulfoxide solvent to give 5,6-dihydro-3,5,5-trimethyl-

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