JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 9, 35–40 (1996)

NITROGEN AND DEUTERIUM KINETIC ISOTOPE EFFECTS ON THE MENSHUTKIN REACTION

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Nitrogen and deuterium kinetic isotope effects were measured in the Menshutkin reaction between methyl iodide and a series of *para*-substituted *N,N*-dimethylanilines in ethanol. The nitrogen kinetic isotope effect increases for the more electron-donating substituents [0·9989, 1·0032, and 1·0036 for 4-C(O)Me, H and 4-Me, respectively], in agreement with the Hammond postulate. The secondary deuterium isotope effect, however, exhibits the reverse trend (1·045, 0·989, 0·975 per deuterium, for the respective substituents). This discrepancy is rationalized in terms of solvent molecule participation in the transition state.

INTRODUCTION

All types of structure–reactivity relationships aim at *a priori* predictions of properties for systems not yet explored based on information available for systems already studied. Achieving this goal would be rewarding not only from the purely scientific point of view in terms of improving our knowledge, but also from the practical point of view, for example in drug design. It is thus not surprising that a lot of experimental and theoretical work is being devoted to this field.[1] Since such studies directly or indirectly address the question of transition-state geometry and how it changes as a function of substituents, a logical extension of these studies is an attempt to find similar correlations for isotope effects, which most directly of all kinetic methods address the question of transition-state structures.

The Menshutkin reaction[2] is one of the best targets of such studies for several reasons. First, its mechanism is well established, a condition necessary for a good model. Second, a wealth of data on solvents effects,[3] substituent effects[4] and isotope effects[5] for many kinds of these reactions is readily available in the literature. Third, theoretical calculations on this class of reactions have been performed.[1c,6]

Heavy atom kinetic isotope effects have usually been studied with the isotopic label placed in a leaving group. Both of the factors which determine the magnitude of an isotope effect, the temperature-independent factor (TIF) and the temperature-dependent factor (TDF), are then larger than unity,[7] yielding normal isotope effects. In contrast, when the isotopic label is contained in the incoming group, the temperature-dependent factor becomes inverse and the magnitude of the kinetic isotope effect depends on the relative sizes of TIF and TDF. Although these effects could be very informative, they are usually small and thus difficult to measure. Nitrogen atoms are frequently nucleophilic centers in chemical and biochemical processes. Hence understanding incoming group nitrogen kinetic isotope effects is most desirable. That the problem is not straightforward

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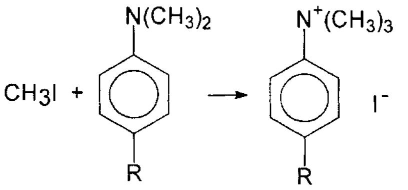
CCC 0894–3230/96/010035–06

Received 28 July 1995
Revised 22 September 1995

is illustrated by the postulated anti-Hammond dependence of nitrogen isotope effects on quaternization of substituted pyridines,[8] which was not confirmed on re-examination.[9]

In this work, we studied nitrogen and deuterium kinetic isotope effects on the quaternization of *para*-substituted *N,N*-dimethylanilines equation (1):



(1)

with the hope that high-precision measurements of nitrogen isotope effects can reveal the actual dependence on the substituent electronic properties. The kinetics of this reaction have been extensively studied.[1c] The reaction is a single-step S_N2 reaction, first order in each reactant. Several kinetic isotope effects have already been reported[10–14] for these reactions. Hence this reaction can serve as a good model system for theoretical calculations of kinetic isotope effects. The outcome of these calculations is described in the accompanying paper.

EXPERIMENTAL

Materials. N,N-Dimethyl-*p*-toluidine (99%; Aldrich, Milwaukee, WI, USA) and *N,N*-dimethyl-*p*-aniline (99·5%; Aldrich) were used without further purification. Ethyl alcohol (Aldrich), iodomethane-d_3 (99·8%; VEB Berlin Chemie, Berlin, Germany), and iodomethane (99·5%; POCh, Gliwice, Poland) were purified using standard procedures.

N,N-Dimethylamino-*p*-acetophenone was obtained by methylation of *p*-aminoacetophenone with dimethyl sulfate by modification of the method of Sekiya *et al.*[15] A solution mixture containing 12 g of amine, 28 g of sodium hydrogencarbonate and 24 ml of dimethyl sulfate in 42 ml of water was heated to 50 °C, after which saturated KOH solution was added to hydrolyze unreacted dimethyl sulfate and the mixture was poured into 300 ml of cold water. The precipitate of ternary amine formed by the above treatment was washed a few times with water, then with heptane, dissolved in chloroform and dried with magnesium sulfate. Subsequently chloroform was removed and the ternary amine was dissolved in hot heptane under reflux and filtered through a hot Shott funnel. After cooling, the crystallized amine was filtered, washed a few times with heptane and dried in a desiccator.

Isotope effects. Both kinetic isotope effects were determined from the difference in isotopic composition of product at low and full conversion levels using dead-end kinetic conditions. In the case of the nitrogen isotope effect, the low-conversion samples were processed using a tenfold excess of amine (0·05M) over iodomethane at 25 °C, so that only 10% of the amine reacted while the entire amount of iodomethane was exhausted. After removal of the solvent, the mixture of the amine and its salt was dissolved in chloroform and separated by passage through a silica gel column. Salt samples obtained in this way were subsequently subjected to mass spectrometric analysis. Full-conversion samples were processed under pseudo-first-order conditions with respect to amine by using a tenfold excess of iodomethane. After the completion of reaction (tested by TLC), the excess of iodomethane and ethanol was evaporated under reduced pressure, yielding crude salt samples. These were used directly for isotopic analysis or recrystallized. No difference in isotopic composition was detected for crude and crystallized samples.

The salt samples obtained in the above way were combusted and the isotopic composition of nitrogen was measured. About 10 mg of sample were required per measurement. Isotope ratio measurements were done using a Finnigan Delta S isotope-ratio mass spectrometer combined on-line with a Hereaus elemental analyzer. The natural isotopic composition of nitrogen was used as a standard.[13]

The experimental conditions in the case of deuterium isotope effects were identical with those described above. Since iodomethane in these experiments is the isotopic species, the reverse ratios were used. A tenfold excess of iodomethane over the amine was used to generate the low-conversion samples, while a tenfold excess of amine led to full-conversion samples.

In the case of the acetophenone derivative, the nitrogen isotope effect for the reaction with deuterated iodomethane was also determined. In these experiments, the samples prepared for deuterium isotopic analysis were used also for the nitrogen isotope analysis as described above. However, the samples which constituted the low-conversion batch for the deuterium isotope effect were regarded as full-conversion samples for the nitrogen isotope effect calculations, and vice versa.

The isotopic ratios of deuterated material were measured using an MI 1201E hybrid FAB–isotope ratio mass spectrometer (PO Electron, Ukraine). Samples of about 1mg were dissolved in thioglycerol (about 15µl) and 1–2 µl of this solution was placed on the copper tip of the direct insertion probe. Xenon atoms of 5 kV hitting the surface of the probe at an incidence angle of 45 were used for ionization. The positive ions formed in this way were accelerated to a potential 5kV and detected in Faraday cup collector system. The mean value of the (M + 3)/M isotopic ratio was obtained from up to 50 separate determinations, each being an average of 10 individual measurements. The total ion current under the above-mentioned conditions was stable for 0·5–2h, allowing a precision of ±0·03–0·07%.

The kinetic isotope effects were calculated from the equation[7]

$$k_L/k_H = \frac{\ln(1-f)}{\ln(1-fR_f/R_\infty)} \tag{2}$$

where the Rs are isotopic ratios. Isotopic ratios for deuterium were measured directly as described above. For calculations of nitrogen isotope effects, the above equation was modified by using the equivalence between isotopic ratios and measured δ values:

$$R_f/R_\infty = (1000+\delta_f)/(1000+\delta_\infty) \tag{3}$$

where δ_f and δ_∞ are relative isotopic compositions of product at fraction of reaction f and at full conversion, respectively. The δ values are relative isotopic ratios, defined as $\delta_i = (R_i/R_{st} - 1)1000$, for product after fraction of reaction f ($i = f$) and full conversion ($i = \infty$). The value depends on the isotopic composition of the standard used in the mass spectrometric measurements, but this value drops out in the final calculation of the isotope effect.

RESULTS AND DISCUSSION

In recent years, only a few attempts to use incoming group nitrogen isotope effects as an indicator of transition-state structure have been reported, and no general conclusion has been reached.[8,9,13,16,17] This is because these effects are primary in nature but exhibit small values, characteristic of secondary isotope effects due to the cancellation of factors governing the magnitude of kinetic isotope effects. Measuring such small isotope effects is no longer experimentally demanding but their interpretation is still a challenge. Since nitrogen atoms play an important role in many biological processes, a thorough understanding of nitrogen isotope effects on model reactions has become a necessity in the analysis of complex biochemical and enzymatic processes.

In this paper, we report measurements of nitrogen and deuterium kinetic isotope effects on a series of *para*-substituted *N*,*N*-dimethylanilines. The measured nitrogen and deuterium kinetic isotope effects are shown in Table 1.

Table 1. Experimental values of kinetic nitrogen and deuterium isotope effects for the reaction between methyl iodide and *para*-substituted *N*,*N*-dimethylanilines at 25°C

Substituent	k_{14}/k_{15}	k_{CH_3I}/k_{CD_3I}	k_H/k_D[a]
4-Me	1·0036 ± 0·0003	0·927 ± 0·004	0·975 ± 0·001
H	1·0032 ± 0·0002	0·968 ± 0·004	0·989 ± 0·001
4-C(O)Me	0·9989 ± 0·0003 0·9985 ± 0·0002[b]	1·143 ± 0·003	1·045 ± 0·001

[a] Recalculated per hydrogen.

[b] Nitrogen isotope effect for the reaction with iodomethane-d_3.

The nitrogen kinetic isotope effect obtained in this work for the toluidine derivative in ethanol is within the experimental error of the value reported previously for a methanolic solution.[13] The discrepancy between the previously reported deuterium kinetic isotope effect for the toluidine derivative and that measured in this work requires further analysis. Owing to the large errors, we have previously failed to recognize the dependence of isotope effects on the reaction progress as illustrated in Figure 1. We assume that this dependence originates from methyl group exchange between the reactants and the solvent methanol under previous experimental conditions, although no experimental evidence for this exchange was detected. Such an exchange depletes the deuterium contents of the product artificially, increasing the observed isotope effect. Extrapolation of the dependence presented in Figure 1, obtained from the previously reported results, leads to a value of the deuterium kinetic isotope effect of well over 0·9. This is in agreement with the value reported here (Table 1). The present studies carried out in ethanol with an excess of amine prevent any isotopic washout.

Unlike the earlier calculated isotope effects of deuterium (and carbon) in similar quaternization,[6a] a bell-shaped dependence of isotope effects is not observed. Instead, on crossing over (changing values from smaller than unity to larger than unity, see Figure 2), a phenomenon already reported[51] is observed.

The nitrogen isotope effects of ±0·2% obtained experimentally for all substituents are very small for primary isotope effects. This result is not surprising, as we expect a cancellation between temperature-independent (TIF) and temperature-dependent factors (TDF) for processes in which bonding to the isotopic atom is increased. A similar magnitude of the nitrogen isotope effect has been reported for the quaternization of substituted pyridines.[8,16] The invariance of the nitrogen isotope effect with regard to isotopic composition of iodomethane, demonstrated for the 4-C(O)Me substituent, supports a single-step mechanism. The observed dependence of the nitrogen isotope effect on the electronic properties of the *para*-substituent is less pronounced than that of deuterium isotope effects, but evidently it is in the direction of the Hammond postulate,[18] contrary to what was observed earlier.[8]

A change from methanol to ethanol decreases the dielectric constant from 32·7 to 24·6, which should cause the transition state to become more reactant-like, and consequently decrease the nitrogen isotope effect. The opposite is observed; k_{14}/k_{15} increases from 1·0019 measured for methanolic solution[13] to 1·0036 for

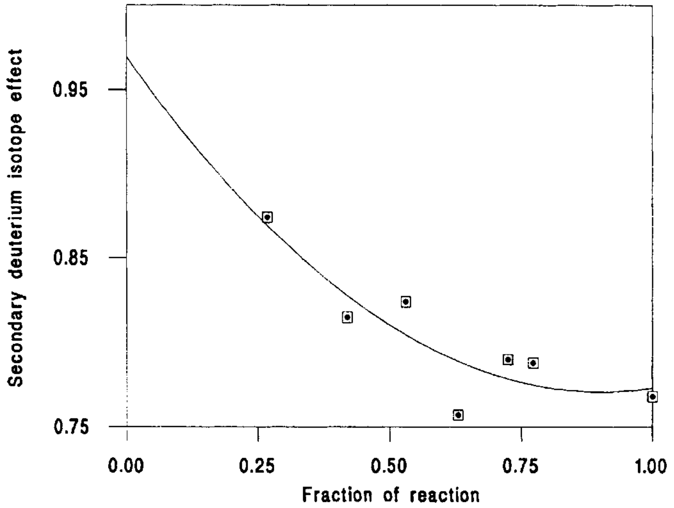
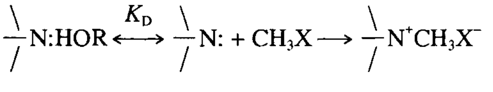


Figure 1. Dependence of individual measurements of deuterium isotope effects for the 4-methyl derivative in methanol on the reaction progress

ethanol. However, reactivity correlations for the Menshutkin reaction are frequently irregular when rate constants in protic solvents, such as alcohols, are compared.[19]

The case studied here is unique in that whereas the nitrogen isotope effects obey the Hammond postulate, the deuterium isotope effects do not. If only the typical interpretation of the transition state as being 'earlier' (more 'reactant-like,' therefore 'looser'*) for the faster reaction is invoked, then it is easy to justify the direction of changes of the nitrogen isotope effects. The TDF is less important for the looser transition state (it is closer to unity since its transition-state component is smaller). The TIF is, therefore, more expressed in the overall isotope effect. The secondary deuterium isotope effects are believed to represent crowdedness around the central atom in the transition state. Hence for the looser transition state they should be less inverse (or normal) than for the 'late' transition states, opposite to the observed sequence.

Among possible explanations of this strange behavior, we favor the one that takes into account explicit interaction with solvent molecules. It has been pointed out[1b] that solvation can modify observed structure–reactivity parameters, preventing them from reflecting the bonding changes within a transition state. The more basic the amine, the stronger is the interaction with a solvent molecule. This can lead to a two-step mechanism of the type shown in equation (4).



$$\rangle\mathrm{N{:}HOR} \xleftrightarrow{K_D} \rangle\mathrm{N{:}} + \mathrm{CH_3X} \longrightarrow \rangle\mathrm{N^+CH_3X^-} \qquad (4)$$

where HOR is the solvent molecule.

The nitrogen isotope effect on the first step of the mechanism in equation (4) should be larger than unity since a bond to nitrogen is being broken (the hydrogen bond between the amine and a solvent molecule). Hence the overall nitrogen kinetic isotope effect should increase for the amine, which reacts faster, strengthening the Hammond behavior of the nitrogen isotope effects. Furthermore, the first step in reaction (4) should be insensitive to deuteration of the methyl group, thus bringing the observed deuterium isotope effects closer to unity for the amines with electron-donating substituents.

However, the mechanism proposed above should lead to a considerable solvent isotope effect, especially for the amine which reacts fastest (4-Me). This is not observed experimentally.[13] A reasonable mechanistic compromise is a single-step mechanism in which a solvent molecule is included in the transition-state structure. Its presence enlarges the Hammond-type response of nitrogen isotope effects to the change of the *para*-substituent. It also causes enough steric hindrance to reverse the response of deuterium isotope effects, and

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*This qualitative terminology needs to be used with care, since it is frequently misleading. For example, an earlier transition state was sometimes referred to as tighter than a 'symmetric' one.[5a] Asynchronicity of bond-breaking and bond-making events may be a cause of such confusion.

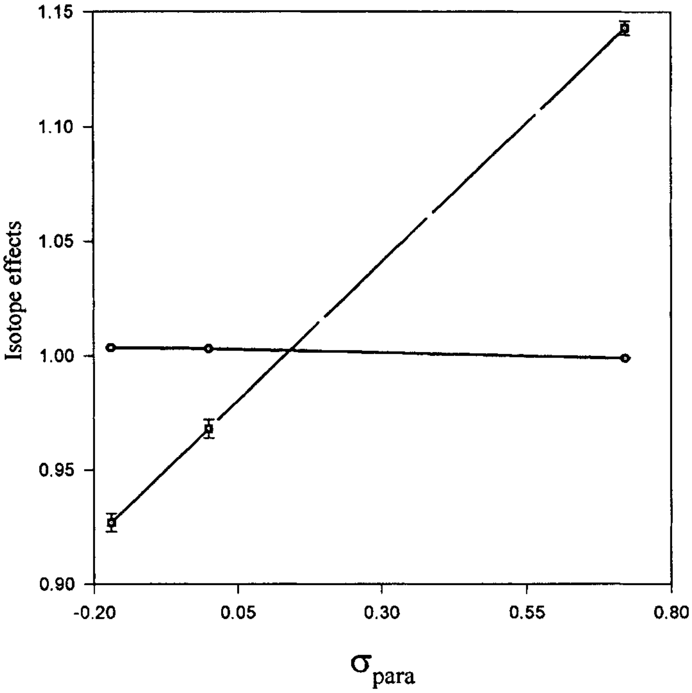

Figure 2. Kinetic isotope effects of nitrogen and deuterium on the Menshutkin reaction (1) as a function of electron-donating properties of *para*-substituents. Squares correspond to deuterium and circles to nitrogen isotope effects

yet may be loose enough not to produce any sizable solvent isotope effect.

ACKNOWLEDGMENTS

We thank Professors Olle Matsson and Ulf Berg for making their results available to us prior to publication. This project was supported by grants from KBN 458/P3/92 (P.P.) and NIH GM43043 (M.H.O'L.).

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