Kinetic and Equilibrium Acidities of Nitrocycloalkanes

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Rates of deprotonation by lyate ion in 50% (v/v) MeOH–H₂O were determined for C₅–C₆ and C₇ nitrocycloalkanes. Equilibrium acidities in this solvent were also determined for C₆–C₈ and C₁₂ nitrocycloalkanes and were determined in Me₂SO for C₅–C₇ nitrocycloalkanes. Equilibrium acidities in the two solvents showed a remarkable similarity in their variation with ring size, despite a (constant) difference of 7.75 \( pK \)'s for these two nitrocycloalkanes in: (a) water (8.56 and 8.75 \( pK \)'s for nitrocyclopropane and nitrocyclohexane, respectively) and (b) Me₂SO solution, and rate and equilibrium data for nitrocyclopropane have been obtained.

Results

Equilibrium Acidities for Nitrocycloalkanes. The relative values for the equilibrium acidities obtained potentiometrically in 50% (v/v) MeOH–H₂O (Table I) agreed reasonably well with those determined conductometrically in 33% (w/w) MeOH–H₂O, except for nitrocyclohexane, for which a higher relative value was found. Repetition of this measurement in 33% (w/w) MeOH–H₂O gave, in our hands, a \( pK \) of 9.58, instead of the value reported (8.92). (On the other hand, we were able to check the values reported for nitrocyclopentane and nitrocycloheptane in 33% MeOH–H₂O to within 0.1 \( pK \) unit.) The value of 9.58 appears to be correct, since it places the \( pK \) of nitrocyclohexane within a few tenths of a unit of that reported for nitrocyclohexane (\( pK = 9.50 \)).

In the preceding paper we discussed the "anomalous" Brønsted coefficients observed for the deprotonation of acyclic nitroalkanes in protic solvents. A lack of the "expected" correlation between kinetic and equilibrium acidities of certain nitrocycloalkanes and was deprotonation by lyate ion in water and by lyate ion in a variety of other protic solvents has been found to vary with ring size in the order: \( 4 < 5 < 7 < 8 > 6 > 3 \). (Nitrocyclopropane failed to react.) In contrast, the order of equilibrium acidities in 33% (w/w) MeOH–H₂O for nitrocycloalkanes was found to vary with ring size in the order: \( 8 > 7 > 5 > 6 > 4 > 3 \). (The acidity constant for nitrocyclopropane was too small to measure.)

Studied of kinetic and equilibrium acidities of nitrocycloalkanes in 50% (v/v) MeOH–H₂O were in progress at the time these data were published. The work was continued, since it seemed worthwhile to obtain kinetic and equilibrium measurements in the same solvent.
Table I. Equilibrium Acidities of Nitrocycloalkanes in 50% (v/v) MeOH-H2O and in Dimethyl Sulfoxide (Me2SO) at 25 °C

<table>
<thead>
<tr>
<th>registry no.</th>
<th>ring size</th>
<th>pK (50% MeOH-H2O)</th>
<th>pK (Me2SO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13021-02-8</td>
<td>3</td>
<td>&gt;18a</td>
<td>26.9 ± 0.2d</td>
</tr>
<tr>
<td>2625-41-4</td>
<td>4</td>
<td>10.05 ± 0.03</td>
<td>17.82 ± 0.05</td>
</tr>
<tr>
<td>2582-38-1</td>
<td>5</td>
<td>8.15 ± 0.02</td>
<td>16.00 ± 0.05</td>
</tr>
<tr>
<td>1122-80-7</td>
<td>6</td>
<td>10.07 ± 0.01</td>
<td>17.90 ± 0.05</td>
</tr>
<tr>
<td>2552-40-5</td>
<td>7</td>
<td>8.15 ± 0.02</td>
<td>15.80 ± 0.05</td>
</tr>
<tr>
<td>2510-92-4</td>
<td>8</td>
<td>7.37 ± 0.03</td>
<td>14.80 ± 0.05</td>
</tr>
<tr>
<td>1781-70-12</td>
<td>9</td>
<td>9.6 ± 0.1*</td>
<td>16.6 ± 0.05</td>
</tr>
<tr>
<td>79-46-9</td>
<td>Me2CHNO2</td>
<td>8.85 ± 0.02</td>
<td>16.89 ± 0.05</td>
</tr>
<tr>
<td>551-88-2</td>
<td>Et2CHNO2</td>
<td>10.17 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

* Determined potentiometrically. a Determined by the indicator method described by W. S. Matthews et al., J. Am. Chem. Soc., 87, 7088 (1965). b Based on the absence of UV absorption typical of >C=N02- in 1 M aqueous NaOH. c Decomposition occurs. d Extrapolated from data in 75% (v/v) MeOH-H2O.

Table II. Rates of Deprotonation of Nitroalkanes by Lyate Ion in 50% (v/v) MeOH-H2O (kD) at 25 °C

<table>
<thead>
<tr>
<th>ring size</th>
<th>kD rel</th>
<th>kH rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.002c</td>
<td>0.0072</td>
</tr>
<tr>
<td>4</td>
<td>5.4</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>0.28</td>
<td>(1.0)</td>
</tr>
<tr>
<td>7</td>
<td>0.87</td>
<td>3.1</td>
</tr>
<tr>
<td>12</td>
<td>0.13</td>
<td>0.46</td>
</tr>
<tr>
<td>Me2CHNO2</td>
<td>0.26</td>
<td>0.98</td>
</tr>
</tbody>
</table>

* Determined spectrophotometrically unless otherwise noted; a Determined by the indicator method described by W. S. Matthews et al., J. Am. Chem. Soc., 87, 7088 (1965). b Based on the absence of UV absorption typical of >C=N02- in 1 M aqueous NaOH. c Decomposition occurs. d Extrapolated from data in 75% (v/v) MeOH-H2O.

8.61; (b) 50% (v/v) MeOH-H2O (10.05 and 10.07); and (c) 50% (v/v) dioxane-H2O (10.88 and 11.16). Our value for nitroctohexane in water is 0.3 pK unit above that reported in another investigation, but agrees with a value we have extrapolated to from measurements in aqueous dioxane (using 50, 40, 25, and 10% of dioxane).4

Comparison of the equilibrium acidities in Me2SO with those in 50% MeOH-H2O for the C4–7 nitrocycloalkanes shows that they differ by an almost constant amount (7.75 ± 0.1 pK unit). Acyclic nitroalkanes show a similar behavior, but the differences are not quite so constant.6a,b

Contrary to the report that trans-2-ethylhydrocyclop propane fails to undergo base-catalyzed deuterium exchange even under strenuous conditions,2 we found that nitrocyclopropane (and cis- or trans-2-methyl nitrocyclopropane) undergoes deuterium exchange readily with either 0.1 N NaOD-D2O or 0.1 N lyate ion in 50% (v/v) MeOD-D2O. The rate of deprotonation for nitrocyclopropane is over 100 times slower than that of nitroctohexane or an open-chain analogue, 2-nitropropane, however, and is over 2500 times slower than that of nitroctohexane (Table II). For deuterodeuteron exchange of the protio compound in D2O, ΔH° is 13 ± 1 kcal/mol, which is the same as that of nitroctohexane in 50% dioxane–water.5 ΔS° for deprotonation of nitrocyclopropene is, however, −27 ± 2 eu, a value much lower than that reported for nitroctohexane (−14.5 eu).3

In comparing the deuterium exchange rates for nitrocyclopropane with the rates for appearance of the nitronate ions (determined spectrophotometrically) for the other nitrocycloalkanes, one must consider the possibility that the rate of deuterium exchange is complicated by internal return. This does not appear to be a major factor, judging from "mixed" kinetic isotope effect, kD/kH of 9.1 observed for nitrocyclopropane. The "mixed" isotope effect is the product of the "normal" substrate isotope effect, kD/kH (both in H2O), and the solvent isotope effect (kD2O/kH2O) (both with the protio compound). For 2-nitropropane, the "normal" isotope effect has been found to be 7.6 ± 0.2, and kD2O/kH2O has been found to be 1.36.8 Solvent isotope effects for carbon acids generally fall in the range 1.2–1.6.9 Judging from these data, the kD/kH isotope effect for nitrocyclopropane in water at 25 °C will be about 6.5, which would appear to rule out internal return as a major factor.

Discussion

Variation of Equilibrium Acidities of Nitrocycloalkanes with Ring Size. Examination of Table I shows that the relative order of equilibrium acidities observed in protic solvents for nitrocycloalkanes, namely, 5, 7 > 4, 6 > 3, is observed also in Me2SO solution. The changes in equilibrium position with changes in ring size are evidently independent of solvent and depend on only the nature of the ring. The changes in these equilibrium constants for the C4–C7 and C12 nitrocycloalkanes are in the same order as the equilibrium constants for formation of ketones from cyanohydrins in 95% EtOH, namely, C4 < C5 < C6 < C7 < C8 < C9 < C10.10 The major effects determining the position of the cyano- hydrin equilibria are believed to be angle strain in the C4 compound and torsional strains in the C5, C6, and C7 compounds.10 Adopting this analysis, the unfavorable dissociation constant for nitrocyclobutane, relative to C5, C6, and C7 nitrocycloalkanes (Table I), can be explained by assuming that angle strain in the C4 nitronate ion overshadows torsional strain in the C5 nitrocycloalkane. Similarly, the remarkably low dissociation constant for nitrocyclopentane (95% units lower than nitrocyclobutane in Me2SO) can be attributed largely to strain in the C5 nitronate ion. Introduction of one trigonal center into cyclopentane has been estimated to increase the total strain energy by 13 kcal/mol, as compared to only about 1 kcal/mol for cyclobutane.11

The greater degree of dissociation of the C5, C6, and C7 nitrocycloalkanes as compared to the C4 or C12 nitrocycloalkanes (Table I) can be attributed to the presence of torsional strains in the nitrocycloalkanes, which are partially relieved in forming the corresponding nitronate ions.10

Comparison of Equilibrium and Kinetic Acidities for Nitrocycloalkanes. The rates of deprotonation of nitrocycloalkanes by lyate ion in protic solvents follow the relative order 4 > 5 > 7, 8 > 6, 12, acyclic >> 3 (see Table I and ref 3). (The reversal in the order of the relative rates and equilibrium constants for the C4 and C5 nitrocycloalkanes has been commented on earlier as an example of an anomalous Brønsted relationship.5) The relative order of kinetic acidities of the C6, C7, and C8 nitrocycloalkanes obtained in this way is 19: 5:0.10, which corresponds closely to the relative order of kinetic acidities of cycloalkanes determined by cesium cyclohex-
The deprotonation of nitrocyclobutane relative to nitrocyclo-

The order observed, breaking can be appreciable (large torsional strain can occur (leading to rate acceleration for transformation of sp2 to sp3 carbon atoms in carbocyclic ring pentane) without much increase in angle strain. (See Figure 4 in ref 6c and the accompanying discussion for more details.)

The rates of protonation of the nitrate ions on carbon by MeOH–H2O solvent (k1/k2) can be calculated from the deprotonation rates and the equilibrium constants (Table II). The order observed, C4 > C9 > Cs, C7, is similar to that for the rate of reduction of the corresponding cycloalkanes by sodium borohydride,13a and follows Brown’s rule13b that the ease of formation of sp2 to sp3 carbon atoms in carbocyclic ring systems is greater for four- and six-membered rings than for five- and seven-membered rings.14 If we assume that the amount of s character in the C-H bond is the dominant factor controlling cycloalkane kinetic acidities,1*J5

According to this mechanism the rate-limiting step is the (endoenergetic) conversion of 1 to 2. The extent of H-C bond breaking can be appreciable (large k1/k2) and some relief of torsional strain can occur (leading to rate acceleration for deprotonation of nitrocyclobutane relative to nitrocyclo-

The rate pattern for deprotonation of nitrocycloalkanes with 7, 8, and 12 members, i.e., 7 > 8 > 12 (Table II), is also the same as that for cycloalkanes,12 although the order of rates relative to the six-membered ring compound differ slightly in the two systems. The mechanism outlined for deprotonation of nitrocyclcopentane, i.e., 1 to 2 = 3, appears appropriate also for these nitrocycloalkanes. On the other hand, the rate of deprotonation for nitrocyclo propane, relative to the rates for other nitrocycloalkanes, shows an opposite behavior from that for the rate for cyclopropane, relative to the rates for other cycloalkanes.

Cyclopropane is deprotonated by cesium cyclohexylamide in C6H6 at a rate about 2500 times faster than is cyclohexane.12 These rates, as well as those for C4–C9 cycloalkanes, correlate linearly with 13C–H NMR coupling constants, which indicates that the amount of s character in the C-H bond is the dominant factor controlling cycloalkane kinetic acidities.12,15

Theoretical calculations also indicate that the C-H bond in cyclopropane has appreciably more s character than do the C-H bonds in higher cycloalkanes.16 Apparently this factor is overshadowed completely in determining the kinetic acidity of the H-C bonds in nitrocyclopropane, since it is deprotonated in protic solvents at a rate about 2500 times smaller than is nitrocyclohexane (Table II). Remarkably enough, the major part of the rate difference appears to be in the ΔS° term, judging from the comparison of the activation parameters made in the Results. These data suggest a mechanistic change for deprotonation of nitrocyclopropane as compared to other nitrocycloalkanes. The deprotonation of nitrocyclopropane is uphill, as compared to other nitrocycloalkanes and acyclic nitro-


Reagents. Partially aqueous solvents were prepared by combining measured volumes of water and either methanol or dioxane to achieve the desired volume/volume percentage composition. Reagent-grade dioxane was refluxed with molten sodium for at least 24 h and then distilled. Baker and Adamson reagent-grade (ACS Code 1212) absolute methanol was used without further purification. Sodium hydroxide solutions were either standardized against Banco Standardized or Fischer Certified standard hydrochloric acid to a phenolphthalein end point or prepared from Anachem Acidity solu-

The basic solutions in mixed solvents were prepared by combining appropriate volumes of aqueous sodium hydroxide and the organic component and diluting with mixed solvent to the desired volume.

Kinetic Procedure. The rates of deprotonation from the ni-

Deuterium exchange rates for nitrocyclopropanes were determined using 5-10-mg aliquots in 4-mL vials containing 3 mL of -1 M NaOD/D2O. After shaking to promote dissolution, the vials were allowed to remain in a constant temperature bath for appropriate times. For analysis, the contents of the vial was extracted with 0.5 mL of carbon tetrachloride, and the ratio of the peak areas for the δ proton (5.5-9.4) and the protons (5.0-2.5) were determined by NMR.

Rate constants were determined from the equation, In kA/k = RT/A - A, where A is the ratio at time t. The accuracy of the method is limited by the low solubility of nitrocyclopropane (~5-10 mg/mL of D2O), and the rates are probably accurate to no better than ±10%. For nitrocyclopropane in D2O k at 25 °C was 5.9 × 10-11 M-1 s-1, and for nitrocyclopropane-d1 in H2O/D2O at 25 °C was 4.3 × 10-11 M-1 s-1. The rate constant for trans-2-methyl-1-nitrocyclopropane in D2O was identical, within experimental error, to that for nitrocyclopropane itself. For cis-2-methyl-1-nitrocyclopropane in D2O at 25 °C was ~4 × 10-11 M-1 s-1.

Rate constants for nitrocyclopropane in D2O were determined at
15 and 35 °C by monitoring the appearance of the OH peak in the solvent by NMR. For this purpose 100 mg of nitrocyclopropane was determined by cut-and-weigh, and the data analyzed as first-order kinetics.

Materials. Nitrocyclohexane was obtained as a gift from the Commercial Solvents Corp. and nitrocyclooctane was obtained as a gift from Professor J. G. Traynham. Other nitrocycloalkanes, except for nitrocyclopropane, were prepared by the oxidation of the keto oximes as described previously.14 Nitrocyclopropane was prepared by the method of Lampman, Horne, and Hager12 and purified by GLC using a 9% in. × 10 ft Carbosieve on acid-washed Chromosorb W column at 110 °C and 160 mL/min flow rate to give a clear liquid: n\(^{20}\)D 1.4382 [lit.\(^{25}\) n\(^{20}\)D 1.4395]; NMR (CDCl\(_3\)) \(\delta\) 1.10 (2 H), 1.60 (2 H), 4.33 (m, 1 H); IR (film) 1540, 1370 cm\(^{-1}\).

Isolation of each was accomplished by preparative GLC using a l/4 in. GLC analysis indicated the presence of two isomers in a ratio of 10:1.6 Isolation of each was accomplished by preparative GLC using a 9% in. × 20 ft 3% Carbosieve on acid-washed Chromosorb W column at 80 °C and a flow rate of 80 mL/min. The products had similar, but slightly different NMR spectra: (CDCl\(_3\)) \(\delta\) 1.12 (2 H, m), 4.2 (m, 1 H). Upon treatment with aqueous 1 M NaOH for 0.5 h at 25 °C each was converted to the same 20:1 mixture of isomers (GLC analysis). The lesser product was therefore assigned the cis structure.

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Registry No.—cis-2-Methyl nitrocyclopropane, 66303-44-4; trans-2-methyl nitrocyclopropane, 15267-24-0; 1,3-dibromobutane, 107-80-2.

References and Notes

6. (a) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, J. Org. Chem., companion paper in this issue; (b) F. G. Bordwell and J. E. Bartmess, ibid., companion paper in this issue; (c) F. G. Bordwell, J. E. Bartmess, and J. A. Hautala, ibid., companion paper in this issue. (These are papers 1-3 in this series.)
14. In ref 3, it was stated that the relative protonation rates did not follow this order, the C\(_5\) nitronate being protonated faster than the C\(_6\) nitronate. A check of the data shows, however, that there is a decadic error in the rate calculated for the C\(_5\) nitronate ion (the relative k\(_{H^+}\) should be 11.3, not 113).