

KINETIC ISOTOPE EFFECTS ON THE MENSCHUTKIN REACTION: THEORY VERSUS EXPERIMENT

E. GAWLITA, A. SZYLHABEL-GODALA AND P. PANETH*

Institute of Applied Radiation Chemistry, Technical University of Łódź, Żeromskiego 116, 90-924 Łódź, Poland

Nitrogen, carbon and secondary deuterium kinetic isotope effects were calculated for the Menschutkin reaction between methyl iodide and *para*-substituted aromatic *N,N*-dimethylamines using quantum mechanical methods. Different semiempirical Hamiltonians and continuum solvent models were evaluated on the basis of comparison between the experimental and theoretical values of these isotope effects.

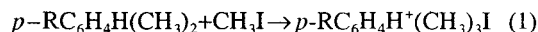
INTRODUCTION

Kinetic isotope effects are unique kinetic tools since their magnitude is directly related to the structure of the corresponding transition state,¹ an entity which still evades direct analysis. Only recently has transition-state spectroscopy² become available but it will take some time before this method will reach the level of a routine kinetic technique.

In a typical procedure, one measures an isotope effect and compares it with values predicted theoretically for different pathways.³ Isotope effects are generally small and for many years the only safe statement which could be made was whether an isotope effect was primary or secondary. Since the experimental values had large errors, the predictions also might not be very accurate. Hence simple models were usually used in calculations with force fields being introduced parametrically.⁴ Regardless of the crudeness of this approach, a skilful chemist could make reasonable predictions about a transition state,⁵ typically categorized as 'early' (reactant-like), 'symmetrical' or 'late' (product-like).

Nowadays, methods for the measurement of isotope effects have evolved to a point where interpretation is limited mainly by the precision of calculations, leading to a need for improvements in this field. Fortunately, this need was paralleled by the advent of new methods in theoretical chemistry combined with the substantial increases in the power of computers. Modern SCF-MO calculations can produce unbiased force fields and geometries for both reactants and transition-states and should prove useful in calculations of kinetic isotope effects.⁶

The aim of the studies presented here was to calculate the nitrogen, carbon and deuterium kinetic isotope effects on the Menschutkin reaction⁷ (1):



(R=H, Me, or C(O)Me), and to make a comparison with experimental values in order to estimate the applicability of the available Hamiltonians and models of solvents to theoretical calculations of kinetic isotope effects. The choice of the reaction was dictated by several factors. It is mechanistically a very simple S_N2 reaction and a number of high-level theoretical studies on these reactions have been published.⁸ Second, these reactions are considered as models for studies of solvation effects and a wealth of experimental data is also available in the literature.⁹ In particular, studies on isotope effects¹⁰ of the reaction in equation (1) have been published, yielding a set of data which can be used for comparison with results of calculations. Also, the choice of isotope effects for calculations is not coincidental; central atom carbon isotope effects are well understood and well documented, giving a good basis for comparisons. Nitrogen isotope effects for similar processes, on the other hand, although also well documented, are not well understood. These are isotope effects of an incoming group, where factors influencing the magnitude of kinetic isotope effects;¹¹ the temperature-independent factor (TIF), connected with the mass difference of isotopic species, and the temperature-dependent factor (TDF), representing changes in bonding around the isotopic atom, partially cancel. The extent of this cancellation is not easily predictable, making calculations of these effects especially important. Finally, secondary deuterium isotope effects have frequently been measured but the interpretation of their origin remains debatable.

*Author for correspondence.

The small size of the incoming group nitrogen isotope effects leads to misinterpretations of their behavior. For example, an anti-Hammett correlation with the substituent constants was once postulated for quaternization of pyridines but was later proved unjustified.¹² It was therefore most desirable to have a theoretical evaluation of such correlations and to find factors responsible for the predicted behavior.

The crucial point in calculations of isotope effects is obtaining unbiased force fields for ground and transition states. Within the quantum chemistry framework, this may be achieved at the *ab initio* or semiempirical level. For *ab initio* calculations, even a reaction as simple as that depicted in equation (1) is still prohibitively time consuming. Semiempirical calculations, on the other hand, can be performed on this system within a reasonable time limit on available computers, so this level of theoretical scrutiny was used throughout this work.

THEORETICAL CALCULATIONS

The programs AMPAC version 5¹³ with the SM2 solvation model¹⁴ (compiled to a DEC 3000/300X computer), Sibiq version 1.0.5 (for a PC platform),¹⁵ MOPAC version 6¹⁶ with the SCRF2 solvation model¹⁷ and MOPAC93 with the COSMO solvation model¹⁸ (compiled to an HP 9000/735 computer) were used throughout. Our own program ISOEFF version 6* was used in calculations of isotope effects.

SCF-MO calculations were performed at the semiempirical level. These calculations included geometry optimization for reactants and products, followed by the transition-state location and subsequent force field analysis and calculations of isotope effects.

The first three goals were achieved by using AM1,¹⁹ PM3²⁰ and, in one case, MNDO²¹ Hamiltonians and eigenvector follow (EF) optimizer at the highest precision level. Four different continuum solvent models were tested. Transition-state structures were located by a combination of NLLSQ, Sigma, TS optimizers and DRC/IRC routines on the basis of previously optimized geometries of reactants and products. Force field calculations were then performed for appropriate isotopomers of reactants and the transition state. Isotopic frequencies of normal vibrations of reactants and transition state, obtained from the theoretical calculations, were used with the Bigeleisen^{11a} equation (2) to calculate kinetic isotope effects. Only

isotopic frequencies larger than 30 cm⁻¹ were included in the calculations.

Minimal information necessary to calculate a kinetic isotope effect consists of two sets of normal modes of vibrations related to the isotope effect by the following equation:^{11a}

$$\frac{k_L}{k_H} = \frac{\nu_L^*}{\nu_H^*} \times \prod_i^{3n^P-6} \frac{u_{iL}^R \sinh(u_{iH}^R/2)}{u_{iH}^R \sinh(u_{iL}^R/2)} \times \prod_i^{3n^* - 7} \frac{u_{iH}^* \sinh(u_{iL}^*/2)}{u_{iL}^* \sinh(u_{iH}^*/2)} \quad (2)$$

where k_L/k_H is the kinetic isotope effect, n are the numbers of atoms in the substrate or transition state, $u = hv/kT$, where h and k are Planck and Boltzmann constants, respectively, T is the absolute temperature, ν_i are the frequencies of normal vibrations, subscripts L and H correspond to light or heavy species, respectively, and superscripts R and † indicate the properties of reactant or transition state, respectively. All data necessary to calculate the isotope effect are available from semiempirical calculations and were extracted from the appropriate output files. The isotope effects were calculated at temperature of 298K. Since there are three indistinguishable deuterium atoms per molecule of methyl iodide, these isotope effects were calculated for triply substituted reactant (which corresponds to the experimental conditions).

RESULTS

Results obtained with combinations of different Hamiltonians and solvent models are summarized in Table 1 and compared with experimental values.

Previously reported experimental data^{10b} were obtained in methanol ($\epsilon=32.7$) while measurements described in the accompanying paper^{10f} were carried out in ethanol ($\epsilon=24.6$). The comparison of our calculations for the toluidine derivative (*p*-CH₃) in these two solvents using the combination of the AM1 Hamiltonian with the COSMO solvent model revealed that such a change in the apparent dielectric constant does not perturb the calculated geometries, force fields and isotope effects. Therefore, we restricted our calculations to one value of dielectric constant, corresponding to methanol.

Isotope effects can be calculated by comparing the force field of the transition state with individual reactants or optimized geometry of their electrostatic complex. With the example of AM1/SCRF calculations for *N,N*-dimethylaniline, we demonstrated that this choice does not influence the value of the final isotope effect. The corresponding equilibrium isotope effects (between free reactants and the complex) were equal to unity and only minimal stabilization of this complex

*The ISOEFF version 6.0 program can be obtained on request from ppaneth1@pleam.edu.pl. This program, written in FORTRAN, extracts all data necessary for calculations of isotope effects from outputs of quantum chemistry packages. MOPAC/AMPAC, AMSOL, SIBIQ, GAMESS and GAUSSIAN formats are currently supported.

Table 1. Calculated and experimental nitrogen (of amine), carbon and deuterium (of methyl iodide) kinetic isotope effects for the Menshutkin reaction

Method	Me			H			C(O)Me		
	k_{12}/k_{13}	$k_{\text{CH}_3\text{I}}/k_{\text{CD}_3\text{I}}$	k_{14}/k_{15}	k_{12}/k_{13}	$k_{\text{CH}_3\text{I}}/k_{\text{CD}_3\text{I}}$	k_{14}/k_{15}	k_{12}/k_{13}	$k_{\text{CH}_3\text{I}}/k_{\text{CD}_3\text{I}}$	k_{14}/k_{15}
PM3 COSMO	1.0661	1.073	1.0026	1.0697	1.124	1.0034	1.075	1.084	1.0019
PM3 SCRF	1.0704	1.108	1.0015	1.0705	1.107	1.0016	1.075	1.135	1.0018
MNDO COSMO							1.064	0.644	1.0009
AMI SM2							1.052	0.800	0.9995
AMI COSMO	1.0552	0.800	1.0008	1.0555	0.818	1.0002	1.058	0.768	0.9994
AMI SCRF	1.0563	0.891	0.9947	1.0552	0.892	0.9955	1.055	0.942	0.9972
Experiment	1.0655 ± 0.0024^a	0.927 ± 0.004^c	1.0036 ± 0.0003^c	1.0615 ± 0.0021^b	0.968 ± 0.004	1.0032 ± 0.0002	—	1.143 ± 0.003^c	0.9989 ± 0.0003^c
	1.060 ± 0.023^b	0.83 ± 0.04^d	1.0019 ± 0.0001^d						

^aRefs 10c, d.^bRef. 10a.^cAccompanying paper.^{10f}^dRef. 10b.^eRef. 10e.

over free reactants of $0.5 \text{ kcal mol}^{-1}$ ($1 \text{ kcal}=4.184 \text{ kJ}$) was found.

DISCUSSION

Two aspects of our calculations seem to be of predominant importance. The first is determining which solvation model can be effectively used in the modeling of kinetic isotope effects, and the other is the structure of the transition state of the studied reaction.

We have reported earlier our attempt to calculate the transition-state properties for the toluidine derivative.^{10b} However, since these calculations were carried out in the gas phase, we failed to locate the transition state and therefore we had resorted to only partially optimized geometries at fixed N–C and C–I bond orders. Bond orders were chosen arbitrarily in two ways: preserving total bonding to the central carbon atom $\sum n = n_{\text{N-C}} + n_{\text{C-I}} = 1$ in the so-called tight transition state, or keeping this sum at 0.6 as in the loose or exploded transition state.

In the present studies, the use of continuous solvation models permitted optimization of the transition-state structures without any geometrical constraints. We compared two solvation models which allow one to change the macroscopic dielectric constant of the solvent. These were the self-consistent reaction field (SCRf) and conductor-like screening model (COSMO). A few calculations were carried out using two other solvation models: solvation model (SM2.1 and SM3) and Langevin dipole model²² (LD). The first of these, however, is parametrized to reproduce properties of aqueous solutions only and therefore could not be directly applied to studies of reactions in methanol or ethanol. Furthermore, we failed to achieve convergence of the transition-state geometry using the PM3–SM3 combination. The Langevin dipole model yielded a nitrogen isotope effect of 0.9754, so remote from the experimental value that we discontinued its usage. A similarly inaccurate nitrogen isotope effect of 0.9846 was obtained using the AM1 Hamiltonian in combination with COSMO solvent model for the *p*-CF₃ substituent. We therefore excluded this substituent from both experimental and theoretical considerations, introducing in its place the *p*-C(O)CH₃ moiety.

Our main criterion for the evaluation of theoretical models here is the agreement between predicted and observed values of isotope effects. We thus only note that although all Hamiltonians correctly predicted the direction of changes of activation energy for the considered series of *para*-substituents, the PM3 Hamiltonian proved superior to the AM1 and MNDO Hamiltonians with regard to the absolute value of these barriers. Compared with calculations in the gas phase, the SM2 model correctly predicts a significant lowering in the activation barrier whereas the SCRf method yields only a negligible lowering.

The comparison of calculated isotope effects with those obtained experimentally (Table 1) indicate that all

theoretical models yielded acceptable values of carbon kinetic isotope effects. The results of PM3 are closer to the experimental values than those obtained using the AM1 Hamiltonian. From the analysis of the nitrogen isotope effects we can conclude that results obtained with the COSMO model leads to qualitative agreement with the observed smaller effect for the *p*-C(O)Me substituent. Values obtained with the SCRf model do not show any dependence (PM3 calculations) or are too inverse (AM1 calculations).

An even more explicit difference between experiment and theory is observed in the case of secondary deuterium isotope effects. These isotope effects are slightly inverse in the case of aniline and toluidine derivatives, which is best modeled by the AM1 Hamiltonian and SCRf solvent treatment. AM1–COSMO results are also acceptable although these calculations yield slightly too low values of this isotope effect of 0.8. The secondary deuterium isotope effect for the acetophenone derivative is normal. This is best modeled by the PM3 calculations. The MNDO method gave an inverse value of 0.644 and AM1–SM2 calculations predicted an isotope effect of 0.8. Analysis of the results obtained leads to the disturbing conclusion that neither of the studied theoretical treatments is adequate for predicting secondary deuterium of isotope effects for all substituents.

The features of the transition state change with the theoretical model, as can be seen in Figure 1, which shows the transition state in the case of *p*-C(O)Me calculated with three different Hamiltonians. The

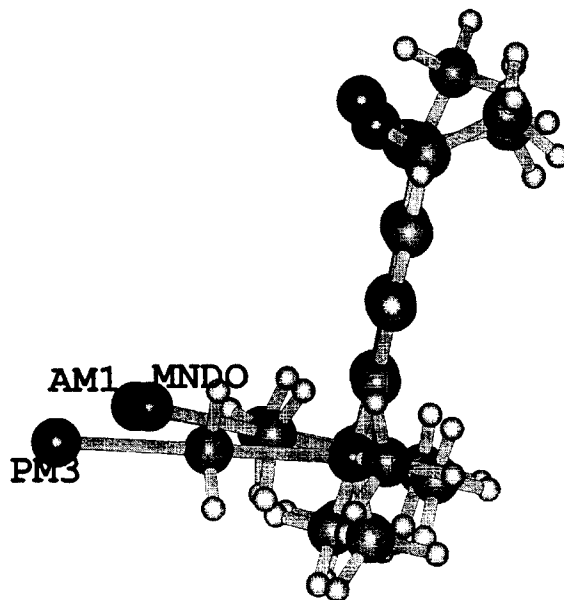


Figure 1. Structures of the transition state calculated using AM1, PM3 and MNDO Hamiltonian and COSMO solvent model for the acetophenone derivative

striking result is the invariance of the structure of transition states obtained with different Hamiltonians and solvation models for such different substituents as p -CH₃ and p -C(O)CH₃. Virtually all geometrical parameters are the same with all studied substituents, as it is illustrated by the structures in Figure 2 and the data given in Table 2. A similar lack of dependence of nitrogen isotope effects on the *para*-substituent was also observed in the case of quaternization of pyridines.²³

Differences in the transition-state structures obtained using different continuum solvent models are shown in Figure 3 on the example of the transition state for the acetophenone derivative.

In all calculations the angle of the nucleophilic attack, defined as an angle formed by nitrogen, carbon and iodine atoms, was close to 180° as expected for an S_N2 reaction. The relative position of this angle versus the plane of the aromatic ring is, however, different for AM1 and PM3 Hamiltonians, as illustrated in Figure 4.

The angle between the ring plane and the line marked by N–C–I atoms is close to 90° in the case of PM3 calculations, while the AM1 model predicts a twist of substituents on the nitrogen atom away from C₁ symmetry. In both cases the valence angle at nitrogen is close to the tetrahedral angle of 109.5. This difference might be a consequence of problems with calculations of charge distribution in nitrogen-containing molecules with the PM3 method. It would be interesting to see if the novel method of correcting this deficiency called CM4P²⁴ would resolve this problem.

Approximately the same C–I lengths are predicted by studied theoretical treatments for the reactants 2.05 Å compared with the crystallographic length of 2.15 Å for C(sp³)–I containing compounds²⁵ and the transition state (2.45 Å). AM1–SCRF calculations give best agreement with the experimental values (Table 2). The MNDO/d Hamiltonian²⁶ together with the LD solvation model yielded a C–I bond length of 2.08 Å in

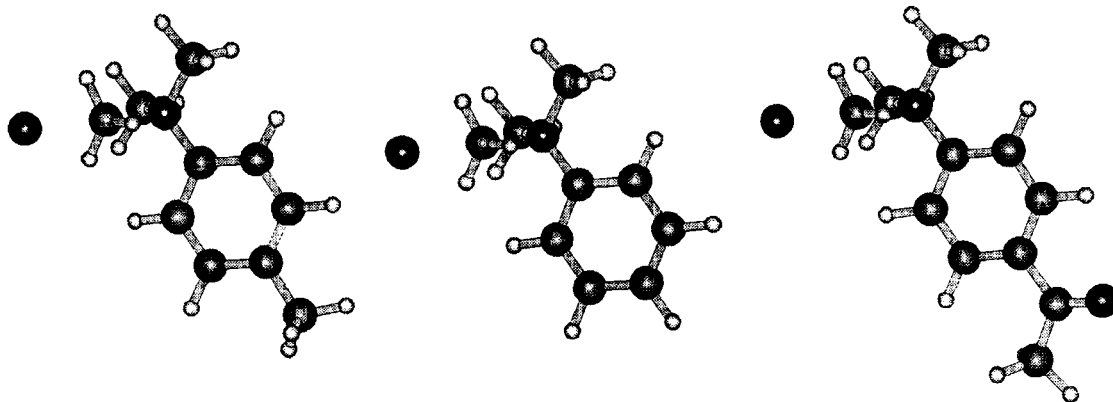


Figure 2. Structures of transition states calculated using the AM1 Hamiltonian and COSMO solvent model for three different substituents in the *para* position of *N,N*-dimethylanilines

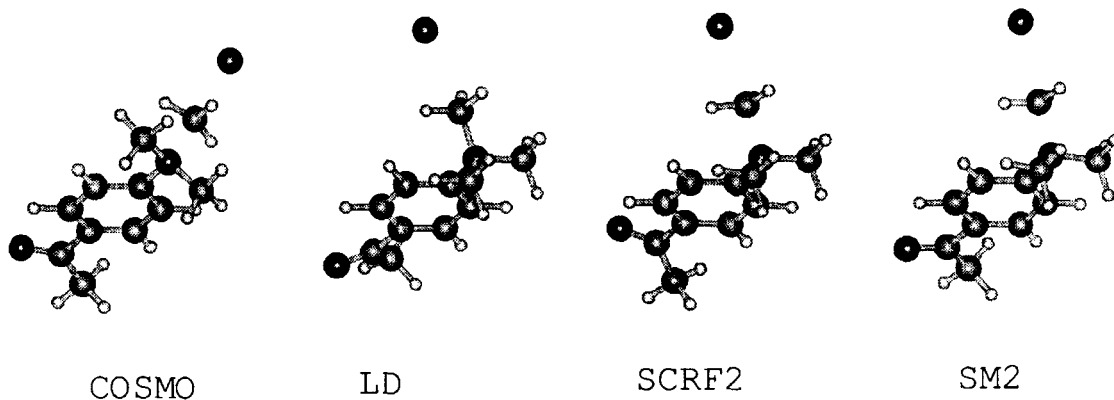


Figure 3. Structures of the transition state calculated using the AM1 Hamiltonian and different solvent models for the acetophenone derivative

Table 2. Calculated properties of the structures of transition states for reaction (1)^a

Method	R	$\angle\text{NCH}$	$r_{\text{N-C}}^{\text{TS}}$ $n_{\text{N-C}}$	$r_{\text{N-C}}$	$r_{\text{C-I}}^{\text{TS}}$ $n_{\text{C-I}}$	$r_{\text{C-I}}$	ΔH^*	ν^*	Σn						
PM3	<i>p</i> -Me	86.0	2.356	1.485	2.467	2.044	18.5	580.3	0.29						
COSMO			0.05		0.24										
PM3			2.140		2.456					2.030	25.0	723.2	0.35		
SCRF			0.11		0.24										
AM1			1.819		1.449					2.432	2.056	52.8	789.7	0.58	
COSMO	<i>p</i> -H	88.4	0.29	1.481	0.29	2.051	52.3	544.3	0.68						
AM1			1.676		1.441					2.504	2.051	52.3	544.3	0.68	
SCRF			0.46		0.22										
PM3			2.361		1.485					2.477	2.044	18.3	573.8	0.29	
COSMO			0.05		0.24										
PM3	<i>p</i> -C(O)Me	88.5	2.140	1.481	2.459	2.029	26.3	725.4	0.35						
SCRF			0.11		0.24										
AM1			1.814		1.459					2.433	2.056	53.0	793.5	0.58	
COSMO			0.30		0.28										
AM1			1.681		1.465					2.501	2.164	61.7	562.6	0.72	
SCRF	<i>p</i> -C(O)Me	100.0	0.49	1.484	0.22	2.470	2.032	28.7	712.0	0.34					
PM3			2.350		1.484						2.480	2.044	33.9	577.1	0.29
COSMO			0.06		0.23										
PM3			2.135		1.482						2.470	2.032	28.7	712.0	0.34
SCRF			0.11		0.23										
AM1	<i>p</i> -C(O)Me	94.6	1.803	1.449	2.440	2.057	54.5	794.9	0.59						
COSMO			0.31		0.28										
AM1			1.679		1.441					2.503	2.050	63.6	561.2	0.67	
SCRF			0.45		0.22										
AM1			1.539		1.437					2.741	2.004	57.9	53.0	0.80	
LD	<i>p</i> -C(O)Me	98.8	0.71	1.436	0.09	2.049	gas	619.7	0.66						
AM1			1.682		2.510		63.1								
SM2			0.44		0.22		gas								
MNDO	<i>p</i> -C(O)Me	96.5	1.838	1.471	2.567	2.021	76.2	722.7	0.45						
COSMO			0.29		0.16		76.1								

^aAngles in degrees, lengths in Å, ν in cm^{-1} , ΔH in kcal mol^{-1} .

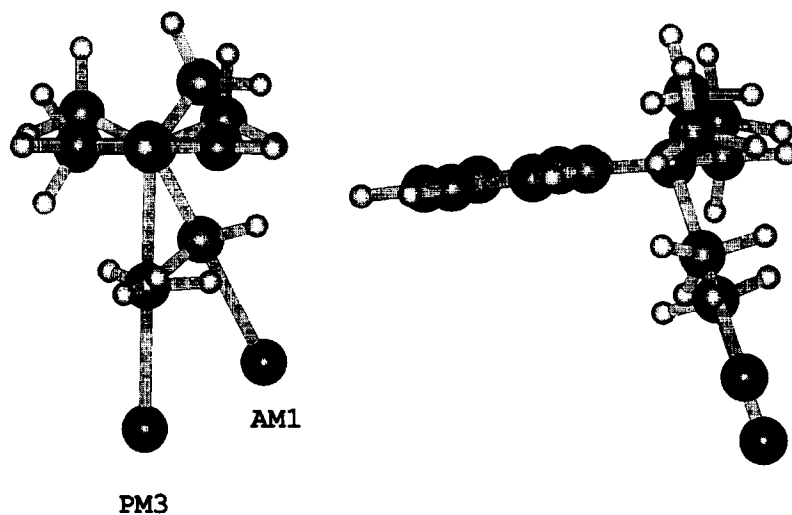


Figure 4. Transition-state structures calculated using AM1 and PM3 Hamiltonians and COSMO solvent model for the aniline derivative overlaid to overlap aromatic rings. The structures on the left are viewed from the back of the ring. The ring plane is perpendicular to the surface of drawing. The structure on the right is rotated 90 showing the valence angle at nitrogen and differences in the center of reaction as calculated by these two methods

the case of methyl iodide, indicating that better results are obtained when d-orbitals are included in calculations.

An important difference between the results obtained with AM1 and PM3 Hamiltonians is the length of the forming N–C bond. For the stable reacting amines, the PM3 method predicts a longer N–C bond than the AM1 method by about 0.03 Å (with the AM1 value closer to the crystallographic value of 1.466 Å obtained as an average from 88 compounds containing C(sp³)₂=N–C(sp²) arrangement). This difference increases significantly in the case of transition-state structures, reaching 0.55 Å. It is also worth noting that solvent models influence this bond length; COSMO calculations yield N–C bonds in the transition state longer by about 0.2 Å than SCRF (while no difference is predicted for stable amines). To discuss this, it is better to consider the formal bond order (*n*) rather than bond lengths (*r*). Bond lengths at partial bond orders can be calculated from²⁷

$$r_n = r_1 - 0.3 \ln(n) \quad (3)$$

where *r_n* is the length of a partial bond with multiplicity *n* and *r₁* is the length of a single bond. The multiplicity of the C–I bond in the transition state is invariably found to be around 0.25. This means that C–I breaking is highly advanced in the transition state. From this point of view, the transition state could be categorized

as ‘very late’ or ‘product-like.’ The PM3 results predict an unrealistically low bond order of the forming N–C bond at the level of 0.1, pointing to an S_N1-like rather than an S_N2 mechanism, as can be seen in the More O’Ferall–Jencks diagram (Figure 5). It should be noted, however, that attempts to optimize a transition state for a ‘pure’ S_N1 mechanism were unsuccessful. This means that the mechanism resulting from the PM3 calculations could be termed ‘nucleophile assisted S_N1.’ More reasonable results of the AM1 calculations predict this bond order to be at the level of 0.3–0.4. Thus, from the point of view of the forming bond, the transition state should be called ‘early’ or ‘reactant-like.’ The above discussion illustrates nicely the deficiencies of simple categorization of transition-state structures used so frequently in earlier interpretations of isotope effects.

The total bonding to the central carbon atom is predicted at about 0.3 by the PM3 calculations, which seems to be too low. The AM1 method yields this value at about 0.6–0.7, as suggested earlier.^{10b} The MNDO calculations give geometrical features of the transition state as the center of reaction similar to those obtained with the AM1 method. All results are therefore pointing to the so-called ‘loose’ or ‘exploded’ transition-state structure.

The little involvement of nitrogen in the reaction coordinate predicted by the PM3 Hamiltonian is reflected in the lack of N–C contributions in the reaction

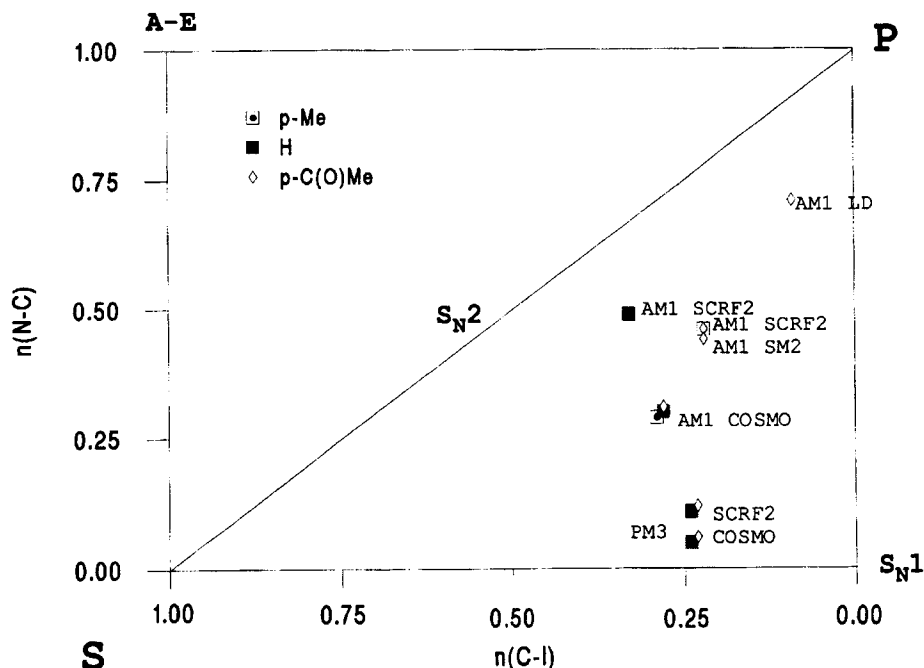


Figure 5. Calculated positions of the transition states for quaternization of *para*-substituted anilines on the reaction coordinate represented in the More O’Ferall–Jencks space.

coordinate in the case of COSMO calculations. Furthermore, the N–C–H angle, averaged over all three hydrogens, obtained using the PM3 method is always less than 90. This angle changes from about 71 found in the reactant complex, preoriented for the nucleophilic attack, to about 109 found in the product. The lack of steric hindrance from the incoming group to the bending of C–H bonds because of the large N–C distance may thus be the reason for the secondary deuterium isotope effect being predicted by this method as larger than unity. In the case of the AM1 calculations the calculated angles are about 95 with the COSMO and about 100 with the SCRF correction. Since a 90 N–C–H angle would be called a 'symmetrical' transition state, the AM1 calculations predict a 'late' transition state whereas the PM3 calculations predict an 'early' transition state.

It was usually postulated that the total bonding of the reactant coordinate N–C–I drops to about 0.8, constituting an 'exploded' transition state. Our results suggest a much larger decrease to about 0.6, which corresponds to an extremely loose transition state. The structures obtained also indicate a lack of synchronicity; 70% of the bond breaking is accompanied by only 30% of bond making, questioning earlier rigorous categorizations into 'early', 'late' or 'symmetrical' transition states.

Comparison of calculated isotope effects for the reaction between methyl iodide and *para*-substituted *N,N*-dimethylanilines with the experimental results indicates that none of the methods tested correctly predicts values of isotope effects. While primary carbon and incoming group nitrogen kinetic isotope effects are predicted by most of these methods, none was able to reproduce the observed cross-over of the secondary deuterium isotope effects. Furthermore, if analysis is restricted to only one type of isotope effect, e.g. heavy atom, a different theoretical treatment leads to acceptable values although the calculated geometries of the corresponding transition state are different. This questions the applicability of such a theoretical treatment to the analysis of transition-state properties. Recently similar conclusions have been reached²⁸ on the basis of high-end *ab initio* calculations of isotope effects on elimination reactions. These stirring findings need closer inspection in future model studies.

The above discussion assumes that the reaction studied is a single-step reaction. We have discussed in the accompanying paper^{10f} the possibility of a more complex scheme, which involves a dissociation of the solvent–amine complex preceding the reaction of the amine with methyl iodide. This mechanism may be valid particularly for the very basic amines. If this was the case, the results of the calculations reported here should be compared directly with the experimental data only for the most electron-withdrawing derivative, i.e. 4-MeC(O). However, the possibility of a two-step mechanism does not agree with the observed absence of

a solvent isotope effect for the 4-Me derivative. For such a mechanism this isotope effect should be significant. We have suggested that a reasonable mechanism might involve a solvent molecule hydrogen bonded to the amine. Hence it may be necessary to include explicitly in the model at least one solvent molecule to account for the observed changes of isotope effects with the change of substituents. Such calculations are much more CPU demanding. Furthermore, accounting for weak intermolecular interactions such as hydrogen bonds is not an easy task.²⁹ An alternative approach is to carry out reactions in an aprotic solvent. Both approaches are currently being explored.

ACKNOWLEDGMENTS

We are indebted to Professors Mati M. Karelson and Toomas Tamm for making their codes available to us. This work was supported by grant No. 0458/92/P3 from the State Committee for Scientific Research (KBN), Poland.

REFERENCES

- (a) K. C. Westaway, in *Isotopes in Organic Chemistry*, edited by E. Buncl and C. C. Lee, Vol. 7, Chapt. 6. Elsevier, New York (1989); (b) V. J. Shiner, Jr and F. P. Wilgis, in *Isotopes in Organic Chemistry*, edited by E. Buncl and W. H. Saunders, Jr, Vol. 8, Chapt. 6. Elsevier, Amsterdam (1992).
- J. C. Pollanyi and A. H. Zewail, *Acc. Chem. Res.* **28**, 119 (1995).
- (a) P. Paneth, *Talanta* **34**, 877 (1987); (b) P. Paneth, in *Isotopes in Organic Chemistry*, edited by E. Buncl and W. H. Saunders, Jr, Vol. 8, Chapt. 2. Elsevier, Amsterdam (1992).
- L. B. Sims, G. Burton and D. E. Lewis, *QCPE* 337 (1985).
- (a) L. B. Sims and D. E. Lewis, in *Isotopes in Organic Chemistry*, edited by E. Buncl and C. C. Lee, Vol. 6, Chapt. 4. Elsevier, New York (1984); (b) F. Mentch, D. W. Parkin and V. L. Schramm, *Biochemistry* **26**, 921 (1987).
- P. Paneth, *Comput. Chem.* **19**, 11 (1995), and references cited therein.
- (a) N. Menshutkin, *Z. Phys. Chem.* **5**, 589 (1890); (b) N. Menshutkin, *Z. Phys. Chem.* **6**, 41 (1890). 8. (a) W.-P. Hu and D. G. Truhlar, *J. Am. Chem. Soc.* **116**, 7797 (1994), and Ref. 3 therein; (b) S. S. Shaik, H. B. Schlegel and S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry: The S_N2 Mechanism*. Wiley, New York (1992).
- (a) M. Sola, A. Lledos, M. Duran, J. Bertran and J.-L. M. Abboud, *J. Am. Chem. Soc.* **113**, 2873 (1991); (b) M. H. Abraham, *Prog. Phys. Org. Chem.* **11**, 1 (1974); (c) M. H. Abraham and R. J. Abraham, *J. Chem. Soc., Perkin Trans.* **2** 1677 (1975); (d) M. H. Abraham, *Pure Appl. Chem.* **57**, 1055 (1985).
- (a) G. J. Buist and M. L. Bender, *J. Am. Chem. Soc.* **80**, 4308 (1958); (b) P. Paneth and M. H. O'Leary, *J. Am. Chem. Soc.* **113**, 1691 (1991); (c) B. S. Axelsson, B. Långström and O. Matsson, *J. Am. Chem. Soc.* **109**, 7233

- (1987); (d) B. S. Axelsson, O. Matsson and B. Långström, *J. Phys. Org. Chem.* **4**, 77 (1991); (e) J. Rudzinski, N. Tadros and P. Paneth, *J. Mol. Struct.* **321**, 97 (1994); (f) A. Szyllabel-Godala, S. Madhavan, J. Rudzinski, M. H. O'Leary and P. Paneth, *J. Phys. Org. Chem.*
11. (a) L. Melander, *Isotope Effects on Reaction Rates*. Ronald Press, New York (1960); (b) L. Melander and W. H. Saunders, Jr, *Reaction Rates of Isotopic Molecules*. Wiley, New York (1980).
 12. (a) J. L. Kurz and M. M. S. El-Nasr, *J. Am. Chem. Soc.* **104**, 5923 (1982); (b) J. L. Kurz, M. W. Daniels, K. S. Cook and M. M. S. El-Nasr, *J. Phys. Chem.* **90**, 5357 (1986).
 13. *Ampac 5.0*. Semichem, Kansas City.
 14. (a) C. J. Cramer and D. G. Truhlar, *AMSOL 3.0, QCPE Bull.* **11**, 57 (1991); (b) C. J. Cramer and D. G. Truhlar, *J. Am. Chem. Soc.* **113**, 8305 (1991).
 15. A. A. Bliznyuk, S. S. Pachkovsky and A. A. Voityuk, *SIBIQ version 1.0.6* (1994).
 16. J. J. P. Stewart, *J. Comput.-Aided Mol. Des.* **4**, 1 (1990).
 17. M. M. Karelson, T. Tamm, A. R. Katritzky, S. J. Cato and M. C. Zerner, *Tetrahedron Comput. Methods* **2**, 295 (1989).
 18. A. Klamt and G. Schuurmann, *J. Chem. Soc., Perkin Trans 2* 799 (1993).
 19. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.* **107**, 3902 (1985).
 20. J. J. P. Stewart, *J. Comput. Chem.* **10**, 209, 221 (1989).
 21. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.* **99**, 4899, 4907 (1977).
 22. V. Luzkhov and A. Warshel, *J. Comput. Chem.* **11**, 199 (1992).
 23. U. Berg, M. Chanon, R. Gallo and M. Rajzmann, unpublished results.
 24. J. W. Strorer, D. J. Giesen, C. J. Cramer and D. G. Truhlar, *UMSI 91/144*. University of Minnesota.
 25. The result of search of Cambridge Structural Database, carried as described by F. H. Allen and O. Kennard, *Chem. Des. Autom. News* **8**, 31 (1993).
 26. W. Thiel and A. A. Voityuk, *Theor. Chim. Acta* **81**, 391 (1992).
 27. L. B. Sims, A. Fry, L. T. Netherton, J. C. Wilson, K. D. Reppond and S. W. Crook, *J. Am. Chem. Soc.* **94**, 1364 (1972).
 28. S. S. Glad and F. Jensen, *J. Am. Chem. Soc.* **116**, 9302 (1994).
 29. (a) E. Gawlita, V. E. Anderson and P. Paneth, *Eur. Biophys. J.* **23**, 353 (1994); (b) E. Gawlita, V. E. Anderson and P. Paneth, *Biochemistry* **34**, 6050 (1995).