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Calculations of Substituent and Solvent Effects on the Kinetic Isotope Effects of Menshutkin Reactions

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Nitrogen, deuterium, halogen, and carbon kinetic isotope effects have been modeled for the Menshutkin reaction between methyl halides and substituted *N*,*N*-dimethylaniline at the HF/6-31G(d) level of theory augmented by the C-PCM continuum solvent model for several solvents. Systematic changes in geometries of the transition states and Gibbs free energies of activation have been found with phenyl ring substituents, solvent, and the leaving group. Kinetic isotope effects also change systematically; however, these changes are predicted to be small, inside the usual precision of the experimental measurements. On the contrary, no correlation has been found between the kinetic isotope effects and the Hammett constants for para substituents. Thus opposite to previous assumptions, our results indicate that kinetic isotope effects on the Menshutkin reaction cannot be used to predict the position of the transition state on the reaction coordinate.

Introduction

Because of their high sensitivity to solvent polarity[1] and the importance of the methyl transfers in biochemical processes,[2] reactions of amine bases with alkyl halide, the Menshutkin reactions, have been subjected to extensive experimental[3] and theoretical studies.[4] Despite these numerous attempts, however, a consistent picture of the electronic, solvent, and steric effects on these reactions has not yet emerged. In particular, a variety of kinetic isotope effects (KIEs) have been studied and their interpretation seems ambiguous. An extensive review of these studies has been recently published by Matsson and Westaway.[5]

KIEs are considered to be the most sensitive probes of transition state structures that are not amenable to direct experimental inspection. Therefore their interpretation plays a vital role in mechanistic studies of chemical and biochemical reactions.[6] Traditionally, qualitative interpretation of KIEs, based on bond order arguments,[7] is being supplanted by quantitative results obtained with quantum chemical calculations. This transformation proceeds with significant successes,[4,8] although in some cases the progress is not satisfactory. In particular, studies by Jensen and Glad[9] have shown that there is no systematic improvement in agreement between the experimental and calculated KIEs for elimination reactions upon upgrading the theory level. Similarly, we have recently shown[10] that many popular theory levels are unable to correctly predict several KIEs simultaneously for a simple S_N2 reaction.

In this contribution we present results of theoretical studies on the Menshutkin reaction between 4-substituted *N*,*N*-dimethylaniline and methyl halides (Scheme 1). We previously have carried out experimental studies on the reaction of methyl iodide and interpreted[11] them

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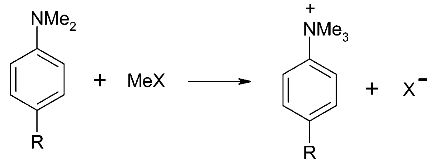
TABLE 1. Comparison of the Key Geometric Features of the Transition States and Gibbs Free Energy of Activation[a] for the Studied Menshutkin Reactions

R	X	theory level	solvent	*r*(C-N)	*r*(X-C)	*r*(H···H)	*r*(N-C_{Ph})	∠X-C-H	∠X-C-N	∠C-N-C_{Ph}-C	Δ*G*‡
2,6-di-CH_3	Cl	C-PCM/HF/6-31G(d)	ethanol	2.186	2.382	1.981[b]	1.469 (1.429)[c]	89.0	178.1	46.1	49.7
4-NO_2				2.148	2.335	2.371	1.428 (1.356)	90.2	179.0	63.6	40.1
4-CN				2.155	2.334	2.386	1.434 (1.365)	90.2	179.1	62.9	37.4
4-F				2.174	2.310	2.353	1.442 (1.420)	90.8	179.0	58.8	33.2
H				2.179	2.307	2.371	1.442	91.0	179.1	60.1	32.9 [31.7]
				{0.25}[d]	{0.46}	[2.371][e]	1.417 ([1.396])				
			cyclohexane	2.056	2.371	[2.315]	1.447 ([1.395])	87.6	178.9	58.8	[41.6]
			THF	2.153	2.320	[2.359]	1.443 ([1.396])	90.4	179.1	60.2	[34.1]
			DMSO	2.184	2.304	[2.371]	1.441 ([1.396])	91.1	179.0	60.2	[32.0]
			water	2.189	2.303	[2.369]	1.441 ([1.396])	91.2	179.2	59.7	[30.8]
4-CH_3			ethanol	2.183	2.293	2.363	1.439 (1.418)	91.4	179.2	59.3	32.5
4-OH				2.186	2.298	2.345	1.445 (1.423)	91.2	179.1	57.2	32.4
H		C-PCM/B3LYP/6-31+G(d)		2.145	2.286	2.409	1.448 ([1.394])	91.0	179.4	64.9	28.0
				{0.33}	{0.54}						
		HF/6-31G(d)		1.930	2.439	2.270	1.454 (1.416)	84.3	178.6	56.4	52.9
				{0.40}	{0.36}						
		C-PCM/HF/6-311G(d)		2.189	2.306	2.383	1.440 (1.414)	91.1	179.1	60.5	31.3
	Br			2.207	2.452	2.385	1.439 (1.414)	91.1	179.0	60.3	29.6
	I			2.243	2.662	2.402	1.438 (1.414)	91.4	179.1	60.4	28.2

[a] Distances in Å, angles in deg, Gibbs free energy in kcal mol^{-1}. [b] The shortest distance between hydrogen atoms in methyl groups of amines and methyl halides in transition states. [c] Values in parentheses correspond to the bond length in the reactant. [d] Wiberg bond orders are given in brackets. [e] Values in square brackets are for the amine with the C_s symmetry.

SCHEME 1



using the semiempirical level of theory. Present computational technology allows us to address the mechanism of these reactions at the ab initio and density functional theory (DFT) levels, providing a better basis for understanding features of the transition states, and thus KIEs and electronic effects.

Results and Discussion

Contrary to the cases of hydrogen transfer reactions, where the precise knowledge of the activation barrier height and shape is required due to quantum effects (e.g., tunneling), for reactions that involve mainly heavy-atom motion in the reaction coordinate modeling of KIEs can be achieved when good geometries of reactants and the corresponding transition states are available. It has been shown[4] that the hybrid B3LYP functional[12] with the 6-31G(d) basis set[13] augmented by diffuse functions[14] adequately describes the Menshutkin reaction. To validate the level of theory on which the Discussion is based we have, therefore, compared our results obtained for the unsubstituted nucleophile at the Hartree−Fock (HF) theory level[15] with the C-PCM continuum solvent model[16] to the results obtained at the DFT level. Since calculations of KIEs require geometries of reactants and the transition state we did not have to optimize geometries of the products, and thus we were not required to perform any calculations on anions. Our previous experience with the decarboxylation of 4-pyridylacetic acid,[7h,i] which involves a zwitterionic reactant and a polar transition state, indicates that the HF/6-31G(d) level with a continuum solvent model[17] can describe adequately such reactions. Comparison of the data shown in Table 1 supports this conclusion signifying that the transition state geometries at these two levels are very similar. The position of the transition state on the reaction coordinate is determined by the bond orders for the forming C−N bond and breaking C−X bond. At the C-PCM/HF/6-31G(d) level we have found these bonds equal to 0.25 and 0.46, respectively. In the qualitative language of describing the reaction progress it means that the transition state is early (the forming bond is weaker than the breaking one) and loose (the sum of these two bond orders is less than unity). C-PCM/B3LYP/6-31+G(d) calculations yield qualitatively the same picture although the transition state is slightly closer to the symmetrical one. A significantly different TS is obtained from gas-phase calculations at the HF/6-31G(d) level, which suggests a more advanced formation of the bond between the central carbon and the incoming nucleophile and a weaker bond to the leaving halide, i.e., a late transition state. The same conclusions can be drawn from the comparison of the X−C−H angles that should be smaller than 90° for a late transition state and larger than 90° for an early one. The above discussion indicates the importance of the inclusion of solvent effects in the calculations. This conclusion is also supported by comparison of the calculated Gibbs free energies of activation for these three theory levels with the DFT results that include solvation effects being closest to the experimental values. A typical

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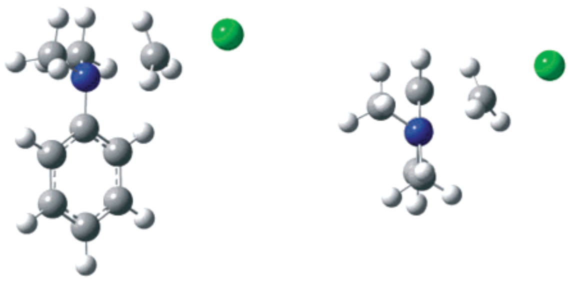

FIGURE 1. Structure of the transition state obtained at the C-PCM/HF/6-31G(d) level for the reaction between *N*,*N*-dimethylaniline and methyl chloride. Side view on the left, top view on the right.

TABLE 2. KIEs for the Reaction between Methyl Halides and Substituted *N*,*N*-Dimethylaniline Calculated for 300 K

R, X, or solvent	σ_p	k_{14}/k_{15}	k_{12}/k_{13}	k_{35}/k_{37}	k_{H6}/k_{D6}	k_{H3}/k_{D3}
		C-PCM/HF/6-31G(d) ethanol, X = Cl				
2,6-di-CH_3		1.0032	1.0573	1.0086	0.657	0.825
4-NO_2	0.78	1.0026	1.0585	1.0082	0.955	0.906
4-CN	0.66	1.0015	1.0592	1.0084	0.899	0.875
4-F	0.06	0.9995	1.0598	1.0084	0.813	0.868
H	0	0.9996	1.0597	1.0084	0.827	0.870
4-CH_3	−0.17	0.9999	1.0592	1.0081	0.815	0.896
4-OH	−0.37	0.9994	1.0600	1.0084	0.820	0.867
		C-PCM/HF/6-31G(d,) R = H, X = Cl				
cyclohexane	0	[0.9986][a]	1.0595	1.0082	[0.867]	0.834
THF	0	[0.9987]	1.0598	1.0083	[0.890]	0.861
ethanol	0	[0.9988]	1.0597	1.0084	[0.898]	0.870
DMSO	0	[0.9988]	1.0597	1.0084	[0.898]	0.871
H_2O	0	[0.9989]	1.0599	1.0085	[0.903]	0.875
		C-PCM/HF/6-311G(d) ethanol, R = H				
Cl	0	0.9996	1.0593	1.0081	0.828	0.893
Br	0	1.0000	1.0566	1.0014[b]	0.832	0.872
I	0	1.0008	1.0525	1.0009[b]	0.839	0.842

[a] Values in square brackets are for the amine with C_s symmetry. [b] k_{79}/k_{81} for bromine and k_{127}/k_{131} for iodine.

transition state structure is shown in Figure 1 for the reaction between methyl chloride and *N*,*N*-dimethylaniline.

Most of the experimental KIEs on Menshutkin reactions have been obtained for methyl iodide. It has been found theoretically[5] that changing from chloride to bromide causes the transition state to become earlier, in accord with the Hammond postulate, and thus one might expect that this trend will be even more pronounced for the further change to iodide. If this were true, the incoming group nitrogen KIE should decrease (become closer to unity) for the series of chloride, bromide, and iodide as leaving anions. Experimental data, however, do not evidence this trend. The nitrogen KIEs for the reaction between pyridine and methyl chloride, bromide, and iodide in water at 25 °C were found[18] to be 0.9960, 0.9972, and 0.9950, respectively. We have compared transition states and corresponding isotope effects for the three reactions with different halogen atoms (Table 2). Since the 6-31G(d) basis set does not contain iodine, we have used the 6-311G(d) basis set for these calculations.[19]

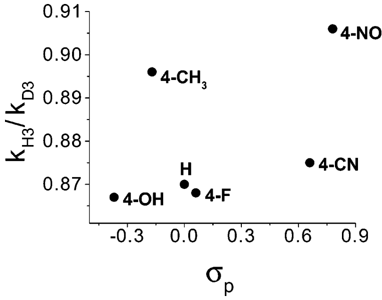

FIGURE 2. Dependence of the deuterium KIE on σ_p for the reaction between methyl chloride and 4-substituted *N*,*N*-dimethylaniline at 300 K in ethanol.

Our results indicate that the transition state becomes earlier in the series Cl, Br, I. This is evidenced by the increasing bond length of the forming C−N bond, and nitrogen KIE; the inverse KIE for the reaction of methyl chloride crosses over to yield a normal KIE (larger than unity) for the reaction of methyl iodide. A similar conclusion is reached when the dependence of the ^{15}N KIEs on the reaction of *N*,*N*-dimethylaniline with methyl chloride in different solvents is studied (see Table 2). In both cases the expected changes are very small, well within typical experimental errors. Practically the same conclusion can be reached from studies of the dependence of the other KIEs on solvent and the leaving group. Furthermore, our calculations show that neither bromine,nor iodine KIEs are useful for the mechanistic interpretations due to their small values, although such attempts can be found in the literature.[18]

The most surprising results were obtained in studies of the substituent effects on KIEs. One finds good correlations between energetics of the studied reaction with the transition state features, e.g., the C−N bond elongates, the X−C bond shortens, and the Gibbs free energy of activation diminishes as the σ_p parameter for the substituent in the 4 position increases. However, there is no such correlation with calculated KIEs. This is illustrated in Figure 2 on the example of the secondary deuterium KIEs (calculated for simultaneous substitution of all three α hydrogen atoms). Inverse values of these isotope effects, together with even more inverse values of the secondary deuterium KIEs of hydrogen atoms in *N*-methyl groups (k_{H6}/k_{D6}), and their increase with the shortening of the distance between hydrogen atoms in the methyl chloride and hydrogen atoms in *N*-methyl groups ($r(H\cdots H)$ in Table 1), indicate that these KIEs result predominantly from the steric hindrance.

KIEs are governed by two factors: isotopic mass difference and the "stiffness" of the isotopic atom surrounding.[6,7] Mass difference always favors the light isotopomer. The same is true for the second factor when a bond to an isotopic atom is being broken, thus leaving group KIEs are usually large. When a bond to an isotopic atom is being made, the two factors act in opposite directions, which can result in normal (larger than unity) or inverse (less than unity) KIEs. Furthermore, an accidental cancellation can lead to no KIE. These situations are encounter usually in the case of the incoming group KIEs, like the nitrogen KIEs studies here. Opposite

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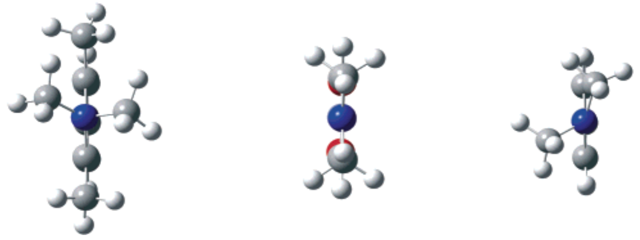

FIGURE 3. Top views of conformations of amines with different substituents. From left to right: 2,6-dimethyl-, 4-nitro-, and unsubstituted *N*,*N*-dimethylaniline.

to the dependencies discussed above on the leaving halide and the solvent, ^{15}N KIEs change with the substituents in an anti-Hammett manner, i.e., the shorter the forming C−N bond the larger the isotope effect. This behavior may be partially explained by the simultaneous elongation of the $N-C_{Ph}$ bond between the nitrogen atom and the carbon atom of the phenyl ring (which is more pronounced in the electron-withdrawing groups) but in fact ^{15}N KIEs seem to be more correlated with the structure of the reacting amine than with any parameter describing the transition state. In our studies three amine conformations have been identified as shown in Figure 3. For the very crowded *N*,*N*-dimethyl-2,6-dimethylaniline, steric hindrance forces two methyl groups into the position perpendicular to the phenyl ring (the structure on the left). Significant elongation of the bonds to the nitrogen atom in the transition state results in a large normal ^{15}N KIE for this reaction. A similar result is obtained for the electron-withdrawing groups although the origin of the effect is different. With electron-withdrawing groups, optimizing resonanse electron delocalization throughout the molecule results in substantial shortening of the bond between the nitrogen and the carbon of the phenyl ring ($N-C_{Ph}$)—these values are listed in square brackets in Table 1. Consequently, the amine is planar with the methyl groups lying in the plane of the phenyl ring (central structure, Figure 3).

Finally, for the electron-donating groups one of the methyl groups is out of the phenyl ring plane while the second is nearly in the plane (structure on the right in Figure 3). For *N*,*N*-dimethylaniline two conformers of similar stability were found one with C_1 symmetry as described above, and the other, favored by about 1 kcal mol^{-1} with C_s symmetry, resembles the central structure of Figure 3 but with methyl groups slightly out of the plane of the phenyl ring, both on the same side of the ring. These two conformations yield different nitrogen KIEs—results obtained for the latter conformation are reported in the tables in square brackets.

In summary, we have found that KIEs change systematically with the solvent and the leaving halide but these changes are very small while no correlation has been found between KIEs and the Hammett constants for para substituents. Thus contrary to previous suggestions, our results indicate that KIEs on Menshutkin reactions cannot be used to predict the position of the transition state on the reaction pathway. This is caused by the transition state structures being similar for all cases studied, with the breaking C−Cl bond order of about 0.5 and the forming N−C bond order of about 0.25 (corresponding to the qualitative description of early, unsymmetric, exploded transition states).

Experimental Section

Theoretical Calculations. Initial optimizations of the transition states were performed by using semiempirical PM3 parametrization[20] and the COSMO continuum solvent model[21] as implemented in Ampac.[22] These preoptimized structures were used as the starting points in the ab initio HF/6-31G(d) calculations with Gaussian03.[23] In the studies involving different halogen atoms (R = H, X = Cl, Br, I) the triple-ζ split valence 6-311G(d) basis set was used since the 6-31G(d) basis set does not contain the required parameters for iodine. Attempts to use an unbalanced basis set, 6-31G(d) for all atoms but the halogen for which 6-311G(d) was used, failed to optimize to the transition state. In the calculations of the transition state geometry for the *N*,*N*-dimethylaniline (R = H) using the B3LYP functional the 6-31+G(d) basis set was used.

All calculations were performed with default convergence criteria and without any constraints on individual reactants or on the transition state. Frequency analysis was performed for each stationary point to confirm that the converged structure represents either a minimum on the potential energy surface (no imaginary frequencies) or a first order saddle point (exactly one imaginary frequency) and to obtain the Hessian matrix necessary for calculations of isotope effects. Kinetic isotope effects were calculated by the conventional transition state theory[24] with a unit transmission coefficient, using the complete equation of Bigeleisen[25] implemented in the program Isoeff98.[26] Frequencies used in the KIE calculations were unscaled.

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Supporting Information Available: Cartesian coordinates of all optimized structures of the reactants and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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