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FORMATION AND STABILITY OF ALKOXYIMIDATES IN THE CYCLOBUTANE BICYCLOBUTANE SYSTEM.[1]

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Abstract - The reactions of CN^- with methyl-3-chlorobicyclobutanecarboxylate and 3-chloro and 3-bromobicyclobutanecarbonitrile in MeOH were investigated. The MeO^- present in the reaction mixture adds reversibly to the carbonitrile function of the various products. The equilibrium constants for the imidate formation were determined. The general notion that the imidate form is favored by an electron withdrawing group was reconfirmed. The order found was CN>Cl≈ Br>C(NH)OMe>CO_2Me. It was also found that the central bond of bicyclobutane is a good mediator for transmittance of electronic effects. The unique stability of the alkoxyimidates compared to the low stability of the corresponding adducts with CN^- is discussed.

The base catalysed conversion of nitrile to imidate (eq. 1) was discovered about 90 years ago by Nef[2] who reacted cyanogen with ethanol in the presence of potassium cyanide. Subsequent workers

$$MeOH + R\text{-}C{\equiv}N \rightleftharpoons R\text{-}\underset{\displaystyle OMe}{\overset{\displaystyle |}{C}}{=}NH \qquad (1)$$

in this field[3] have established that the major characteristic features of the nitrile-imidate conversions are the following: 1) the reactions are relatively fast as compared to the corresponding acid catalysed reaction; 2) the equilibrium position is independent of the catalyst concentration; 3) the equilibrium position is highly dependent on the substituents on the carbon atom; and 4) electron withdrawing substituents favor the imidate form.

This paper reports the formation of imidates in the course of nucleophilic displacements of halide by cyanide in bicyclobutanic systems. The ability of the bicyclobutane ring to transfer electronic effects and the factors affecting the stability of the derived imidate are discussed.

RESULTS

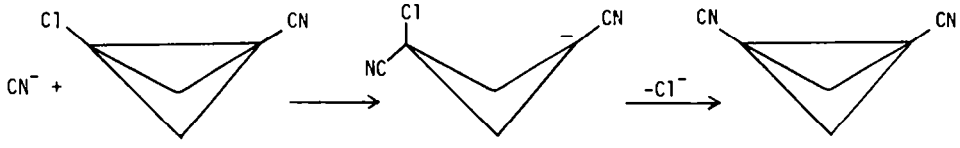
The reactions of CN^- in MeOH at 30°C with methyl-3-chlorobicyclobutanecarboxylate (1) as well as 3-chloro and 3-bromobicyclobutanecarbonitrile (2Cl and 2Br respectively) were investigated. GC analysis of these reactions reveals that some of the primary products are converted to the corresponding imidates in the course of the reaction. This conversion is catalysed by methoxide ion, which is present in the solution due to the relatively high basicity of NaCN in MeOH (pKa of HCN in MeOH is[4] 13). The reactions are slow and in the presence of 0.2M NaCN (substrate concentration ca. 0.04M) go to completion (with respect to the reaction with CN^-) and reach equilibrium (nitrile — imidate) in two to three weeks. The primary products of the reaction of 2 are the dimethoxyketal 3, the cyano derivative 4 and the HCN adduct 5. Of the three only the last two are converted to their imidates. The product 4 is partly converted to its imidate 6 whereas 5 is completely converted to its imidate 7 (a mixture of two cis and trans isomers which was not separated). The

reaction is described in Scheme 1 and the numbers denote the percents of each compound at its equilibrium concentration.

When 2 (Scheme 2) reacts with methoxide the imidate 8 is reversibly formed and the dimethoxyketal 9 is obtained as one of the end products. There is a distinct difference in the distribution of products obtained from 2Cl and 2Br. This difference is most pronounced in the reactions of CN^- with 2. While with 2Cl the primary products are 2CN and 12, the bromo-derivative 2Br gives only 2CN but not 12. 2CN is completely converted to the monoimidate 10 which is partly converted further to the diimidate 11. Within the limits of the experimental analysis (±2%) 12 is completely converted to its imidate 13.

DISCUSSION

As we have shown in previous papers,[5,6,7] there are two operative mechanisms in nucleophilic substitution reactions of activated bicyclobutanes. The first of these is an addition-elimination mechanism (equation 2) observed with nucleophiles lacking strong mesomeric effects.[7]



(2)

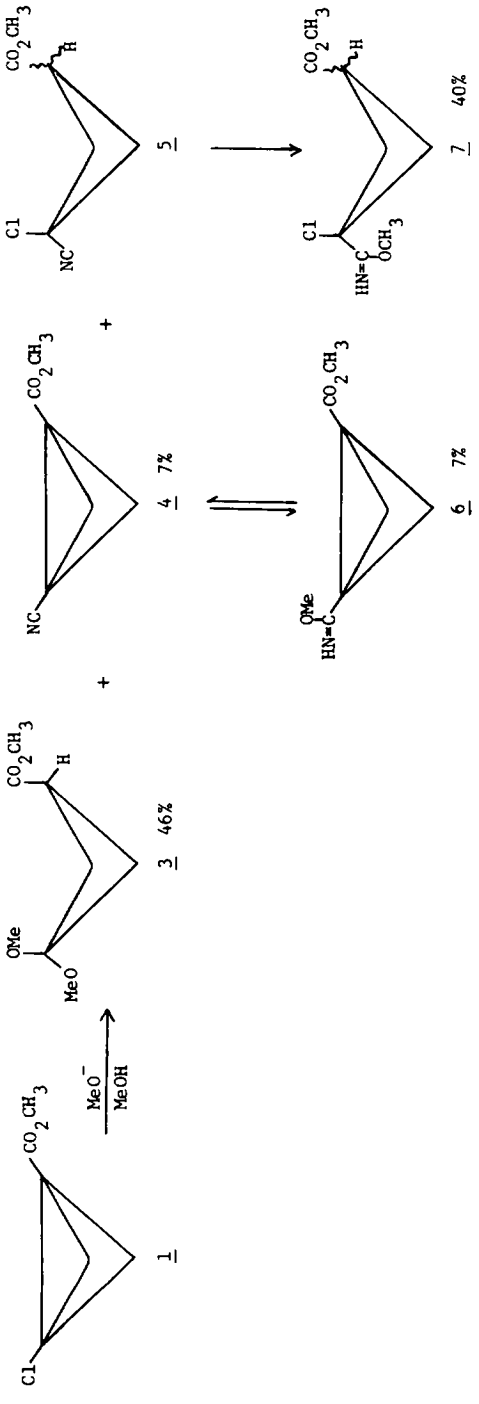
This mechanism accounts for the formation of the primary product shown in Schemes 1 and 2, with the exception of ketals 3 and 9. The formation of the latter is rationalized by a second mechanism which involves the intermediacy of an ionic bicyclobutane and is typical of the reaction of alkoxides and thiophenoxides with these substrates.[5,6] Because of its secondary role in the overall reaction scheme, it will not be discussed here.

The focus of this work are processes by which the primary products are converted to their corresponding imidates.

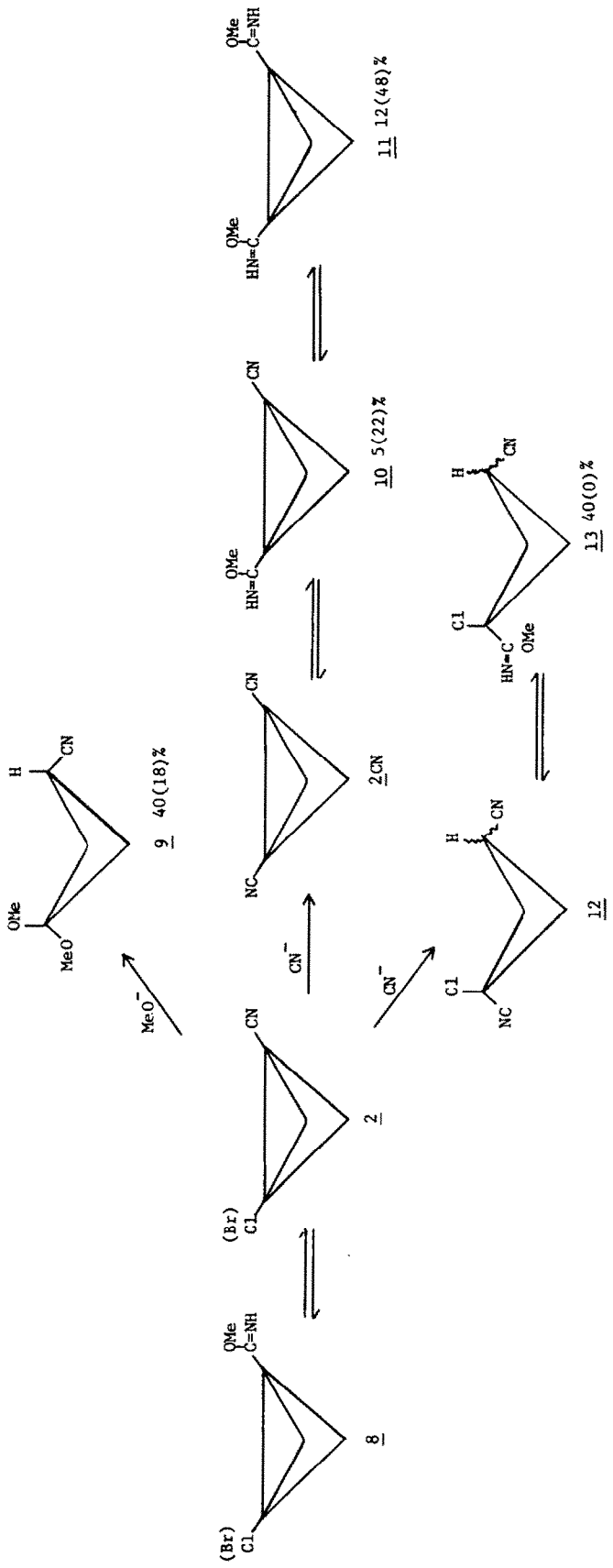
Substituent effects on the nitrile-imidate equilibrium. From the product distribution data (given in Schemes 1 and 2) the equilibrium constants (K = [imidate]/[nitrile]) can be evaluated. In some cases where the nitrile is essentially completely converted to the imidate, only a lower limit for K can be estimated. These estimates are based on the assumption that the upper limit for the percent of the nitrile present at equilibrium, in case where it was not directly observed, is equal to the experimental error (2%). The equilibrium constants are given in Table 1.

In general, the previous notions[3] that electronegative substituents favor the imidate at equilibrium is seen to be reconfirmed. The data indicate that the equilibrium constant decreases in the order CN>Cl≈Br>C(NH)OMe>CO_2Me. This order parallels the expected electron withdrawing ability of the substituents with a single exception of the relative ordering of the imidate and the ester groups.

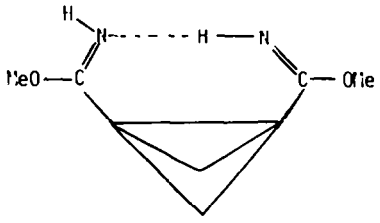
In the absence of quantitative data regarding the electronic effects of the imidate group, it may be assumed that replacing an oxygen atom in an ester for a nitrogen atom will reduce its electron withdrawal ability. Yet, the imidate group exerts a somewhat larger effect on the equilibrium position than does the ester moiety. If this indeed reflects a larger electronic effect of the imidate group it may stem from strong hydrogen bonding with the imino functioning as the acceptor. This hydrogen bonding if stronger than that of a carbonyl in an ester group could in principle lead to the observed effect. An alternative explanation could be an internal hydrogen bonding between the two imidate groups of 11 (14).



Scheme 1


OMe
C=NH
(Br)
Cl
8
(Br)
Cl
CN
2
NC
2CN
CN
OMe
HN=C
10 5(22)%
OMe
C=NH
OMe
HN=C
11 12(48)%
H
CN
OMe
MeO
9 40(18)%
MeO⁻
CN⁻
CN⁻
H
CN
Cl
NC
12
H
CN
Cl
HN=C
OMe
13 40(0)%

Scheme 2



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The latter explanation however, is somewhat less likely since McDonald et.al.[8] showed that intramolecular hydrogen bonding was not effective in stabilizing the mono-ionized form of bicyclobutanedicarboxylic acid. Their conclusion was supported by INDO calculations which show that both CO_2H as well as CO_2^- preferentially adopt a conformation in which the π like orbital of the central bond overlaps with the π system of the CO_2 group. The other conformation in which the two groups are positioned in the plane of symmetry of the molecule and are suitably oriented for the formation of the intramolecular hydrogen bond is of higher energy (5.3 and 3.1 Kcal/mol for CO_2H and CO_2^- respectively).[8] If the imidate group is similar in this respect to the carboxyl group then the second explanation can be ruled out.

Table 1. Equilibrium constants for the formation of imidates from the corresponding carbonitrile compounds in MeOH

carbonitrile function	imidate	K
4	6	1
2Cl,Br	8Cl,Br	4-5[a]
2CN	10	>11[b]
10	11	2
5	7	>20[b]
12	13	>20[b]

[a] From reference 5. [b] Estimated lower limit; see text.

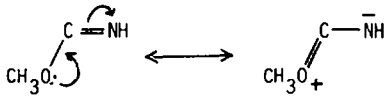
The last two entries in Table 1 demonstrate the proximity effect of the substituent. Placing the electronegative chlorine atom at an α-position further increases the equilibrium constant favoring the imidate formation. Clearly this can not be attributed to the remote substituent on C-3 since even in the bicyclic system (entry 1) the substituent has only a relatively weak effect on the equilibrium.

Transfer of electronic effects through bicyclobutane. Electronic effects are effectively transmitted[8,9] through small rings. As is evident from a comparison of ρ_I values for the ionization of 3-X-bicyclobutane-1-carboxylic acid and other cyclic compounds[8], bicyclobutane is especially effective as a mediator for polar effects. It is clear that a primary role is played by the central bond rather than by the side methylene bridge in the through bond mechanism. Moreover, a comparison with data reported by Schaefer and Peters[10] shows that this central bond is more effective in this respect than a normal σ bond. These authors have found that the equilibrium

constant for $NC-CH_2-CH_2-CN$ is only 0.5 whereas in the case of 2CN (in which the two cyano groups are also separated by two carbon atoms) the nitrile is essentially completely converted to the corresponding imidate. While this could be attributed to field effect[11] which is expected to be larger in the rigid conformation of bicyclobutane, comparison of substituent effects on the acidities of cis substituted cyclopropanecarboxylic acid and the analogous bicyclobutane[8] reveals that even in this case bicyclobutane is a better mediator(ρ_I = 2.8 and 3.3 respectively). Since the central bond of bicyclobutane closely resembles a π bond both in composition (96% p character)[12] and reactivity[13], it is likely that in addition to the probably dominant field effect there is also a significant contribution from a π polar effect.

The stability of alkoxy imidates. The formation of imidates is a two step reaction. In the first step the alkoxide reversibly attacks the nitrile function which is followed by protonation of the negatively charged nitrogen atom. Although in some experiments the concentration of the cyanide was about 40 times larger than that of the methoxide, no adducts between the cyanide and the nitrile function were observed. This is in clear contrast with the addition of the two nucleophiles to a carbonyl function. In the latter case, the cyano adduct, namely, cyanohydrin, is much more stable than the corresponding hemiacetal. It is clear that this can not be traced to the second step of the reaction since any difference in the acidity of the derived adducts should be similar in the carbonyl and the nitrile systems.

The nucleophilicity of CN towards LL (low LUMO)[14,15] substrate is smaller by a factor of 0.3 to 1.7 than that of methoxide.[15,16] However its nucleofugality as determined by Stirling is ca. 11 orders of magnitude smaller than that of methoxide.[17] Thus the nucleophilicity - nucleofugality ratio for cyanide and methoxide applied to the nitrile system implies that the anionic adduct (and therefore the neutral one as well) with cyanide should be much more stable than the methoxide adduct. A possible explanation for this discrepancy may stem from a resonance effect unique to



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the alkoxy imidates 15. This hypothesis is highly consistent with the order of the double bond stability scale established by Hine[18] (MeO >> CN).

EXPERIMENTAL

General: The progress of the reactions was followed by gas chromatography using a Packard 878 (FI detector) gas chromatograph. For preparative separations a Varian 920 gas chromatograph was used. The column used was 3-5% Xe60 on chromosorb W. ^1H NMR spectra were recorded on a Varian EM 360 A spectrometer. Mass spectra were taken with a Finnigan 4021 mass spectrometer.

Solvents and reactants. Methanol was dried by the magnesium method.[19] 3-Chlorobicyclobutanecarbonitrile (2Cl) was prepared according to published procedure.[13c] 3-Bromobicyclobutanecarbonitrile (2Br) was prepared from 1Cl according to a published procedure.[3] Methyl-3-chlorobicyclobutanecarboxylate (1) was prepared in three steps from 3.3-dichlorocyclobutanecarbonitrile.[13c] This was hydrolyzed to the acid followed by esterification[20] to give the ester methyl-3.3-dichlorocyclobutanecarboxylate. The ester is obtained in a 65% yield from distillation (60°C, 10 mm Hg) ^1H NMR $CDCl_3$ δ 3.7 (s, 3H), 3.15 (m, 5H) ms. ($CI-CH_4$) 187, 185, 183, 149, 147. The distilled ester was converted to 2 by t-BuO$^-$ assisted elimination of HCl.[13c] Due to trans esterification the product 2 (55%) is accompanied by its t-butyl ester analog. The two esters were separated by preparative gas chromatography (column temperature 90°C, the methyl ester has a shorter retention time) ^1H NMR for the methyl ester (2) $CDCl_3$ δ 3.8 (s, 3H), 2.8 (s, 2H exo) 1.75 (s, 2H endo), ms. ($CI-CH_4$) 149, 147, 111. The compound is unstable and was usually prepared shortly before the experiment was performed, otherwise it was stored (as a white solid) at -78°C. ^1H NMR data for the t-butyl ester in $CDCl_3$ δ 2.7 (s, 2H exo), 1.7 (s, 2H endo) 1.45 (s, 9H), ms. ($CI-CH_4$) 191, 189, 175, 173, 163, 161, 135, 133. Satisfactory C,H, analysis was obtained.

Reactions of 1 and 2 with CN^- in MeOH: The reactions were performed in a thermostated bath at 30°C. A similar procedure was employed for both substrates. Since the study was not synthetically oriented, no attempt was made to optimize yields. Reported yields are gc yields. Isolation of products was made by taking aliquots from the reaction mixture and separating them by gas chromatography until the desired quantities were obtained. The reactions were followed up by analytical gas chromatography and by gc-ms combination. The general procedure is demonstrated in the following reaction of 1. To a stirred solution of 0.8 gr NaCN (16 mmol) in 60 mL methanol, 0.6 g of 1 (4 mmol) were added. the reaction mixture was incubated at 30°C for two weeks. During this time, aliquots were periodically removed, ca. two thirds of the methanol was evaporated at room temperature. After addition of ether, the solids were filtered and the solution was analysed (gc-ms or gc with temperature programing in the range 85-110°C. Preparative separation of the products was performed at 105°C). The products according to their appearance on the gas chromatogram were: methyl-3.3-dimethoxycyclobutanecarboxylate (3, 46%), ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 3H-CO_2CH_3), 3.2 (s, 3H-OCH_3), 3.15 (s, 3H-OCH_3), 2.9-2.2 (m, 5H); ms.(CI-CH_4) 143 (M-OMe), 83. Satisfactory C,H, analysis; methyl-3-cyanobicyclobutanecarboxylate (4, 7%), ^{1}H NMR $CDCH_3$ δ 3.65 (s, 3H), 2.75 (s, 2H exo), 1.65 (s, 2H endo). Gc-ms (CI-CH_4) 138, 106, 78. ethyl-3-carboiminomethoxybicyclobutanecarboxylate (6, 7%), ^{1}H NMR $CDCl_3$ δ 3.8 (s, 3H), 3.7 (s, 3H), 2.7 (s, 2H exo), 1.65 (s, 2H endo). Gc-ms (CI-CH_4) 170, 138, 110, 106, 57. Elemental analysis for 4 and 6 was not obtained since we were unable to separate them to the desired purity by preparative gas chromatography; methyl-3-chloro-3-cyanocyclobutanecarboxylate (5) ^{1}H NMR $CDCl_3$ δ 3.7 (s, 3H), 3.35-2.9 (m, 5H), ms. (CI-CH_4), 176, 174, 149, 147, 138. In order to obtain this compound, the reaction has to be quenched at an intermediate time since toward the end of the reaction it is completely converted to its imidate 7; methyl-3-chloro-3-carboiminomethoxycyclobutanecarboxylate (two isomers 7, 40%), ^{1}H NMR $CDCl_3$ δ 3.8 (s, 3H), 3.7 (s, 3H), 3.3-2.75 (m, 5H), ms. (CI-CH_4) 208, 206, 176, 174, 170, 138. Satisfactory C,H,N, analysis was obtained. The product distribution of the reactions of 2 with NaCN are depicted in Scheme 2. Both the primary products as well as the imidates are known compounds.[7]

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