Steric Effects in S_N2 Reactions. Primary Carbon Kinetic Isotope Effects in Menshutkin Reactions

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The $^{11}C/^{14}C$ kinetic isotope effect (KIE) has been used to probe steric hindrance in the Menshutkin reactions of different substituted amines with labeled methyl iodide. The KIEs for the reaction of 2,6-lutidine and 2,4-lutidine with labeled methyl iodide in acetonitrile were determined to 1.220 ± 0.009 and 1.189 ± 0.012, respectively. The $^{11}C/^{14}C$ KIEs for the reaction of triethylamine and quinuclidine, with labeled methyl iodide in 1,2-dimethoxyethane were determined to 1.221 ± 0.006 and 1.220 ± 0.005, respectively.

Steric effects are of indubitable importance in controlling the reactivity and selectivity of chemical reactions. Systematic experimental and theoretical investigations are, however, much more scarce when it comes to steric effects than they are for electronic (substituent) effects. The quaternization reaction of tertiary amines by alkyl substrates (the Menshutkin reaction) is characterized by neutral reactants and charge separation developing during the course of the reaction. The reaction has been extensively studied in solution with respect to effects of variations in substituents, leaving group, solvent, etc., and reactivity–selectivity relations have been considered as indicators of structural variations of the transition state (TS).[1] The Menshutkin reaction using pyridines as nucleophiles is strongly affected by the size of the substituents in the ortho positions and is one of the few reactions for which steric effects have been systematically studied and for which steric and electronic effects can be easily separated.[2] It is clear that a deeper understanding of the effect of a steric perturbation on the transition state for this reaction is desirable.

One of the more powerful methods for investigating the finer details of a chemical reaction is the use of isotopic substitution leading to kinetic isotope effects (KIEs).[3] This technique has been applied to the Menshutkin reaction also with respect to steric effects.[4] Thus, primary $^{35}Cl/^{37}Cl$ KIEs were determined for the quaternizations of triethylamine and quinuclidine[5] and of pyridine and 2,6-lutidine[6] by methyl chloride. Such KIEs are in principle easily interpreted since they decrease monotonically with the magnitude of the stretching force constant for the $C\cdots X$ bond within the TS. However, these KIEs are very small and difficult to measure accurately and in the cases mentioned show conflicting results.[7] Inverse deuterium secondary KIEs are observed for 2- and 2,6-alkylpyridines in their reactions with methyl iodide.[8,9] The inverse KIE was attributed by Brown and McDonald[8] to the size of CD_3 which was smaller than CH_3, but Balaban and co-workers[9] concluded that both steric and electronic contributions were involved. In contrast, the KIEs are almost nil for 3- and 4-substituted (CH_3 and CD_3) pyridines.

This work reports the primary central carbon KIEs for the quaternization reactions of pairs of tertiary amines which exhibit essentially the same electronic contribution (measured as pK_a (water) of the corresponding ammonium ion), and any induced variations in reaction rates can thus be attributed to steric factors.

Since heavy atom KIEs are usually small, very accurate experimental methods[10] are required to be able to observe minor variations in these effects due to structural variations in the reaction system. In this study, the short-lived radionuclide ^{11}C (half-life of 20.4 min) is used in combination with the long-lived radionuclide ^{14}C (half-life of 5730 years). In the $^{11}C/^{14}C$ method,[11] the large mass difference between the two isotopes makes it possible to measure small carbon KIEs. The method is a one-pot technique based on HPLC separation of the product and reactant and subsequent radioactivity measurements using liquid scintillation counting. The $^{11}C/^{14}C$ method has earlier been used to determine the KIE for the quaternization of *N*,*N*-dimethyl-*p*-toluidine with labeled methyl iodide.[11b]

More systematic studies of the structural variation of the transition states for Menshutkin reactions by isotopic mapping for successively labeled positions have been performed by Paneth and O'Leary[12] and by Yamataka and Ando.[13] In both cases, *N*,*N*-dimethylanilines were

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(3) (3) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; John Wiley & Sons: New York, 1980.

(4) Reference 1, p 64.

(5) Swain, C. G.; Hershey, N. D. *J. Am. Chem. Soc.* **1972**, *94*, 1901.

(6) le Noble, W. J.; Miller, A. R. *J. Org. Chem.* **1979**, *44*, 889.

(7) In the triethylamine/quinuclidine case, the $^{35}Cl/^{37}Cl$ KIE is larger for the sterically more hindered reaction (triethylamine), whereas the opposite is true in the pyridine/2,6-lutidine case. The electronic effect is not constant for the latter pair though.

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(11) (a) Axelsson, B. S.; Långström, B.; Matsson, O. *J. Am. Chem. Soc.* **1987**, *109*, 7233. (b) Axelsson, B. S.; Matsson, O.; Långström, B. *J. Phys. Org. Chem.* **1991**, *4*, 77 and references cited therein. (c) Axelsson, B. S.; Matsson, O.; Långström, B. *J. Am. Chem. Soc.* **1990**, *112*, 6661.

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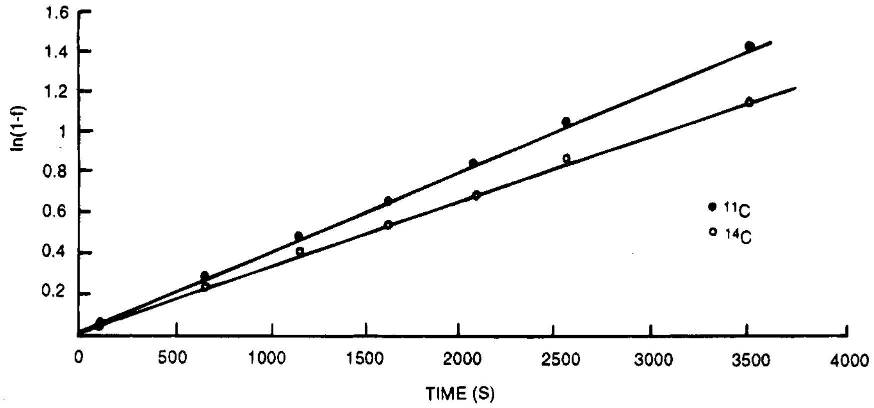

Figure 1. Plots of $-\ln(1-f)$ versus reaction time for the reaction between labeled methyl iodide and 2,6-lutidine in DME in a representative experiment.

Scheme 1

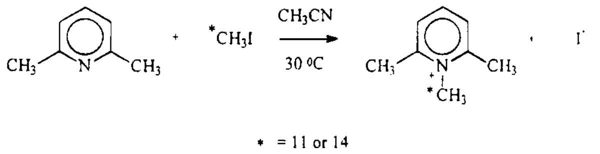

Table 1. Results from KIE Experiments

substrate	solvent	temperature (°C)	KIE	pK_a
triethylamine	DME	15.00	1.221 ± 0.006 1.212 (30 °C)[d]	10.65[a]
quinuclidine	DME	15.00	1.220 ± 0.005 1.212 (30 °C)[d]	10.95[b]
2,6-lutidine	acetonitrile	30.00	1.220 ± 0.009	6.77[c]
2,4-lutidine	acetonitrile	30.00	1.189 ± 0.012	6.72[c]

[a] Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441. [b] Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965. [c] Clarke, K.; Rothwell, K. *J. Chem. Soc.* **1960**, 1885. [d] Corrected to 30 °C using the temperature dependence of the ^{13}C KIE for cyanization of methyl bromide reported in: Lynn, K. R.; Yankwich, P. E. *J. Am. Chem. Soc.* **1961**, *83*, 3220.

employed as nucleophiles. In these studies, however, the question of steric effects was not addressed.

Results

The results from the KIE experiments are shown in Table 1. Each KIE is the mean value of three independent experiments.

Reactions were pseudo-first order; in each case, the amine was in approximately 1000-fold excess relative to methyl iodide. The KIE was calculated as the mean value of the KIE in each point sampled from the kinetic run. The kinetic method including the procedure for calculation of the KIE has been described earlier.[11b] A plot of $-\ln(1-f)$ versus time is shown in Figure 1. The radiochromatograms showed only the reactant peak (methyl iodide) and the product peak (quaternary amine). The radiochromatogram for a typical experiment is shown in Figure 2. The only detectable side product in the ^{11}C synthesis was labeled methanol, usually less than 0.3%. The methanol did not increase during the kinetic experiment, i.e. no additional hydrolysis was detected.

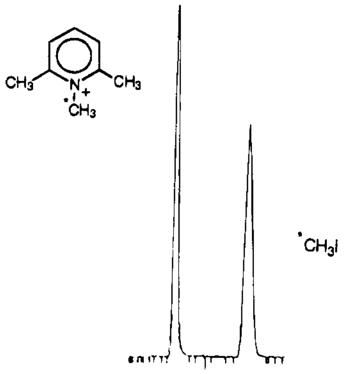

Figure 2. Radiochromatogram from a typical experiment using 2,6-lutidine as the nucleophile.

Discussion

There are three main features in the observed data. (i) The observed primary ^{11}C/^{14}C KIEs are almost the same for all four reactions, and (ii) the KIEs are all large, close to maximal as estimated on the basis of loss of zero-point energy in going from initial to transition state. A large primary carbon kinetic isotope effect of k^{11}/k^{14} = 1.202 ± 0.008 has previously been determined for the reaction of *N,N*-dimethyl-*p*-toluidine with methyl iodide in methanol at 30 °C.[11b,14] This value is within the range of carbon KIEs displayed in Table 1. As for the case of deuterium KIEs on hydron transfer, maximal primary carbon KIEs are expected for "symmetric" transition states[15] where donor and acceptor are bound with equal strength to the isotopic atom in transfer.[16-18] (iii) A small increase in primary carbon KIE is observed for 2,6-lutidine as compared to 2,4-lutidine. Thus, steric hindrance seems to be reflected in a higher primary central carbon KIE for this reaction system since electronic effects are the same. Steric hindrance has often been associated with large primary deuterium KIEs, a fact which has usually been explained by a larger amount of tunneling.[19] One example of this is the primary deute-

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(12) (a) Paneth, P.; O'Leary, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 1691–1693. (b) Rudzinski, J.; Tadros, N.; Paneth, P. *J. Mol. Struct.* **1994**, *321*, 97–99.

(13) (a) Yamataka, H.; Ando, T. *J. Phys. Chem.* **1981**, *85*, 2281–2286. (b) Ando, T.; Tanabe, H.; Yamataka, H. *J. Am. Chem. Soc.* **1984**, *106*, 2084–2088.

(14) Corresponds to ^{12}C/^{13}C KIE = 1.062 and ^{12}C/^{14}C KIE = 1.122. See ref 11c and references cited therein.

(15) A TS which is symmetric in the sense of force constants may be early or late in terms of bond order for the forming and breaking bonds, depending on the type of atoms to which the central atom forms and breaks bonds.

(16) Reference 3, p 29.

(17) (a) Yamataka, H.; Ando, T. *J. Am. Chem. Soc.* **1979**, *101*, 266–267. (b) Yamataka, H.; Ando, T. *Tetrahedron Lett.* **1975**, 1059–1062.

(18) Reference 3, p 239ff.

(19) Reference 3, p 152.

rium KIE of 24.8 reported by Lewis and Funderburk for proton transfer to 2,4,6-trimethylpyridine.[20] For the transfer of a heavy atom as in the present case, tunneling is less likely to play a significant role. However, Saunders has pointed out that the tunnel effect cannot be overlooked when interpreting heavy atom KIEs for cases where the motion of an isotopic carbon atom is strongly coupled to hydrogen motion along the reaction coordinate in the TS.[21] Such coupling of carbon and hydrogen atom motion is a feature of the S_N2 transition state, and thus, a variation of the tunneling contribution to the carbon KIE cannot be totally ruled out as an explanation for the small increase in carbon KIE observed for the sterically more hindered 2,6-lutidine.

Primary carbon KIEs for the reactions of labeled methyl iodide with 3,5-substituted pyridines have previously been reported by Yamataka and co-workers.[22] In agreement with our present observations, they found the ^{13}C KIEs to be very high and rather constant for a wide reactivity range.

Leaving group KIEs for this type of reaction have been studied by Le Noble and Miller[6] (pyridine and 2,6-lutidine reacting with MeCl in bromobenzene at 100 °C) and by Swain and Hershey[5] (quinuclidine and triethylamine reacting with MeCl in 1,2-dimethoxyethane at 25 °C). The results of these workers were apparently contradictory. Le Noble and Miller found that the more sterically hindered nucleophile 2,6-lutidine yielded the higher leaving group chlorine KIE ($k^{35}/k^{37} = 1.003\,84 \pm 0.000\,26$) as compared to that of pyridine ($k^{35}/k^{37} = 1.003\,55 \pm 0.000\,08$). This result was interpreted in terms of a sterically more crowded situation yielding a later TS. However, the electronic effect of the methyl groups in lutidine, i.e. reactivity-enhancing, is likely to change the KIE in the same direction as is demonstrated by the significantly higher chlorine KIEs for the reactions of quinuclidine (Q) and triethylamine (TEA). Swain and Hershey's results for the comparison of the Q/TEA pair reacting with MeCl show a stronger leaving group KIE (later TS) for the less hindered, more reactive, nucleophile Q ($k^{35}/k^{37} = 1.007\,09 \pm 0.000\,11$) than for TEA ($k^{35}/k^{37} = 1.006\,40 \pm 0.000\,09$). In this case, approximately half of the difference in activation energy between the rigid quinuclidine and flexible triethylamine molecules has been ascribed to the difference in activation entropy.[4] The leaving group KIEs observed are significantly higher for TEA/Q (approximately 7%) than for the pyridines (approximately 4%). This fact is in part due to the temperature dependence of the KIE. The temperature dependence of a leaving group chlorine KIE has been investigated for the S_N2 reaction between n-butyl chloride and thiophenoxide in methanol (temperature range: 0−60 °C),[23] and the KIE was found to decrease by almost 20% with increasing temperature in this interval. Applying the same temperature dependence as a correction increases the chlorine KIEs for the pyridines to ca. 6% at 25 °C. The leaving group KIEs are all lower than estimated for a half-broken C−Cl bond, indicating early transition states.

Kurz et al.[24] determined the nitrogen KIEs for methyl transfer reactions from methyl halides and other substrates to a number of amines including 2,6-lutidine and quinuclidine in aqueous solution or acetonitrile at 25 °C. This is a rare example of the measurement of an incoming group KIE.[25] This KIE is expected to decrease (be more inverse) with increasing N−C bond formation in the TS. It was found that the nitrogen KIE was almost constant and very close to unity (0.995−0.998).[26] It was concluded that the N−C bond order is close to 0.2−0.3 for methyl transfers to the pyridines.

The secondary α-deuterium KIE probe was applied to Menshutkin reactions by Harris et al.[27] who determined the α-D KIEs for the reactions of 3,5-substituted pyridines with methyl iodide in 2-nitropropane at 25 °C. They observed increasingly inverse values for five substrates of decreasing reactivity, i.e. tighter transition states for slower-reacting compounds. It was concluded that the transition states were positioned early along the reaction coordinate with little N−C bond formation and little C−I bond breaking. This conclusion is consistent with the incoming group N KIEs determined by Kurz and co-workers.[23]

The combined evidence from incoming and leaving group KIEs for the reactions of the substituted pyridines thus seems to demonstrate a modest structural variation of the TS as the steric demand of the nucleophile changes. Steric hindrance as modeled by dimethyl substitution in the 2- and 6-positions to the nucleophilic nitrogen increases the C−X bond distance as reflected in the larger leaving group chlorine KIE. Thus, the sterically more hindered nucleophile has a slightly looser TS which should be expected to yield a larger primary central carbon KIE. This is also what we observe experimentally (Table 1).

In a computational study using semiempirical quantum chemical methods, the steric effects in the Menshutkin reaction between 2-alkylpyridines and methyl halides were examined.[28] Increasing the steric strain in the 2-position (methyl to *tert*-butyl or 2,6-dimethyl) led to looser transition states, whereas substitution with electron-withdrawing groups in the 4-position had very little effect on the TS structure. Although these calculations refer to gas-phase reactions with a substantially later TS, we see no reason why the responses to a steric perturbation should be qualitatively different for reactions in solution.

The interpretation of the collected KIE data for Q/TEA is less straightforward. An electronic effect as mirrored by the higher pK_a of both these substrates as compared to those of the lutidines is reflected by their higher leaving group KIEs.[5] The primary carbon KIEs are, within error limits, the same for Q and TEA (1.210) and somewhat larger than for 2,4-lutidine (1.189). Thus, the

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[20] Lewis, E. S.; Funderburk, L. H. *J. Am. Chem. Soc.* **1967**, *89*, 2322.

[21] See: Wilson, J. C.; Källsson, I.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 4780.

[22] Ando, T.; Kimura, T.; Yamataka, H. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987; Chapter 7.

[23] Turnquist, C. R.; Taylor, J. W.; Grimsrud, E. P.; Williams, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 4133.

[24] Kurz, J. L.; Daniels, M. W.; Cook, K. S.; Nasr, M. M. *J. Phys. Chem.* **1986**, 90, 5357.

[25] For other examples of incoming group KIEs in S_N2 reactions, see: (a) Lynn, K. R.; Yankwich, P. E. *J. Am. Chem. Soc.* **1961**, *83*, 53;.(b) Ando, T.; Yamataka, H.; Wada, E. *Isr. J. Chem.* **1985**, *26*, 354. (c) Paneth, P.; O'Leary, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 1691. (d) Westaway, K. C.; Fang, Y. R.; Jobe, D.; Matsson, O.; Persson, J.; Axelsson, S. *Abstracts from IUPAC 12th Conference on Physical Organic Chemistry*; Padova, Aug. 28−Sept. 2, 1994; p 223.

[26] Earlier published data and conclusions were withdrawn in ref 24.

[27] Harris, J. M.; Paley, M. S.; Prasthofer, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 5915.

[28] Berg, U.; Chanon, M.; Gallo, R.; Rajzmann, M. *J. Org. Chem.* **1995**, *60*, 1975.

variation in TS structure suggested on the basis of the reported difference in leaving group chlorine KIE between Q and TEA[5] is not supported by any corresponding difference in the primary central carbon KIE. However, the larger carbon KIEs for Q/TEA as compared with those of 2,4-lutidine are consistent with the corresponding larger leaving group KIEs.

Conclusion

The variation of the carbon KIE is very small, indicating an almost constant TS structure, consistent with the nearly constant incoming group nitrogen KIEs reported by Kurz et al. The highest carbon KIE is observed for 2,6-lutidine, which is the most sterically hindered nucleophile used, supporting the idea of a looser TS in this case. There is no corresponding indication of a looser TS for TEA as compared with Q. Safer conclusions may be drawn when a more systematic study of the KIEs for different positions in the reacting system has been performed. Theoretical calculations of the KIEs may also prove helpful in assigning TS structures, and such calculations are in progress.

Experimental Section

General. A proportional regulating thermostat (HETO) with an accuracy of ±0.005 °C was used. The temperature never deviated more than ±0.05 °C during a kinetic run. HPLC analyses were performed using a Hewlett-Packard 1084 HPLC instrument equipped with a fraction collector (Hewlett-Packard 79825 A) slightly modified by removing the Teflon insert. The HPLC instrument was equipped with a UV detector in series with a β^+-flow detector. All HPLC analyses were performed using a column (200 × 4.6 mm) packed with Nucleosil C-18 (10 μm). The mobile phase was 0.05 M ammonium formate: pH 3.5 and methanol, 50/50 (v/v); isocratic flow, 2.00 mL/min. The ammonium formate buffer contained 0.03 M tetramethylammonium hydrogen sulfate, acting as an amine modifier. The injection volume was 5−10 μL depending on the amount of radioactivity present. The wavelength used was 254 nm, using 430 nm as a reference.

Materials. The pyridines were purified according to literature procedures.[29] The purity (>99%) was checked using GC. Quinuclidine was sublimed several times under reduced pressure and kept in the freezer under a nitrogen atmosphere.

Dimethoxyethane (DME), acetonitrile, and tetrahydrofuran (THF) were purified according to literature procedures and kept over 3 Å molecular sieves under a nitrogen atmosphere.

[^{14}C]Methyl iodide was purchased from Amersham, 1.85 MBq and 2.0 GBq mmol^{-1}, and at delivery was 99% pure. The [^{14}C]methyl iodide was distilled according to literature procedures[11] and trapped in a vial containing 1 mL of dry acetonitrile. The solution was kept in a capped flask in a desiccator over Drierite in the freezer.

The ^{11}C was obtained as [^{11}C]carbon dioxide at the PET center at Uppsala University. [^{11}C]Methyl iodide was synthesised using [^{11}C]carbon dioxide according to a three-step route previously reported.[30] The produced [^{11}C]methyl iodide was distilled and trapped in a 2 mL vial containing 1 mL of DME or acetonitrile.

Kinetic Procedure. Solutions containing the different amines in DME or acetonitrile, with concentrations between 0.25 and 1.0 M, were prepared and thermostatted prior to the synthesis of the [^{11}C]methyl iodide. Approximately 5 μL of the [^{14}C]methyl iodide solution was transferred to the [^{11}C]methyl iodide solution and was thermostatted. Approximately 500 μL of the solution was transferred to the capped reaction vial containing 1 mL of the amine solution at the same time the reaction clock was started. Samples of the reaction solution were quenched at different times. The quenching procedure was performed by direct injection of the reaction solution into the HPLC, recording the reaction time at the moment of injection. The labeled reactant (methyl iodide) and product (quatenary amine) were separated on the HPLC column and collected in scintillation bottles containing 16 mL of scintillation liquid. The ^{11}C radioactivity combined with the ^{14}C radioactivity of the samples was measured immediatley, measuring the fraction of least radioactivity first. The ^{14}C radioactivity was measured after complete decay of the ^{11}C, usually the next day.

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