Kinetics of Iodination of 4-Methylimidazole and 2-Methylimidazole

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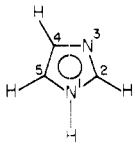
Since the rate law for the diiodination of imidazole provides information on the iodination of C4(5) but not C2 in the imidazole ring,[3,4] we have investigated the kinetics of iodination of the two positions separately in 2-methylimidazole and 4-methylimidazole, respectively. The observed rate laws for the methylimidazoles exhibited hydrogen ion dependencies that differed from that of imidazole; the iodinations of all three substrates were base catalyzed, but like imidazole, 2-methylimidazole undergoes uncatalyzed iodination, while 4-methylimidazole does not. The overall rate of iodination of 4-methylimidazole was faster than that of 2-methylimidazole which was faster than that of imidazole.

Imidazoles, pyrazoles, and related five-member heterocycles are aromatic compounds; like benzene, the molecules are planar with six π electrons. Unlike benzene and its derivatives, the reactivities of these heterocycles do not, in general, conform to theoretical studies of aromatic reactivity.[1] For example, only to a limited extent has it been possible to correlate observed electrophilic and nucleophilic reactivities of the heterocycles with calculated reactivity indices such as localization energies and electron densities.[2] For a basis for a theory of aromatic reactivity for heterocyclic systems there is a need for more kinetic studies of electrophilic and nucleophilic reactions of various heterocycles to clarify the often complicated mechanisms and to generate reactivity data for the positions in the rings. Typically, halogenation of ring positions has been used to determine relative electrophilicities of heterocyclic ring positions.

Imidazole (1) has been shown[3] to undergo diiodination to 2,4(5)-diiodoimidazole (2) in aqueous solution when the concentration of 1 exceeds that of I_3^-. The kinetics of this



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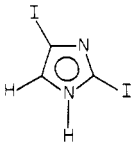

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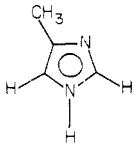
reaction has been reported.[3,4] Although the substrate was diiodinated, the order with respect to iodine was found to be first, not second;[3a] further, iodination of C4(5) exhibited a deuterium isotope effect, but C2 did not.[3b] Evidently, the C2 position is activated by the iodine substituent at the C4(5) position, causing the second iodination to occur almost instantly after the first. Clearly, the experimental rate law found for the iodination of 1 pertains only to C4(5), revealing nothing about the iodination of C2.

The purpose of the present investigation was to study separately the kinetics of iodination of C2 and C4(5) in the imidazole ring system. The substrates chosen were 4-(5)-methylimidazole (3) and 2-methylimidazole (4). If the substrate concentration is sufficiently larger than $[I_3^-]$, 3 is monoiodinated at C2 and 4 at C4(5) (see Experimental Section). A further objective was to determine the effect of the methyl substituent on the rates of iodination and on the experimental rate laws for the iodinations of substrates 3 and 4.



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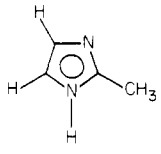

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Results and Discussion

Rate Laws. The experimental rate law for the iodination of imidazole (1) reported in the literature[1,2] is

$$-d[I_3^-]/dt = k_1^{obsd}[I_3^-]$$

where the pseudo-first order rate constant is given by eq 1. Here, k_0 is the rate constant for the uncatalyzed iodination, k_B that for the base-catalyzed iodination, and [S] the concentration of free imidazole, i.e., total imidazole minus the amount of conjugate acid; the base-catalyzed reaction is second order in imidazole, indicating that imidazole is itself the base catalyst. If $k_1^{obsd}/[S]$ is plotted against [S], k_0 is found from the intercept and k_B from the slope. The dependence of the rates of iodination of the methylimidazoles 3 and 4 upon iodide ion, like that of imidazole, was found by the usual procedure to be inverse second order. Similarly, $k_1^{obsd}/[S]$ for the iodinations of 3 and 4 varied linearly with [S]. Unlike 1, however, the iodinations of 3 and 4 did not exhibit inverse first-order dependence upon the hydrogen ion concentration. In Figures 1 and 2, $k_1^{obsd}[H^+][I^-]^2/[S]$ is plotted against [S] for 3 and 4, respectively; were the iodinations inverse first order in hydrogen ion, all the points would fall onto a single straight line, irrespective of the pH. Further, the absence of an intercept in Figure 1 indicates there is no uncatalyzed (i.e., water catalyzed) iodination of 3 at 30 °C; there is no intercept even at 40 °C for this substrate.[5] The intercept exhibited in Figure 2 indicates that there is an uncatalyzed iodination of 4, which is inverse first order in hydrogen ion. Thus, it is the base-catalyzed iodinations of 3 and 4 that exhibit an inverse order in hydrogen ion with a magnitude larger than unity. Plots of log $(k_1^{obsd}/[S])$ vs. log $[H^+]$ for the two substrates indicate orders in hydrogen ion between −1 and −2, about −1.3 to −1.4 for each substrate. Such a nonintegral order in hydrogen ion is characteristic of parallel reactions having different hydrogen ion dependencies. Accordingly, we propose the rate law in eq 2 for

$$k_1^{obsd} = \left(\frac{k_0}{[H^+]} + \frac{k_{B1}[S]}{[H^+]} + \frac{k_{B2}[S]}{[H^+]^2} \right) \frac{[S]}{[I^-]^2} \qquad (2)$$

$$k_1^{obsd} = (k_0 + k_B[S]) \frac{[S]}{[H^+][I^-]^2} \qquad (1)$$

(1) K. Schofield, M. R. Grimmett, and B. R. T. Keene, "The Azoles", Cambridge University Press, Cambridge, 1976.
(2) J. D. Vaughan, Z. Mughrabi, and E. C. Wu, *J. Org. Chem.*, 35, 1141 (1970).
(3) (a) J. H. Ridd, *J. Chem. Soc.*, 1238 (1955). (b) A. Grimison and J. H. Ridd, *ibid.*, 3019 (1959).
(4) J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Am. Chem. Soc.*, 86, 2857 (1964).
(5) From a plot of $k_1^{obsd}[H^+][I^-]^2/[S]$ vs. [S] from data at 40 °C and a single pH value.

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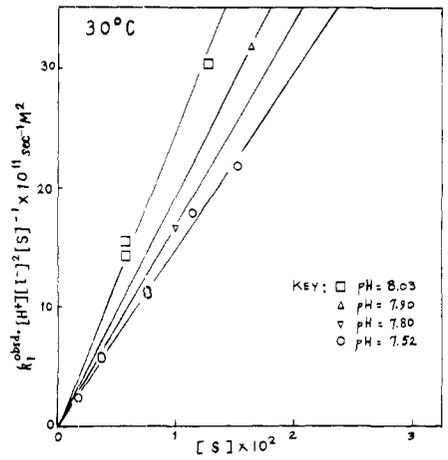


Figure 1. Iodination of 4-methylimidazole: buffer and hydrogen ion dependence.

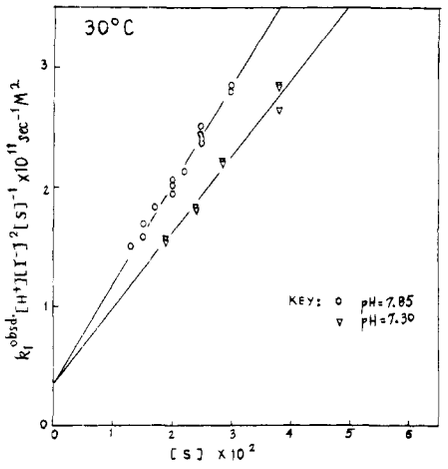


Figure 2. Iodination of 2-methylimidazole: buffer and hydrogen ion dependence.

the iodinations of **3** and **4**, where k_{B1} and k_{B2} are rate constants for parallel base-catalyzed iodinations exhibiting inverse first and inverse second order in hydrogen ion, respectively; k_0, the rate constant for uncatalyzed iodination, is zero for **3**.

The values of k_{B1} and k_{B2} were estimated from the data at 30 °C as follows. For **3**, we let $k_B = k_{B1}[H^+]^{-1} + k_{B2}[H^+]^{-2}$; since $k_0 = 0$ for this substrate, $k_B = k_1^{obsd}[I^-]^2[S]^{-2}$. A plot of $k_B[H^+]^2$ vs. $[H^+]$, shown in Figure 3, yields k_{B1} as the slope and k_{B2} as the intercept. For **4**, eq 2 was solved simultaneously for k_{B1} and k_{B2} by using values of $k_1^{obsd}/[S]$ and k_0 taken from the two pH-dependent lines in Figure 2. The results are given in Table I. Typically, for **3**, letting [S] = 0.20 M, $[I^-]$ = 0.24 M, and $[H^+] = 3.02 \times 10^{-8}$ M (pH = 7.52), one calculates $k_1^{obsd}/[S]$ to be 1.6×10^{-1} s^{-1} M^{-1}, compared to the value 1.7×10^{-1} s^{-1} M^{-1} from Figure 1. Similarly, for **4**, letting [S] = 0.20 M, $[I^-]$ = 0.24 M, and $[H^+] = 1.41 \times 10^{-8}$ M (pH = 7.85), one finds that the calculated and Figure 2 values are 2.5×10^{-2} and 2.6×10^{-2} s^{-1} M^{-1}, respectively.

Mechanism. The mechanism of Grovenstein and Aprahamian[6] for the iodination of 4-nitrophenol has been shown to account equally well for the iodination of imidazole.[4] Here, the anion (conjugate base) of imidazole is attacked by I_2, forming a σ intermediate, followed by rate-determining proton removal from the site of iodination by water (uncatalyzed reaction) or by imidazole (base-catalyzed reaction). To account for the different hydrogen ion dependencies of the base-catalyzed iodinations of the methylimidazoles, three elementary reactions (in eq 4 and 7) are added to the scheme for the iodination of imidazole.

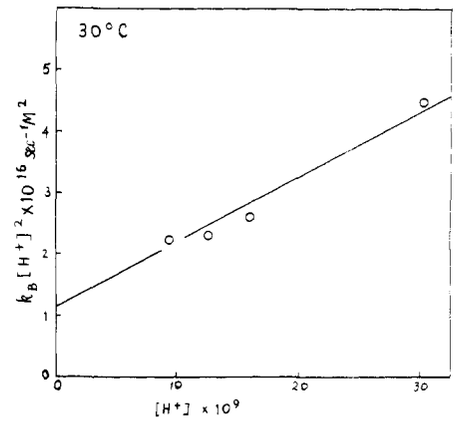
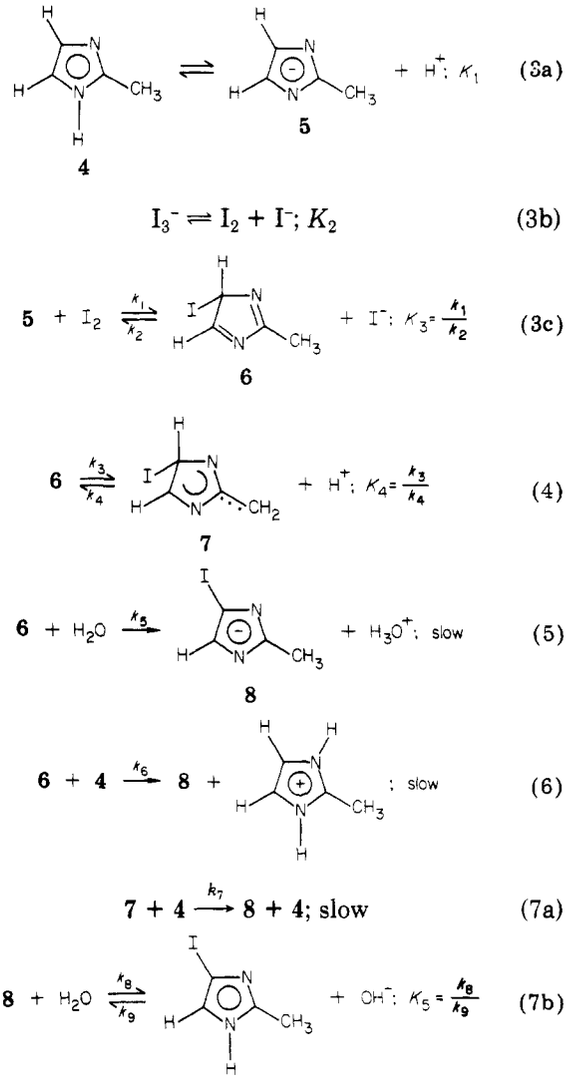


Figure 3. Iodination of 4-methylimidazole: dependence upon hydrogen ion concentration.



The complete scheme shown features 2-methylimidazole as the substrate. However, the scheme applies to the iodination of 4-methylimidazole if eq 5 is deleted. Assuming that the concentrations of σ intermediates **6** and **7** attain steady states, that parallel reactions 5, 6, and 7 are rate determining, that $k_1[5][I_2] \gg k_4[7][H^+]$ and that $k_2[I^-] \gg k_3$, the derived pseudo-first order rate law is found

(6) E. Grovenstein, Jr., and N. S. Aprahamian, *J. Am. Chem. Soc.*, 84, 212 (1962).

Table I. Rate Constants for the Uncatalyzed and Catalyzed Iodinations of 4-Methylimidazole and 2-Methylimidazole at 30 °C

	4-methylimidazole[a]	2-methylimidazole[a]
k_0, s^{-1} M^2		5.3×10^{-12}
k_{B1}, s^{-1} M	1.0×10^{-8}	5.1×10^{-10}
k_{B2}, s^{-1} M^2	1.2×10^{-16}	3.5×10^{-18}

[a] Error of ~±15% (estimated graphically).

to be given by eq 8. Equation 8 conforms to the observed

$$k_1^{obsd} = \left(\frac{k_5}{[H^+]} + \frac{k_6[S]}{[H^+]} + \frac{k_7K_4[S]}{[H^+]^2} \right) \frac{K_1K_2K_3[S]}{[I^-]^2} \quad (8)$$

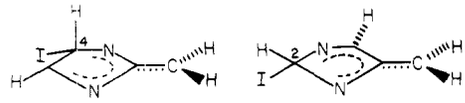
rate law, eq 2, with k_0, k_{B1}, and k_{B2} as in eq 9–11.

$$k_0 = k_5K_1K_2K_3[H_2O] \quad (9)$$

$$k_{B1} = k_6K_1K_2K_3 \quad (10)$$

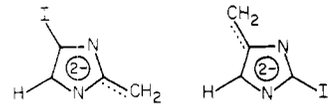
$$k_{B2} = k_7K_1K_2K_3K_4 \quad (11)$$

σ intermediate **7**, formed by the loss of a methyl proton from intermediate **6**, is stabilized by π-electron delocalization arising from overlap of the methylene 2p π orbital and the ring π orbital; the prime notation is used for 4-



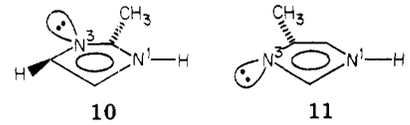
7 **7′**

methylimidazole intermediates. Loss of the C4(5) proton from **7** or the C2 proton from **7′** is catalyzed by methylimidazole base (**4** or **3**). Two mechanisms for this loss, and the gain of a proton by the methylene carbon, are conceivable. First, the proton at C4 in **7** or that at C2 in **7′** could be removed by the base catalyst to form an iodinated dianion (**9** or **9′**), which could then react rapidly with water

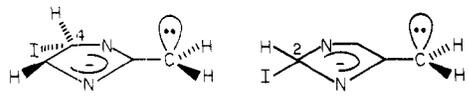


9 **9′**

to form the iodinated anion **8**. Second, the process could be concerted, as illustrated by structures **10**, **7** and **11**, **7′**.



10 **11**



7 **7′**

Here, the proton on N1 of the catalyst is transferred to the methylene carbon while the C4 proton (intermediate 7) or C2 proton (intermediate 7′) is transferred to N3 of the catalyst.

Relative Rates of Iodination of Imidazoles. The relative uncatalyzed and base-catalyzed rates of iodination of imidazole and the two methylimidazoles were calculated from the rate constants in Table I and from literature data on imidazole.[4] For the uncatalyzed iodination $k_0^{Im}:k_0^{2\text{-MeIm}}:k_0^{4\text{-MeIm}} \approx 1:28:0$, and for the base catalyzed reactions $k_{B1}^{Im}:k_{B1}^{2\text{-MeIm}}:k_{B1}^{4\text{-MeIm}} \approx 1:34:667$ and $k_{B2}^{2\text{-MeIm}}:k_{B2}^{4\text{-MeIm}} \approx 1:34$. As expected, the rates of iodination of the methylimidazoles are faster than that of imidazole. However, in view of the fact that C4(5) in imidazole is more reactive than C2,[3b] it is surprizing that C2 in 4-methylimidazole iodinates faster (via base catalysis) than C4(5) in 2-methylimidazole. At pH 7 with [3], [4], and [1] each at 1 M, **3** is iodinated 20 times more rapidly than **4** and 750 times faster than **1**. An alternate view is that **3** is first iodinated at C5 instead of C2 and then undergoes rapid isomerization to form 2-iodo-4-methylimidazole.[7]

The overall effect of the methyl substituent on the iodination rates of imidazoles can be conveniently dissected into four parts. First, the electron release by the methyl group increases the nucleophilicity of the C positions in the ring. Hence, the steady-state (or equilibrium) concentrations of σ-type intermediates (**6** and **6′**) will be larger for methyl-substituted imidazoles than for imidazole. Second, methyl groups increase the basicity of the N3 position of the imidazole ring, thereby enhancing the base catalytic activity of the heterocycle in eq 6 and 7a. Third, methyl groups decrease the acidity of the N1 position, which reduces the equilibrium concentration of the reactive conjugate base (i.e., by decreasing the magnitude of K_1). Fourth, the relatively acidic methyl groups in the σ intermediates (**6** and **6′**) by losing a proton provide an alternative path not accessible to the unsubstituted imidazole. All of the subeffects except the third are rate enhancing. Of the two methylimidazoles, 2-methylimidazole is the stronger base[8,9] and therefore is likely to be the better base catalyst.[10] That C2 in 4-methylimidazole is more reactive than C4(5) in 2-methylimidazole is probably attributable to the relative acidities of the substrates. Because the methyl group in 4-methylimidazole can be in the C4 or in the equivalent C5 position, it is, on the average, 1.5 ring positions away from the acidic pyrrole-type nitrogen atom. In 2-methylimidazole, the methyl group is sandwiched between N1 and N3, once removed from either, suggesting strongly that 2-methylimidazole is a weaker acid than 4-methylimidazole.[11] The greater *acidity* of 4-methylimidazole must be sufficient to offset the greater *basicity* of 2-methylimidazole.

Summary. The kinetic data found for the iodinations of the two methylimidazoles show that C2 and C4(5) monoiodination occur via the same mechanism (except for the absence of an uncatalyzed reaction for C2). However, iodination of C2 in 4-methylimidazole differs from C2 iodination in imidazole, which is accelerated by the immediately prior C4(5) iodination. The proposed mechanistic scheme and the simple model for methyl group electron release can account for the observed kinetics of the C positions in imidazoles, can account qualitatively for their relative reactivities, but cannot explain why 4-methylimidazole undergoes base-catalyzed but not water-catalyzed iodination.

Experimental Section

Materials. 4(5)-Methylimidazole (**3**) from Chemical Procurement Laboratories, Inc., was purified by vacuum distillation (85 °C at 0.5 mm). 2-Methylimidazole (**4**) from Aldrich Chemical Co. was recrystallized three times from benzene; mp 147 °C.

(7) Suggested by a referee.

(8) The pK_a values for the conjugate acids of 4-methyl- and 2-methylimidazole are 7.52 and 7.86, respectively.

(9) A. Albert, "Physical Methods in Heterocyclic Chemistry", Academic Press, New York, 1963.

(10) This is assuming that the two methylimidazole base catalysts participate to the same extent in the transition states of the rate-determining steps 6 and 7.

(11) pK_a values for the formation for the conjugate bases of **3** and **4** have not been reported. For imidazole (**2**),[9] $pK_a \simeq 10^{14}$.

Reagent grade KI and $NaNO_3$ were dried at 110 °C and used without further purification. Reagent grade sublimed iodine was resublimed before use. Perchloric acid stock solution prepared from reagent grade $HClO_4$ (70%) was standardized against potassium acid phthalate.

Kinetic Runs.[12] All kinetic runs were carried out in aqueous solution, adjusted to a constant ionic strength of 1.00 M with 2.5 M $NaNO_3$. Since **3** and **4** are weak bases, the substrates were buffers in the kinetic runs; aqueous $HClO_4$ was used to set the buffer ratios ([conjugate acid]/[base]) to preselected values. In all runs, the ratios of substrate concentration to $[I_3^-]$ and of $[I^-]$ to $[I_3^-]$ were greater than 20. Pseudo-first-order rates were followed spectrophotometrically at 400 nm[2] by using a Bausch and Lomb Spectronic 20 fitted with an Arthur H. Thomas rotocell and a Bausch and Lomb Spectronic 600 fitted with water-jacketed cuvettes. In a few instances, rates were determined by titration.[4] A Beckman Zeromatic pH meter was used to determine pH values. Except in runs designed to determine the order in I^-, $[I^-]$ was set at 0.24 M for both substrates. The temperature was held at 30.0 ± 0.2 °C.

Product Analysis. The products of the iodination of **3** were studied by Pauly and Arauner.[14] Both mono- and diiodo products were found. At 30 °C under conditions similar to those of the kinetics runs, the product was found to be 2-iodo-4-methylimidazole by comparing the NMR spectra of the iodination product and **3**; the proton peak corresponding to C2 in **3** was absent in the product.[15] The product was prepared by refluxing a solution containing 0.1 M **3** and 0.5 M I_3^- for 45 min. Excess iodine was removed with sodium bisulfite, and the product was separated from the aqueous solution by extraction with ether.

If I_3^- is in excess, **4** is diiodinated. A solution of **4** together with K_2HPO_4 catalyst was titrated with aqueous I_2 to the starch end point. The indicated stoichiometric equation is given by eq 12.

$$C_4H_6N_2 + 2I_3^- \rightarrow C_4H_4N_2I_2 + 2H^+ + 4I^- \quad (12)$$

The diiodo product was prepared for elemental analysis by refluxing a solution 0.05 M in **4**, 0.01 M in $HClO_4$, 0.10 M in I_2, and 1.0 M in KI for 30 min. The white crystals that separated from the cooled solution were recrystallized from water; mp 204–206 °C uncor (melting attended by loss of I_2). The purified product was analyzed by Bernhardt Microanalytical Laboratory. Anal. Calcd for $C_4H_4N_2I_2$: C, 14.4; H, 8.4; N, 1.2; I, 76.0. Found: C, 14.4; H, 8.4; N, 1.1; I, 76.2. The NMR spectrum of **4** exhibited a singlet at δ 7.1 relative to Me_4Si attributed to protons in the equivalent 4 and 5 positions. The NMR spectrum of the purified diiodo product revealed peaks for the methyl protons but none for the protons at the 4 and 5 positions, indicating the compound to be 4,5-diiodo-2-methylimidazole. In kinetic runs, the ratio of the initial concentrations of **4** and I_3^- was never less than 20. For the investigation of the iodinated product of the kinetic runs, a solution with a ratio of [**4**] to $[I_3^-]$ of 20 was prepared. This solution, essentially the same as those of actual kinetic runs, was allowed 48 h to react, after which all I_3^- had disappeared. The solution was then extracted with ether. The solid extract (mainly **4**) was dissolved in acetone and analyzed by ascending paper chromatography. Whatman No. 1 paper was used together with BuA solvent and iodine vapor location agent.[16] Two spots with R_f values of 61 and 75 were located. In separate chromatographic runs, R_f values for **4** and 4,5-diiodo-2-methylimidazole of 61 and 93 were observed. In view of the absence of a spot for 4,5-diiodo-2-methylimidazole in the chromatogram for the kinetic run, we conclude that the spot with the R_f value of 75 is the monoiodinated product 4(5)-iodo-2-methylimidazole.

Registry No. **3**, 822-36-6; **4**, 693-98-1; 2-iodo-4-methylimidazole, 73746-43-7; 4,5-diiodo-2-methylimidazole, 73746-44-8; 4-iodo-2-methylimidazole, 73746-45-9.

(12) Adapted from the kinetic techniques reported by Berliner.[13]
(13) E. Berliner, *J. Am. Chem. Soc.*, **72**, 4003 (1950).
(14) H. Pauly and E. Arauner, *J. Prakt. Chem.*, 118, 33 (1928).
(15) G. S. Reddy, R. T. Hobgood, and J. H. Goldstein, *J. Am. Chem. Soc.*, **84**, 336 (1962).
(16) I. Smith, Ed., "Chromatographic and Electrophoretic Techniques", Vol. I, Interscience, New York, 1960.

N-Nitrosodecahydroquinolines. Conformational Analysis by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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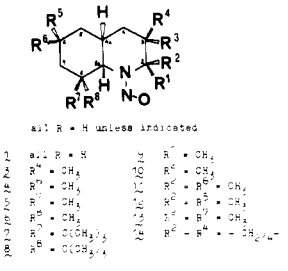
NMR spectra (^{13}C and ^1H) of *N*-nitroso-*trans*-decahydroquinoline (**1**), *N*-nitroso-*cis*-decahydroquinoline (**2**), 17-methyl- or 17-*tert*-butyl-substituted *N*-nitrosodecahydroquinolines, and *N*-nitroso-*trans-syn-trans*-perhydroacridine were recorded, and the conformational properties of the compounds were determined by comparison with the spectra of the parent amines and with the aid of substituent parameters. Molecular strain in 2β- and 8β-substituted trans compounds is minimized by partial escape of the piperidine moiety into nonchair conformations.

N-Nitrosamines have drawn considerable interest as synthetic intermediates since it was found that the α carbanions obtained by lithiation will react in good yields with various electrophiles.[1,2] It was also found that the methyl groups in *N*-nitroso-2,6-*cis*-dimethylpiperidines prefer the sterically constrained syn-axial conformation to relieve the still more severe strain of the alternate form[2-4] and that equilibration between *cis*- and *trans*-2,6-dimethyl compounds could be achieved by catalysis

Chart I



all R = H unless indicated

1 all R = H
2 R4 = CH3
3 R7 = CH3
4 R2 = CH3
5 R5 = CH3
6 R7 = C(CH3)3
R8 = C(CH3)3
7 R7 = CH3
8 R6 = CH3
9 R5 = R8 = CH3
10 R5 = R7 = CH3
11 R6 = R4 = -CH2CH2-

(1) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **14**, 15 (1975); D. Seebach, D. Enders, and B. Renger, *Chem. Ber.*, **110**, 1852 (1977); B. Renger, H.-O. Kalinowski, and D. Seebach, *ibid.*, **110**, 1866 (1977).
(2) R. R. Fraser and T. B. Grindley, *Can. J. Chem.*, **53**, 2465 (1975); R. R. Fraser, T. B. Grindley, and S. Passannanti, *ibid.*, **53**, 2473 (1975).

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