

Solvent Effects on Methyl Transfer Reactions. 1. The Menshutkin Reaction

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Abstract: A full quantum mechanical description of the Menshutkin Reaction has been obtained for gas phase and solution by using density functional theory (DFT) and the self-consistent isodensity polarizable continuum model (SCI-PCM). Ammonia and pyridine are compared as nucleophiles, and methyl chloride and bromide are used as methyl transfer reagents. In the gas phase, all of the reactions proceed via an initial dipole complex, followed by a transition state leading to an ion pair. Methyl bromide shifts the position of the transition state to an earlier position than that found with methyl chloride. In the reaction with methyl chloride, replacing ammonia with pyridine stabilizes the transition state by 3 kcal/mol and stabilizes the ion pair by 17 kcal/mol. In the SCIPCM solvent effect calculations, the dipole complex disappears in both cyclohexane and DMSO. The transition state is shifted to an earlier stage of the reaction and is stabilized with respect to the gas phase. The ion pair product is strongly stabilized, and in DMSO it is calculated to dissociate into free ions. The reactions also were studied using Monte Carlo free energy perturbation. The results were in good agreement with the reaction field calculations. The rates of reaction between pyridine and methyl bromide were determined at 25 °C in cyclohexane, di-*n*-butyl ether, and acetonitrile and compared with the computational results. Activation free energies calculated using the SCR-SCI-PCM model agree remarkably well with the experimental values.

1. Introduction

Methyl (or alkyl) transfer reactions are important in organic syntheses,¹ and in a wide variety of biochemical processes² including the conversion of homocysteine to methionine, the methylation of glutamate residues in chemoreceptors, and in gene regulation. These processes are always carried out in solution, and it is known that some of them are strongly affected by solvent polarity. We have been interested in making use of computational methods to explore the effects of nucleophilicity, leaving groups, and medium on some representative reactions.

There are two general types of these reactions using neutral nucleophiles:



An oxonium or sulfonium salt would be a typical methyl donor in the latter reaction. In the first reaction, the transition state structure is more polar than the reactants, and polar solvents will lead to increased rates of reaction. On the other hand, with the second reaction, the charge is dispersed in the transition state, and polar solvents would be expected to lead to reduced rates of reaction.

The present study is concerned with the Menshutkin reaction in which N: is an amine base. This type of reaction is known to give large solvent effects³ and has received extensive

theoretical study.⁴ The studies for solutions have generally been concerned with the reaction in water, even though this is not the solvent commonly used for this reaction. The reaction of methyl chloride with ammonia in water has been studied using a hybrid QM/MM approach,^{4d} and the reaction with methyl bromide in water was studied using both a supermolecule approach, and via a continuum representation of the solvent.^{4g} Most of the other studies have used a reaction field model such as the polarizable continuum model. In view of the strong hydrogen bonding found in aqueous medium, a reaction field model does not appear to be appropriate. However, it should be noted that a model of this type has reproduced the results of the QM/MM study.^{4h}

Despite the extensive investigations of this reaction, there does not appear to be any study in which the reaction variables (leaving group, nucleophile, and solvent) have been examined in a systematic fashion. In the following, ammonia and pyridine will be compared as nucleophiles, and methyl chloride and bromide will be used as methyl transfer reagents. The course

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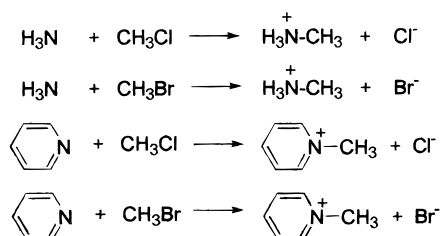
(1) For a review of the Menshutkin reaction, see Abboud, J.-L. M.; Notario, R.; Betran, J.; Sola, M. *Prog. Phys. Org. Chem.* **1993**, 19, 1.

(2) Cf. Stryer, L. *Biochemistry*, 4th ed.; Freeman: New York, 1995; pp 328, 722, and 998.

of the reactions will first be examined by ab initio calculations for the reaction in the gas phase. The effect of cyclohexane, di-*n*-butyl ether, and dimethyl sulfoxide as solvents will be studied making use of a reaction field model,⁵ and the effect of dimethyl sulfoxide, acetonitrile, and water as the solvent will be examined using the Monte Carlo free energy perturbation method.⁶ Experimental data on the solvent effect for the reaction of pyridine with methyl bromide also will be presented.

2. Gas-Phase Calculations

The reactions that have been studied are:



To obtain satisfactory calculations of the solvent effects, it is first necessary to be able to model the reaction in the gas phase with reasonable accuracy. Previous calculations have used a variety of theoretical models including MP2/6-31G**,^{4b} MP3/6-31G*,^{4c} CAS(4,4)/6-311G**,⁴ⁱ and DFT/6-31G**.^{4h} Here we have chosen to use the B3LYP/6-31+G* theoretical level.⁷ This density functional model has been shown to give very satisfactory results for a variety of reactions.⁸ The basis set is fairly flexible, and includes diffuse functions that are thought to be important for the proper description of lone pairs and anions.⁹

Geometry optimizations were carried out for all of the compounds in the above reactions giving the data summarized in Table 1. The zero-point energies were calculated at the B3LYP/6-31+G* theoretical level and were scaled by a factor of 0.98. The calculated energies were corrected using the zero-point energies to give heats of formation. The reactions lead to significant entropy changes, and they were estimated using the usual statistical mechanics method.¹⁰ The values are summarized in Table 2.

With the first two reactions, experimental data are available,¹¹ and the agreement between experiment and calculations is quite satisfactory (Table 2). The heat of formation of methylpyridinium ion is not known. It was estimated from a correlation between the proton affinity of an amine¹² and the methyl

Table 1. Total Energies and Zero Point Energies in kcal/mol at B3LYP/6-31+G*

compound	zpe	gas phase	cyclohexane	DMSO
MeCl	23.40	-500.11152	-500.11285	-500.11460
MeBr	23.05	-2611.63242	-2611.63371	-2611.63541
NH ₃	21.23	-56.55699	-56.55930	-56.56250
pyridine	54.09	-248.29579	-248.29770	-248.30049
CH ₃ NH ₃ ⁺	49.10	-96.21602	-96.27622	-96.33053
Pyr-CH ₃ ⁺	80.35	-287.97883	-288.02402	-288.06387
Cl ⁻		-460.27472	-460.32119	-460.36285
Br ⁻		-2571.80219	-2571.84551	-2571.88399
NH ₃ CH ₃ Cl(dp) ^a	45.21	-556.67103		
NH ₃ CH ₃ Cl(ts)	47.32	-556.62008	-556.63851	-556.65509
NH ₃ CH ₃ Cl(ip)	48.32	-556.62105	-556.65319	
NH ₃ CH ₃ Br(dp)	45.26	-2668.19517		
NH ₃ CH ₃ Br(ts)	47.30	-2668.14652	-2668.16467	-2668.18028
NH ₃ CH ₃ Br(ip)	48.20	-2668.14750	-2668.17869	
Pyr-CH ₃ Cl(dp)	78.31	-748.40944		
Pyr-CH ₃ Cl(ts)	78.88	-748.36147	-748.37524	-748.388642
Pyr-CH ₃ Cl(ip)	79.74	-748.36988	-748.39649	
Pyr-CH ₃ Br(dp)	78.26	-2859.93655		
Pyr-CH ₃ Br(ts)	78.83	-2859.89143	-2859.90452	-2859.91741
Pyr-CH ₃ Br(ip)	79.89	-2859.89971	-2859.92474	

^a dp refers to the dipole complex, ts to the transition state, and ip to the ion pair.

Table 2. Reaction Free Energies and Entropies

reaction	ΔS_r	ΔS^\ddagger	ΔG_r (kcal/mol)	
			calcd	expt
CH ₃ Cl + NH ₃ → CH ₃ NH ₃ ⁺ + Cl ⁻	-7.2	-30.1	118	111 ± 5
CH ₃ Br + NH ₃ → CH ₃ NH ₃ ⁺ + Br ⁻	-7.6	-30.9	114	105 ± 5
CH ₃ Cl + Pyr → CH ₃ Pyr ⁺ + Cl ⁻	-8.8	-31.2	102	98 ± 5
CH ₃ Br + Pyr → CH ₃ Pyr ⁺ + Br ⁻	-9.2	-31.9	99	93 ± 5

affinity¹³ and the known proton affinity of pyridine, leading to $\Delta H_f = 173$ kcal/mol.¹⁴ Using this value, the calculated energy changes for the reactions of pyridine were obtained and are in good agreement with the experimental values (Table 2).

Since the overall reactions are well described at this theoretical level, the stationary points on the potential energy surface were located. In each case, the first was an dipole-dipole complex, which is easily found since it is a minimum on the surface. The transition state was located by first carrying out a series of calculations in which the N-C distance was given a fixed value, and the remaining structural parameters were optimized. Having an approximate location for the transition state, its geometry could be fully optimized using the usual gradient technique. The energies are given in Table 1, and the most relevant geometrical parameters and relative energies are summarized in Table 3. Here, %BS is the percent of C-X bond stretching. A typical asymmetric double-well energy profile with a late transition state was obtained for all the reactions (Figure 1). The reaction coordinate was taken as the difference between the C-X and C-N distances.

The first minimum corresponds to the dipole complex formed as the molecular dipoles align with each other. This is a common feature of gas-phase reactions involving dipolar reactants. The second minimum corresponding to the ion pair is quite close to the transition state in the reaction path and only slightly more stable, which makes it a transition state-like species. The value of the HCX angle in the transition state indicates that the methyl group has almost completely undergone the inversion umbrella motion.

2a. Effect of the Halogen. Methyl bromide and methyl chloride were compared as methyl transfer reagents. Bromine slightly shifts the position of the transition state to an earlier stage of the reaction and stabilizes it by 3 and 4 kcal/mol in the

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(14) Full data are available in the Supporting Information.

Table 3. Critical Points in the PES in Gas Phase at B3LYP/6-31+G*

entity	$r(\text{C}-\text{N})$	$r(\text{C}-\text{X})$	$\angle\text{HCX}$	E_{rel} (kcal/mol)	%BS
MeCl-NH ₃					
reactants	—	1.805	108.49	0.0	0.0
dipole complex	3.397	1.813	108.63	-1.0	0.4
transition state	1.769	2.564	79.16	33.1	42.0
ion pair	1.604	2.761	73.50	33.5	53.0
products	1.516	—	—	116.1	—
MeBr-NH ₃					
reactants	—	1.964	107.97	0.0	0.0
dipole complex	3.238	1.968	108.05	-2.6	0.2
transition state	1.771	2.707	78.45	30.0	37.8
ion pair	1.601	2.909	73.2	30.3	48.1
products	1.516	—	—	112.3	—
MeCl-Pyridine					
reactants	—	1.805	108.49	0.0	0.0
dipole complex	3.416	1.812	108.54	-0.5	0.4
transition state	1.848	2.461	82.85	30.2	36.3
ion pair	1.504	2.911	70.24	25.8	61.3
products	1.486	—	—	99.4	—
MeBr-Pyridine					
reactants	—	1.964	107.97	0.0	0.0
dipole complex	3.158	1.965	108.03	-4.1	0.1
transition state	1.836	2.586	82.13	26.5	31.7
ion pair	1.501	3.015	70.26	20.7	53.5
products	1.486	—	—	95.7	—

reaction with ammonia and pyridine, respectively. The stabilization also occurs at the other critical points of the reaction path, although it is smaller in the dipole complex. The amount of negative charge transferred to the halogen increases along the reaction (Figure 2).¹⁴ The positive charge, on the other hand, is spread over the methyl group and the nucleophile. The increasing polarization is responsible for the destabilization of reaction complex in gas phase and its strongly stabilizing interaction with polar solvents. An overall comparison for MeCl and MeBr reacting with ammonia shows that the reaction energy profile for the latter is stabilized by about 3 kcal/mol which is about the difference in proton affinity between Cl⁻ and Br⁻.

2b. Effect of the Nucleophile. Replacing ammonia by pyridine in the reaction with methyl chloride stabilizes the transition state by about 3 kcal/mol. However, as the reaction proceeds and the charge separation becomes more important, this stabilization increases to 17 kcal/mol for the final products. Similar changes are found for the reaction with methyl bromide. The larger stabilization in the final products appears to be a consequence of the greater basicity of pyridine in gas phase.¹⁵ The effect of pyridine as a nucleophile is stronger beyond the transition state when the charge separation is close to completion. Thus, pyridine provides a stronger stabilization of the ion pair with a larger charge separation.

3. Charge Shifts during the Reaction

The electron populations for all of the species in the above reactions were obtained using the AIM method.¹⁴ Little charge transfer occurs in the dipole complex, but over half of the net change occurs on going to the transition states. The change for the amino group at the transition state is larger than for the methyl group, but both contribute to the increase in charge at the halogen. On going to the product, the increase in charge for the methyl group is greater for methyl bromide than for

methyl chloride. This arises from the greater initial electron population at the methyl group of methyl bromide. The changes found for the gas phase will be compared to those for reactions in solution below.

We were interested in examining the changes in electron populations that occur when pyridine is converted to pyridinium ion. Pyridine will react with methyl halides using its in-plane lone pair. Will the positive charge that develops affect the electron distribution in the π system? This question is explored in Table 4 for the reaction of pyridine with methyl cation. The changes in electron population are separated into σ and π contributions.

If the methyl group were neutral, it would have 6 σ electrons along with 2 π electrons (aligned with the π electrons of the ring) that contribute to the formation of the C-H bonds. The methyl group in methylpyridinium ion has gained σ electrons and lost π electrons, making a total gain of 0.4 e. There is little net effect at the nitrogen atom, with a 0.26 gain in π electrons and a 0.21 loss of σ electrons for a net gain of 0.05 e.¹⁶ It is the ring CH groups that suffer the net loss of electron population, and much of this loss is found at the hydrogens. This has also been found in other systems¹⁷

4. Solvent Effects Calculated via Reaction Field Theory

We have found that the reaction field model is successful in reproducing experimental solvent effects for a variety of processes when aprotic solvents having normal polarizabilities are used.¹⁸ Examples of such solvents include cyclohexane, di-*n*-butyl ether, acetonitrile, acetone, and dimethyl sulfoxide. The model predicts that about 40% of the effect of going from the gas phase to a highly polar solvent will be found on going from the gas phase to cyclohexane, and this has been verified experimentally.¹⁸

In the reaction field model, the solute is placed in a cavity in the solvent. The surface charges of the solute are calculated, and their interactions with the solvent are obtained. This leads to the free energy of solvation. The use of the solvent's bulk dielectric constant in these calculations is justified if the solvent is free to adopt random orientations with respect to the solute. This is not the case with hydrogen bonding solvents such as water and methanol. In addition, if the solvent has high polarizability or a large quadrupole moment,¹⁹ the solvent effect will be larger than expected based on the dielectric constant. Solvents of this type include benzene derivatives and many chlorides and bromides.

We have calculated the effect of cyclohexane, di-*n*-butyl ether, and dimethyl sulfoxide on the energetics of the Menshutkin reaction using the SCIPCM model.²⁰ Here, the cavity is defined

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(15) The proton affinity of ammonia is 204 kcal/mol whereas that for pyridine is 221 kcal/mol (ref 12). The greater basicity of pyridine is presumably associated with its larger size and greater polarizability.

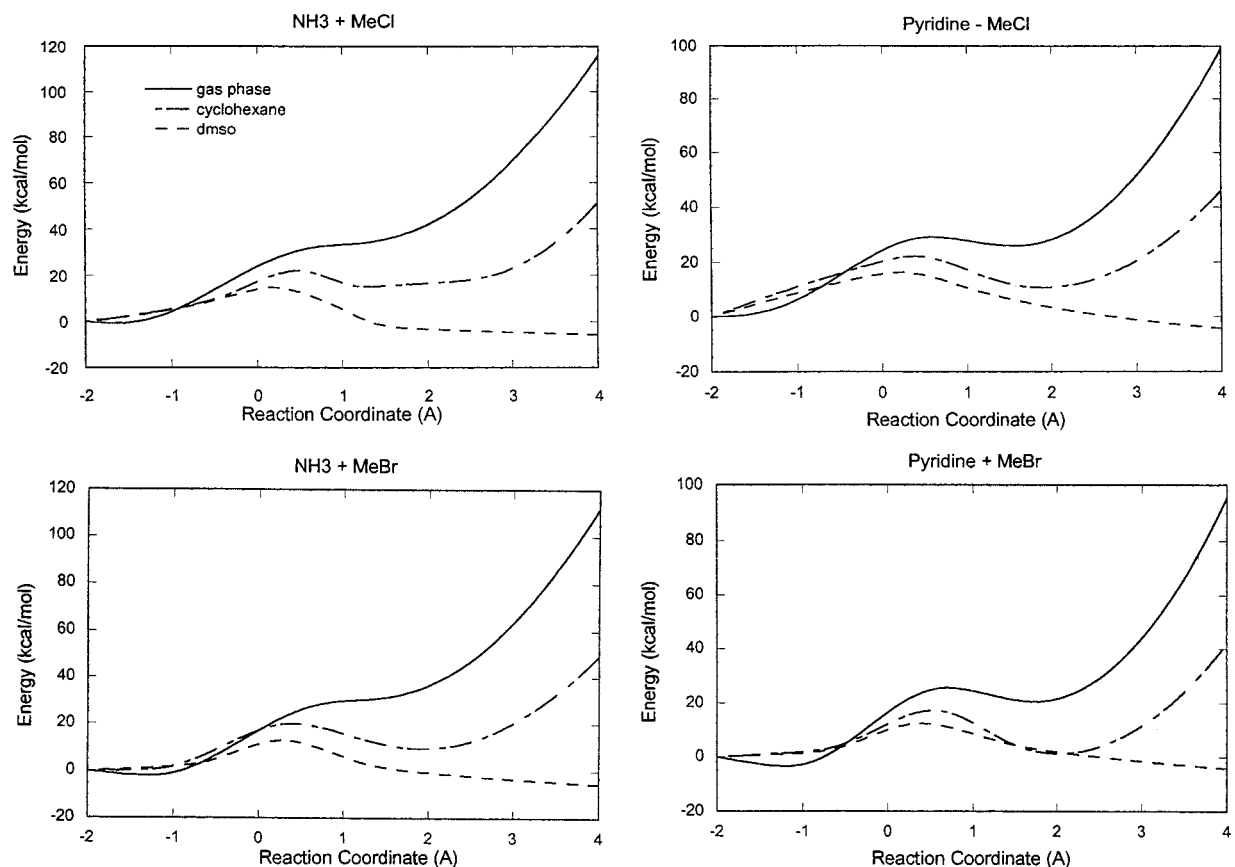


Figure 1. Potential energy curves for the reaction of methyl chloride and bromide with ammonia and pyridine in the gas phase, in cyclohexane, and in dimethyl sulfoxide.

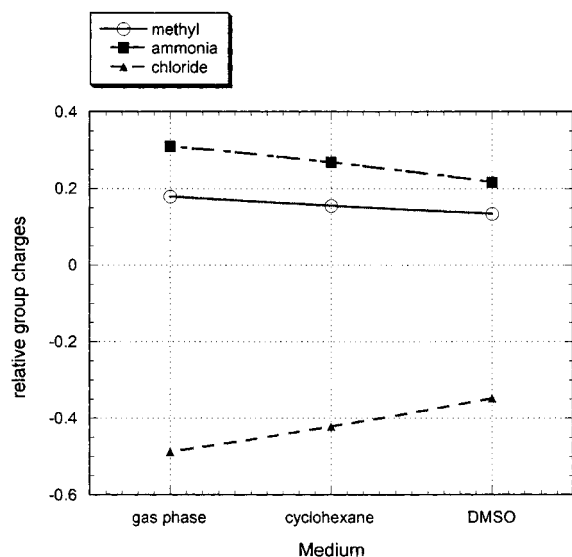


Figure 2. Changes in group charges on going from the reactants to the transition state in the reaction between methyl chloride and ammonia. The changes for the other reactions are similar. Full data are available as Supporting Information.

by an isodensity surface of the solute. A value of 0.0004 e/au^3 leads to molar volumes that are in good agreement with the experimental values. Geometry optimizations in the presence of the solvent were carried out for all of the species in the reactions. Figure 1 shows the effect of the solvents on the energy profiles for all of the reactions in this study.

Although cyclohexane has a very low dielectric constant, significant changes can be observed along the reaction path.

Table 4. Charge Separation into σ and π Components

atom	σ	π	total
Pyridine			
N1	6.907	1.324	8.231
C ₂ H ₇	5.544	0.855	6.399
C ₃ H ₈	5.545	0.855	6.399
C ₄ H ₉	5.992	1.004	6.996
C ₅ H ₁₀	5.992	1.004	6.996
C ₆ H ₁₁	6.021	0.958	6.979
total	36.000	6.000	42.000
Methyl-Pyridinium			
CH ₃	6.501	1.938	8.439
N ₁	6.696	1.581	8.277
C ₂ H ₇	5.515	0.860	6.375
C ₃ H ₈	5.515	0.860	6.375
C ₄ H ₉	5.897	0.945	6.842
C ₅ H ₁₀	5.897	0.945	6.842
C ₆ H ₁₁	5.979	0.871	6.851
total	42.000	8.000	50.000
Difference			
CH ₃	6.501	1.938	8.439
N ₁	-0.211	0.257	0.046
C ₂ H ₇	-0.029	0.005	-0.024
C ₃ H ₈	-0.029	0.005	-0.024
C ₄ H ₉	-0.095	-0.059	-0.154
C ₅ H ₁₀	-0.095	-0.059	-0.154
C ₆ H ₁₁	-0.042	-0.087	-0.129
total	6.000	2.000	8.000

The separated reactants are stabilized enough to make the dipole complex disappear. The transition state has been shifted to an earlier stage of the reaction and energetically stabilized with

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Table 5. Critical Points in the PES in Cyclohexane at B3LYP/6-31+G*

entity	$r(\text{C}-\text{N})$	$r(\text{C}-\text{X})$	$\angle\text{HCX}$	E_{rel} (kcal/mol)	%BS
MeCl-NH ₃					
reactants	—	1.808	108.39	0.0	0.0
transition state	1.960	2.408	86.01	23.8	33.2
ion pair	1.534	3.018	71.49	15.7	66.9
products	1.509	—	—	51.5	—
MeBr-NH ₃					
reactants	—	1.968	107.79	0.0	0.0
transition state	2.000	2.444	77.56	20.9	24.1
ion pair	1.535	3.161	71.50	10.0	60.6
products	1.509	—	—	49.7	—
MeCl-Pyridine					
reactants	—	1.808	108.39	0.0	0.0
transition state	1.960	2.385	86.59	23.6	31.9
ion pair	1.498	3.065	70.48	11.1	69.5
products	1.486	—	—	46.1	—
MeBr-Pyridine					
reactants	—	1.968	107.79	0.0	0.0
transition state	1.942	2.510	85.98	18.6	27.5
ion pair	1.491	3.199	—	8.8	62.6
products	1.486	—	—	42.1	—

respect to the gas phase (Table 5). The ion pair has become a more product-like species, and it is farther from the transition state, both energetically as well as along the reaction path. In general, all the species along the reaction path have been stabilized by about 30% of their respective relative energies in gas phase and the overall reaction is less endothermic.

Here, the influence of pyridine on the transition state in the reaction with methyl chloride is decreased with respect to ammonia, and it is inverted in the reaction with methyl bromide. In the former case, it only shifts the transition state to an earlier stage with virtually no stabilization, while in the latter it delays its formation.

Figure 2 shows that the amount of charge transfer to the halogens in the transition states is reduced on going from the gas phase to cyclohexane, whereas the charge transfer in the ion pairs is increased. This is accord with the transition states being earlier in cyclohexane. The ion pairs can be more fully relaxed in cyclohexane, leading to their greater polarity.

Figure 1 also shows the effect of dimethyl sulfoxide as the solvent. It is in this solvent where the most dramatic changes are observed. The dielectric constant of the solvent is large enough to separate both the dipole complex and the ion pair,²¹ which are no longer observed as energy minima in the reaction path. The transition state is shifted far to an earlier stage of the reaction (Table 6), it is strongly stabilized with respect to that in both gas phase and cyclohexane, and the reaction becomes exothermic. The effect of the halogen remains the same, namely replacing Cl by Br lowers the energy of the transition state and makes it earlier, whereas using pyridine instead of ammonia delays the formation of the transition state. This is in accord with the observation that whereas pyridine is a stronger base than ammonia in the gas phase, it is a weaker base in most solvents.²²

Figure 2 shows that the charge transfer in the transition states continues to decrease on going from cyclohexane to dimethyl

Table 6. Critical Points in the PES in Dimethyl Sulfoxide at B3LYP/6-31+G*

entity	$r(\text{C}-\text{N})$	$r(\text{C}-\text{X})$	$\angle\text{HCX}$	E_{rel} (kcal/mol)	%BS
MeCl-NH ₃					
reactants	—	1.815	108.10	0.0	0.0
transition state	2.125	2.265	92.03	16.7	24.8
products	1.500	—	—	-5.6	—
MeBr-NH ₃					
reactants	—	1.973	107.55	0.0	0.0
transition state	2.120	2.392	90.92	14.1	21.2
products	1.500	—	—	-5.5	—
MeCl-Pyridine					
reactants	—	1.815	108.10	0.0	0.0
transition state	2.075	2.302	90.57	18.1	26.8
products	1.484	—	—	-4.4	—
MeBr-Pyridine					
reactants	—	1.973	107.55	0.0	0.0
transition state	2.050	2.434	89.64	13.3	23.4
products	1.484	—	—	-4.2	—

sulfoxide as the solvent. The ion pairs now completely dissociate, and the products have slightly more charge transfer in dimethyl sulfoxide than the ion pairs in cyclohexane.

In the above, we have only been concerned with how the potential energy surfaces are affected by the solvation free energies. The energy changes may also be affected by the change in cavity size on going from the reactants to the transition states, and from the change in the repulsion and dispersion energies between the solute and the solvent during the reaction. It has been found that these energy terms are approximately equal and opposite, and therefore will approximately cancel.²³ We will make use of this approximation.

The quantity of interest is the free energy since it is the quantity that controls the rate of reaction. The gas phase enthalpies of reaction are readily converted to free energies since the entropy terms may be calculated using statistical mechanics (Table 2). This becomes more of a problem in solution since translation becomes diffusion, and the overall rotation of the molecules may be hindered. No completely satisfactory treatment of the problem has appeared. However, it may be noted that for reactions of nonpolar molecules giving nonpolar transition states, such as in the dimerization of cyclopentadiene,²⁴ the rates of reaction are often nearly independent of medium, having essentially the same rate constant in the gas phase as in any one of several solvents. The entropy change also is found to be essentially constant. Thus, the use of the gas-phase entropies should be satisfactory in estimating the change in entropy resulting from the reactions. A comparison of the calculated and experimental free energies of activation will be given below.

Monte Carlo Simulations of Solvent Effects. As noted above, the reaction field model is not appropriate for hydrogen bonding solvents, although some success has been obtained by using artificially small molar volumes, which serve to accentuate the solvent effect.²⁵ Monte Carlo free energy perturbation methods have proven to be quite successful in reproducing solvation effects in polar and protic solvents.²⁶ Gao and Xia

(23) Cf. Table 2 of ref 4i. It should be noted that the calculation of each of these terms involves considerable uncertainty.

(24) Wasserman, A. *Monatsh.* **1952**, *83*, 543.

(25) Cf. Stefanovich, E. V.; Truong, T. N. *Chem. Phys. Lett.* **1995**, *244*, 65.

(26) (a) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (b) Severance D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966.

(21) Ion-pairs involving singly charged ions have been found to exist only in solvent having a dielectric constant less than about 40 (Fuoss, R. M.; Krauss, C. A. *J. Am. Chem. Soc.* **1933**, *55*, 1019).

(22) In water, the pK_a's of ammonia and pyridinium ion are 9.24 and 5.17, respectively (Dean, J. A. *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, 1985). The gas-phase values are given in ref 15.

have successfully modeled the reaction of ammonia and methyl chloride by using a combined quantum mechanical and statistical mechanical method.^{4d} The free energy of activation reported in that work is in good agreement with the value calculated in this work using the SCRf method.

The reactions of MeCl with pyridine and ammonia were studied in acetonitrile, dimethyl sulfoxide, and water using the BOSS program.²⁷ The calculations were done in two stages. First, a full characterization of the energy profile in gas phase was done using the B3LYP/6-31+G* level of theory. The reaction path was traced from the transition state to the reactants at intervals of 0.05 Å in the C–N bond distance. This procedure produced essentially a movie of the reaction between the two critical points on the energy profile. CHELPG charges²⁸ and structural parameters were obtained at every interval of the reaction path. Calculations for the solvated systems were carried out in the NPT ensemble at 1.0 atm and 25 °C. The solvated system in each case consisted of a periodic cube containing the transition state complex surrounded by 512 water molecules, 400 dimethyl sulfoxide molecules, or 400 acetonitrile molecules. Preferential sampling was used in the Metropolis algorithm, and the perturbations along the reaction path were carried out using double-wide sampling in 24 windows for each solvent. Equilibration over 3 million configurations was carried out for each window, followed by averaging over 5 million configurations. Pairwise additive intermolecular potential functions were used for the solute–solvent and solvent–solvent interactions. No intramolecular terms were included. TIP4P water, acetonitrile, and dimethyl sulfoxide were used as defined by the OPLS potential functions and supplied directly by the BOSS database. CHELPG charges calculated at every step of the reaction path were used for the coulomb term of the potential while the Lennard–Jones parameters were taken from the BOSS database of all-atom parameters. The energy barriers for the reactions were obtained by converting the transition state complex into the reactants in a stepwise fashion along the reaction energy profile calculated in the gas phase.

The Monte Carlo simulation makes use of the gas phase reaction coordinate. Petersson has shown that because the reaction coordinate is a relatively “soft” mode in contrast to the other vibrational modes, reaction coordinates calculated at a lower theoretical level can be used as the basis for calculations with higher theoretical levels.²⁹ The location of the transition state will move, but to a good approximation it will remain on the reaction coordinate. The same should hold true for the Monte Carlo calculations along the gas-phase reaction coordinate. Starting at the gas-phase transition state geometry and moving toward reactants, the free energy first increases, and after the new transition state location is reached, it will begin to decrease.

Table 7 shows the structural parameters of the transition states obtained from BOSS calculations for the reactions of methyl chloride with ammonia, and with pyridine in acetonitrile ($\epsilon = 35$), dimethyl sulfoxide ($\epsilon = 42$), and water ($\epsilon = 78$). The first two solvents lead to the same transition state structures. Despite the explicit representation of the solvents, the performance of the Monte Carlo method in this case is similar to that of the SCRf method, which cannot distinguish between these two solvents due to their similar dielectric constants. However, the transition states in the two reactions are shifted to an earlier position in the reaction path compared to those obtained by the SCRf method. Thus, the C–Cl bond in methyl chloride is

Table 7. Transition State Structures from BOSS Simulation

solvent	$r(\text{C}-\text{N})$	$r(\text{C}-\text{Cl})$	$\angle\text{HCCl}$	ΔG^\ddagger (kcal/mol)
(a) MeCl–NH ₃				
gas phase	1.769	2.564	79.2	41.9
acetonitrile	2.069	2.044	96.9	22.3
dimethyl sulfoxide	2.069	2.044	96.9	22.9
water	2.119	1.995	100.7	21.7
(b) MeCl–Pyridine				
gas phase	1.848	2.461	82.9	39.5
acetonitrile	2.048	2.060	94.6	25.8
dimethyl sulfoxide	2.048	2.060	94.6	24.7
water	2.098	2.005	97.6	23.4

Table 8. Rates of Reaction of Pyridine with Methyl Bromide, 25 °C

solvent	k , L mol ⁻¹ s ⁻¹	ΔG^\ddagger (kcal/mol)
cyclohexane	3.8(–8)	27.6
di- <i>n</i> -butyl ether	1.13(–6)	25.6
acetonitrile	2.04(–4)	22.5

stretched from 1.815 to 2.044 Å (13%) in the reaction with ammonia and to 2.060 Å (14%) in the reaction with pyridine. These changes represent only 50% of those obtained in the SCRf calculations. The shift of the transition states to earlier positions is also accompanied by a reduction of their relative energy of 2.7 kcal/mol in both reactions. Such an additional stabilization may be the result of the conformational orientation of the solvent molecules around the reaction complex. This reorganization of the solvent may add some configurational contribution to the polarization of the solvent medium, which is represented only by the electronic component in the SCRf.

When water is used as the solvent, the effect on the transition state is more pronounced. The C–Cl bond is only stretched to 1.995 Å in the reaction of methyl chloride with ammonia, and to 2.005 Å in the reaction with pyridine. These changes represent an advance of the reactions of 8 and 11%, respectively. Such dramatic effect on the structure of the transition state agrees with that reported by Gao and Xia,^{4d} who found that “the transition state is shifted significantly toward the reactants in water”. Further reduction of the activation free energy in water, as compared to that in dimethyl sulfoxide and acetonitrile, is not very significant, despite the considerable changes in the transition state geometry. A plausible explanation is that ammonia is strongly solvated by water through the lone pairs in the nitrogen atom. Thus, the energy required for desolvation increases the activation energy of the overall reaction. An examination of snapshots of the reaction complex taken from the BOSS simulation before the formation of the transition state showed the solvation of the ammonia molecule. The solvation free energies of ammonia and pyridine in water are –4.3³⁰ and –4.7³¹ kcal/mol, respectively. This will produce the values of about 17.4 and 18.4 kcal/mol for the activation free energies of the reaction of methyl chloride with free ammonia and pyridine, respectively, in aqueous solution.

5. Experimental Results

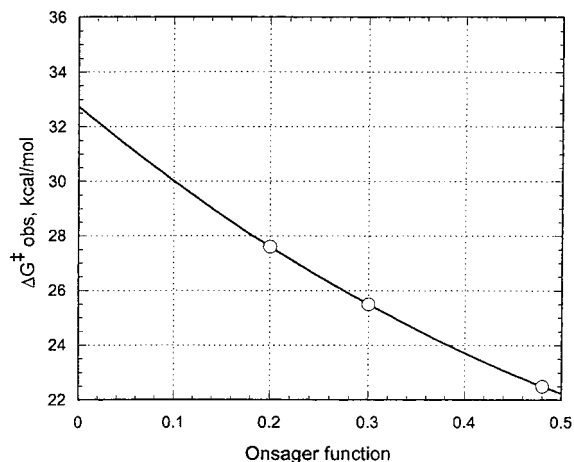
To compare the performance of both the statistical mechanics Monte Carlo method and the quantum SCRf method on the estimation of the activation free energy of the Menshutkin reaction, the rate of the reaction of methyl bromide with pyridine

(27) BOSS, version 3.6. William L. Jorgensen. Yale University.

(28) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.(29) Malik, D. K.; Petersson, G. A.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1998**, *108*, 5704.(30) Kubo, M. M.; Gallicchio, E.; Levy, R. M. *J. Phys. Chem. B* **1997**, *101*, 10527.(31) Cramer, C. J.; Truhlar, D. G. *J. Comput.-Aided Mol. Des.* **1992**, *6*, 629.

Table 9. Activation Free Energies for the Reactions in Solution

reaction	GP	SCRF			BOSS			expt		
		C ₆ H ₁₂	Bu ₂ O	DMSO	MeCN	DMSO	water	C ₆ H ₁₂	Bu ₂ O	MeCN
MeCl-NH ₃	41.9	32.6	27.5	25.5	22.3	22.9	21.7			
MeCl-Pyr	39.5	32.9	29.5	27.4	25.8	24.7	23.4			
MeBr-Pyr	36.0	28.1	24.5	22.8				27.6	25.6	22.5

**Figure 3.** Correlation of the observed activation free energies for the reaction of methyl bromide with pyridine with the Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$.

was determined at room temperature in three different solvents: cyclohexane, di-*n*-butyl ether, and acetonitrile. The experimental rate constants and activation free energies are shown in Table 8. The reaction rate follows the expected trend, namely, the more polar the solvent, the faster the reaction. The reactions in acetonitrile and di-*n*-butyl ether proceeded rapidly enough to allow the determination of reliable values for the rate constants in those solvents. In cyclohexane, on the other hand, the reaction is so slow that the method used to monitor it only produces values in the precision limit of the technique. However, because the values of the dielectric constant of the solvents used span the range of the Onsager function evenly, it is possible to check whether the rate constant in cyclohexane is reasonable by plotting the observed activation free energy against the Onsager function. Figure 3 shows that the experimental value of the rate constant in cyclohexane correlates well with those more accurate values obtained in acetonitrile and di-butyl ether, and extrapolation to the gas phase (i.e. 0.0 in the *x* axis) gives 33 kcal/mol which is close to the calculated value, 36 kcal/mol.

Table 9 shows the comparison between the experimental and the calculated values using both the SCRf and the BOSS simulation. The calculated values of the activation free energy for the reaction of methyl bromide and pyridine, obtained using self-consistent reaction field, agrees very well with the experimental values. No BOSS simulation could be performed for this reaction due to the lack of BOSS parameters for bromine. However, a BOSS simulation should be expected to yield similar values, given the similar performance in aprotic solvent found for both methods.

6. Conclusions

Density functional theory provides a good description of the overall path of the Menshutkin Reaction in gas phase. The calculated values of the activation free energies for all of the studied reactions fall within the accuracy of the experimental values.

The use of methyl bromide as methyl transfer reagent instead of methyl chloride causes a lowering of the energy of all the species along the reaction path and shifts them to earlier position in the reaction path, also by almost a constant amount. Switching from ammonia to pyridine as the base, on the other hand, seems to have a greater effect on the charged species that appear after the formation of the transition state, namely, the ion pair and the ionic products. The gas phase stabilization of these charged species by pyridine appears to be the consequence of the redistribution of charge in the ring, which affects predominantly to the CH groups.

The results of the solvent effect calculations show the transition states become more reactant-like and the reaction activation free energies decrease with the increasing polarizability of the solvent. The relative nucleophilicity of pyridine vs ammonia is reversed on going from the gas phase to dimethyl sulfoxide solutions.

The self-consistent reaction field and Monte Carlo methods give similar results in polar aprotic solvents, but the latter method predicts somewhat earlier transition states. The SCRf calculations agree remarkably well with the experimental results for the reaction of methyl bromide with pyridine. Although no BOSS simulation was possible for this reaction, the similarity of behavior of both methods in aprotic solvents allows us to expect similar results from a BOSS simulation for that reaction.

It should be possible to further improve the Monte Carlo simulations by making use of an SCRf reaction coordinate calculated for a polar medium. This is a significantly more computationally intensive approach, but this and other aspects of comparisons between SCRf and Monte Carlo methods are under investigation.

Calculations. The ab initio calculations were carried out using Gaussian-95.³² In the SCI-PCM model, a single origin and 1800 surface points were used for the methyl halide ammonia reactions, and 2880 for the methyl halide pyridine reactions. This is achieved by including the following line after the *z*-matrix: *D* 0.0004 60 30 2 where *D* is the desired dielectric constant, 0.0004 is the value of ρ for the isodensity surface, 60 and 30 are the number of θ and ϕ planes used to define the surface points, and 2 indicates that a single origin should be used. With the pyridine reactions, 72 and 40 θ and ϕ planes were used. The Monte Carlo calculations were carried out using BOSS. The nonbonded solvent-solvent (RCUT) and solute-solvent (SCUT) cutoffs were set to 12 Å, and a value of 200 was used for the WKC parameter in the preferential sampling.

7. Experimental Section

Materials. All chemicals were analytical grade and were used without further purification. Standard solutions of HCl and NaOH were obtained from Baker and Mallinckrodt, respectively.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Sefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian 95, Development Version (Rev. D) Gaussian, Inc., Pittsburgh, PA, 1995.

Procedure. Pyridine solutions were prepared by mixing measured amounts of pyridine with the solvent to give the desired concentration (0.0621 M). Methyl bromide solutions were prepared as follows: a known amount of methyl bromide (determined by pressure and volume) was placed in a flask and frozen using liquid nitrogen. While cooled, a known amount of solvent was added to the flask. The mixture was allowed to warm to room temperature and to equilibrate for 24 h. The concentration of methyl bromide was 0.312 M. The reaction was initiated by mixing equal volumes (50 mL) of the two solutions. The reactions were carried out at 25 °C under pseudo-first-order conditions with pyridine as the limiting reagent. Rate constants were determined by monitoring the disappearance of pyridine. At known times, 20 mL aliquots were taken from the reaction container and quenched with 10 mL of 0.1 N HCl. A potentiometric titration with NaOH was carried out, and a plot of the pH against the volume of NaOH was prepared. The first inflection corresponded to titration of excess HCl, and the second corresponded to the complete conversion of pyridinium ion to pyridine. The concentration of pyridine was obtained from the difference

in NaOH volume between the two inflection points. The pseudo-first-order rate constants were obtained in the usual fashion. The second-order rate constants were obtained by dividing the observed k by the average methyl bromide concentration during the reaction and are given in Table 8.

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Supporting Information Available: Tables of changes in charge during the reactions and the correlation between proton affinities and methyl affinities. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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