Solvent Effects on Methyl Transfer Reactions. 2. The Reaction of Amines with Trimethylsulfonium Salts

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Abstract: The reaction of ammonia and pyridine with trimethylsulfonium ion has been studied in gas phase and solution. Density functional theory at the B3LYP/6-31+G* level was used to describe the energy changes along the reaction coordinate in the gas phase, and the self-consistent isodensity polarizable continuum model (SCI-PCM) was used to calculate the effect of cyclohexane and dimethyl sulfoxide as the solvent on the energy changes. The effect of water as the solvent was studied using the Monte Carlo free energy perturbation method. The reaction with both ammonia and pyridine follows a similar rather convoluted path in gas phase, with the formation of several reaction complexes before and after the formation of the transition state. All the species found in gas phase persist in cyclohexane, yielding a reaction path very similar to that in gas phase but with significant differences in the relative energy of the critical points. In DMSO, the energy profile is greatly simplified by the disappearance of several of the species found in gas phase and in cyclohexane. The activation free energy increases with the polarity of the solvent in both reactions. Increasing the polarity of the solvent also increases the exothermicity of the reaction of trimethylsulfonium ion with ammonia and reduces it in the reaction with pyridine. In water, the free energy profile follows the same trend as found for DMSO, and free energy of activation is calculated to be larger by about 2−3 kcal/mol. This is in good agreement with an experimental measurement of the effect of solvent on the rate of reaction.

Introduction

Methyl transfer reactions are of importance in both synthesis[1] and biochemical processes.[2] The reactions are often reversible, which is of importance in processes such as gene regulation.[3] Here, methylation may be used to inactivate a gene, and subsequently, demethylation may be used to reactivate it.

There are two basic types of methyl transfer reactions involving neutral acceptors. In the first, the methyl transfer reagent is neutral, as in the Menshutkin reaction. Here, the transition state is dipolar and will be strongly stabilized by polar solvents leading to the well-known rate acceleration in these solvents.[4]

$$R_3N\!: + MeX \rightarrow [R_3N{-}Me{-}X] \rightarrow R_3NMe^+ + X^-$$

In the second type, the methyl transfer reagent bears a positive charge. Here, the transition state for the reaction is less polar than the reactant because the charge is spread out over a large volume. Now, polar solvents should decrease the rate of reaction.

$$R_3N\!: + Me_3S^+ \rightarrow [R_3N{-}Me{-}SMe_2]^+ \rightarrow R_3NMe^+ + Me_2S$$

We have previously reported the results of an investigation of solvent effects on Menshutkin reactions using the self-consistent isodensity polarizable continuum model (SCI-PCM) for aprotic solvents and Monte Carlo free energy perturbation for water as the solvent.[5] The rate of reaction of pyridine with methyl bromide in several solvents was measured, and the calculated free energies of activation were in very good agreement with the experimental values.

This study has now been extended to an examination of the reactions of amines with trimethylsulfonium salts. These reactions are of some special interest in that the sulfonium salt is a model for *S*-adenosylmethionene (**1**), an important biological methyl transfer reagent,[2] in which the methyl group is activated by the positive adjacent sulfur atom. It is responsible for the formation of phosphatidylcholine,[6] a phosphoglyceride found in most membranes of higher organisms, as well as the conversion of homocysteine to methionine[2] and other reactions.

The reaction of the trimethylsulfonium cation with ammonia and with pyridine has now been studied in the gas phase via density functional theory calculations. The effect of aprotic solvents was examined making use of the SCI-PCM,[7] and the Monte Carlo free energy perturbation[8] method was used to study the reaction in aqueous solution.

Calculations

The reactions in the gas phase were studied at the B3LYP/6-31+G* level, which has generally been found to give a good representation of reaction energies. Diffuse functions (+) were included in order to

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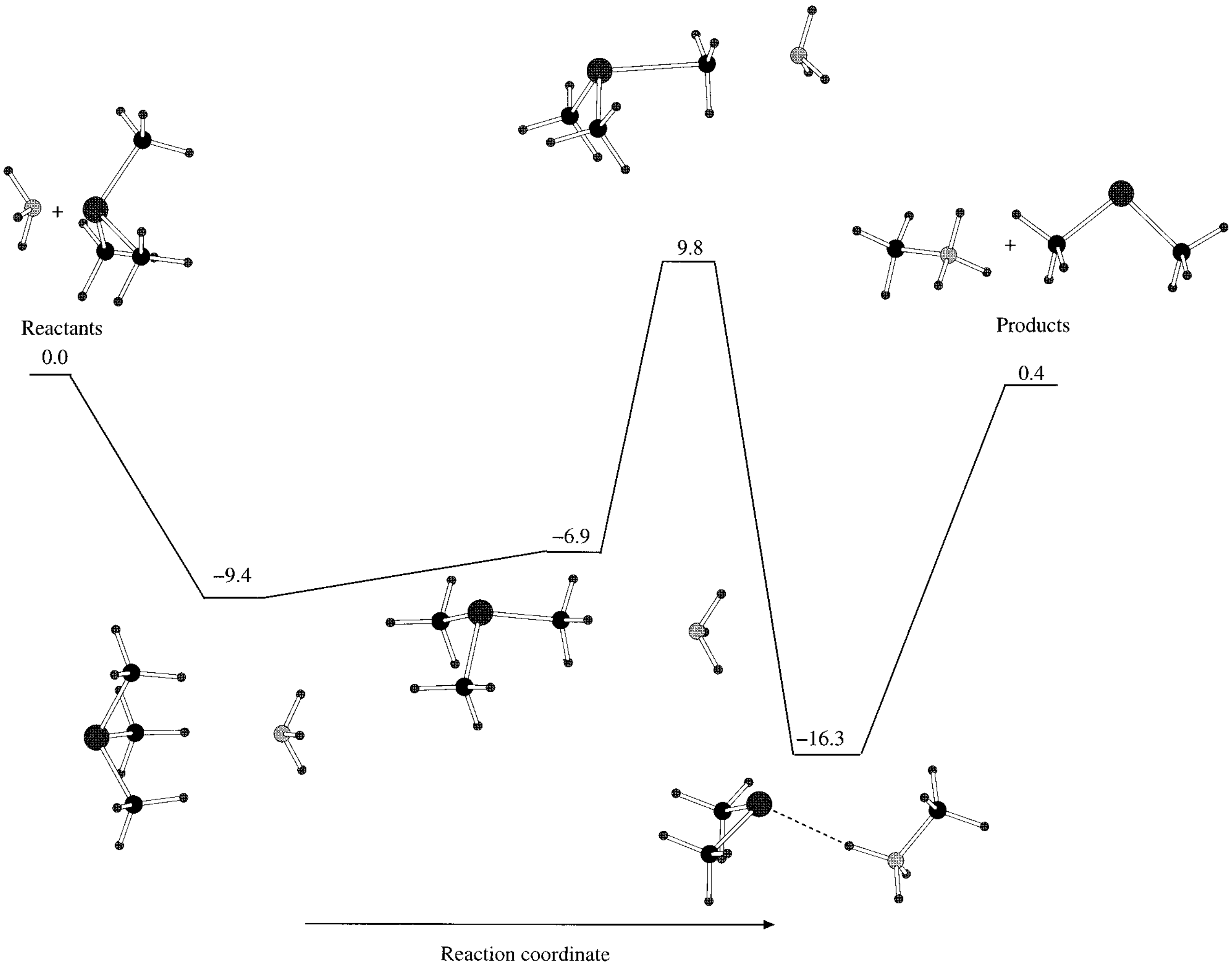

Figure 1. Reaction path for the reaction of ammonia and trimethylsulfonium ion in the gas phase. Relative energies in kilocalories per mole.

correctly represent the lone pairs[9] on nitrogen. The calculations were carried out using Gaussian-99.[10]

The solvent effects of cyclohexane and dimethyl sulfoxide were studied using the SCI-PCM, which has been found to be quite successful in reproducing the effects of aprotic solvents such as cyclohexane, ethers, acetone, acetonitrile, and dimethyl sulfoxide.[7] This reaction field method requires only two parameters: the dielectric constant of the solvent and the value of the electron density used to describe the size and shape of the cavity into which the solute will be placed. The latter is chosen to be 0.0004 e/au^3 since it leads to molar volumes that are in good accord with experimental data. The method cannot be used for protic solvents such as water because the model assumes that the solvent molecules will adopt all random orientations with respect to the solute. This is not true if there is hydrogen bonding between the solvent and the solute.

In the calculations, dielectric constant values of 2.02 and 46.7 for cyclohexane and dimethyl sulfoxide, respectively, were used. Surface integration was done using both single origin and multiple origins.

The reaction in water was studied using the Monte Carlo free energy perturbation method of Jorgensen, making use of the BOSS program.[11] In the present case, an NTP ensemble at 1.0 atm and 25 °C was used. The solvated system consisted of a periodic cube containing the solute system and 512 water molecules. Preferential sampling was used in the Metrolpolis algorithm, and perturbations were carried out using double-wide sampling windows. Equilibration was carried out over 3 million configurations, followed by averaging over 5 million configurations for each window.

Pairwise additive intramolecular potential functions were used for the solvent−solvent and solvent−solute interactions, with a nonbonded solvent−solvent and solute−solvent cutoff distances set at 10 Å, and the value of WKC parameter of 200. No intramolecular terms were included. TIP4P water was used with Lennard-Jones parameters taken directly from the BOSS database. CHELPG charges[12] were calculated at each point along the reaction coordinate and used in the coulomb term of the intermolecular potentials.

Reactions in Gas Phase

The energy profile for the reaction of ammonia with trimethylsulfonium ion, as calculated at the B3LYP/6-31+G* theoretical level, is shown in Figure 1. When approaching each other, the reacting molecules initially form an ion−dipole complex. The strong electrostatic interaction between the ion and the dipole of the ammonia molecule stabilizes the complex by −9.4 kcal/mol, with respect to the separated reactants. The structure of this complex corresponds to the most stable arrangement of the two interacting species in gas phase.

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Table 1. Critical Points in the Gas Phase Energy Profile for the Reaction of Trimethylsulfonium with Ammonia and with Pyridine[a]

entity	r(C−N)	r(S−C)	∠HCS)	E_{rel}	% BS[b]	CT[c]
			$NH_3-(CH_3)_3S^+$			
reactants		1.824	108	0.0	0.0	0.000
ion−dipole complex	3.624	1.824	108	−9.4		0.018
second complex	3.074	1.831	109	−6.9	0.4	0.047
transition state	2.065	2.402	90	9.8	31.7	0.442
third complex	1.506	3.916		−16.3		0.667
products	1.516			0.4		0.778
			Pyridine−$(CH_3)_3S^+$			
reactants		1.824	108	0.0	0.0	0.000
ion−dipole complex	3.583	1.824	108	−11.3		0.025
second complex	3.043	1.831	109	−8.0	0.4	0.050
transition state	2.102	2.321	92	4.9	27.2	0.408
third complex	1.487	3.938		−24.1		0.739
products	1.486			−16.9		0.781

[a] Bond distances in angstroms, bond angles in degrees, and energy in kilocalories per mole. The E_{rel} include the zero point energies. [b] Percent of the S−C bond stretching. [c] Percent of charge transferred to the B:CH_3 moiety for B = ammonia, pyridine.

However, in order for the methyl transfer reaction to occur, the leaving methyl group must be aligned with the lone pair in the nitrogen atom. This aligning process destabilizes the ion−dipole complex and leads to a complex having a slightly higher energy, −6.9 kcal/mol. A transition state between these complexes was not located, but the activation energy is presumably very low.

From this point up to the formation of the transition state for the overall reaction, a good description of the reaction path can be made by using the difference between the C−N and S−C bond distances as the reaction coordinate. The transfer of the methyl group to ammonia leads to a transition state at the reaction coordinate value of 0.337 Å with an activation energy of 9.8 kcal/mol. The value of 90° for the HCS bond angle indicates that the methyl group is halfway in the inversion of conformation that it undergoes upon transfer to the ammonia.

After the transfer of the methyl group is completed, the C−S bond initially continues to lengthen, but then the strong electrostatic interaction between the hydrogen atoms bonded to the nitrogen of the methylammonium and the lone pair of the sulfur atom causes the methylammonium to rotate to form a hydrogen-bonded complex as depicted in Figure 1. This interaction strongly stabilizes the complex by −16.3 kcal/mol with respect to the reactants. A further separation of the products brings the energy of the system up to 0.4 kcal/mol, indicating a very similar methyl affinity for ammonia and dimethyl sulfide.

When ammonia is replaced with pyridine, the overall energy profile is shifted down in energy. Table 1 shows the energy of the critical points in the reaction path for the reactions with ammonia and with pyridine. The changes in relative energies between ammonia and pyridine as the base are largest at and after the transition state.

The value of the reaction coordinate for the pyridine reaction transition state, taken again as the difference between the C−N and C−S bond distances, is 0.219 Å as compared to 0.337 Å for the transition state in the reaction with ammonia. The C−S bond is stretched half as much as in the ammonia reaction, and the H−C−S angle is 92°, indicating that the methyl group has not passed the middle point of the inversion umbrella mode. No hydrogen-bonded complex is found after the transition state, since methylpyridinium ion has no protons attached to the nitrogen.

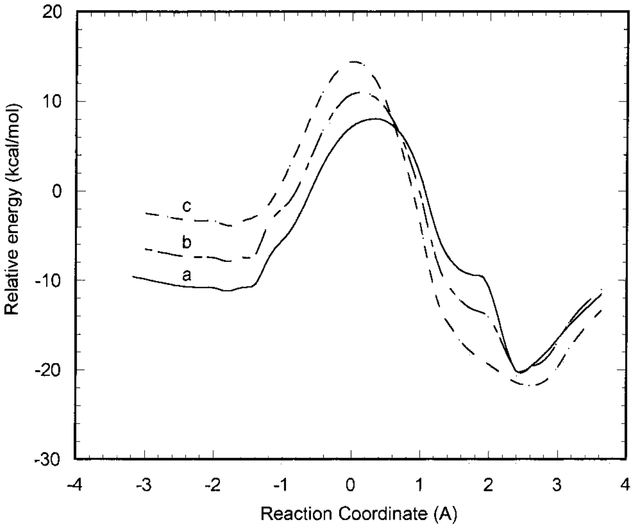

Figure 2. Reaction paths for the reactions of trimethylsulfonium ion with ammonia in the gas phase (a), in cyclohexane (b), and in DMSO (c). The energies are given relative to the reactants in each of the media and do not include the zero point energies. The reation coordinate is the difference between the C−N and S−C bond lengths. The discontinuity following the transition state represents the rotation of the methylammonium fragment in order to form a hydrogen bond with dimethyl sulfide, a process in which the above reaction coordinate changes little.

The larger basicity of pyridine in the gas phase stabilizes the ion−dipole complex of methylpyridinium ion and dimethyl sulfide with respect to that in the ammonia reaction. This effect is also observed in the relative stability of the products: those in the pyridine reaction are 16.9 kcal/mol below the reactants, while in the ammonia reaction, they are 0.4 kcal/mol above the reactants. Similar trends were found in the Menshutkin reaction.[5]

The last two columns in Table 1 show the reaction coordinate as a percent of the S−C bond stretching and the amount of charge transferred at each critical point on the reaction path. It can be seen that although the transition state for the pyridine appears at an earlier stage on the reaction path, the amount of charge transferred is almost the same as in the ammonia reaction.

Solvent Effect Calculations

(a) Aprotic Solvents. The SCI-PCM reaction field model has been found to be quite successful in modeling solvent effects for aprotic solvents.[13] It is capable of representing the significant effect of solvents with low polarity such as cyclohexane, long thought to be equivalent to gas phase as a reaction medium.[14] As an example, the calculated barrier for the Menshutkin reaction of methyl bromide with pyridine in cyclohexane agreed remarkably well with the experimental value.[5] The polarizability of cyclohexane, which gives it a dielectric constant of 2, is responsible for its small solvent effect. Figures 2 and 3 and Table 2 show the reaction path and the relative energy of the critical points along the path for the reaction of trimethylsulfonium with ammonia and with pyridine in cyclohexane.

Even though the relative energies of the critical points in cyclohexane solution are different, the reaction path is essentially the same as in gas phase since all of the species found in gas phase persist in solution. The energies of all of the initial species and that of the transition state have been raised. It is only with the separated product species that solvent stabilization is found.

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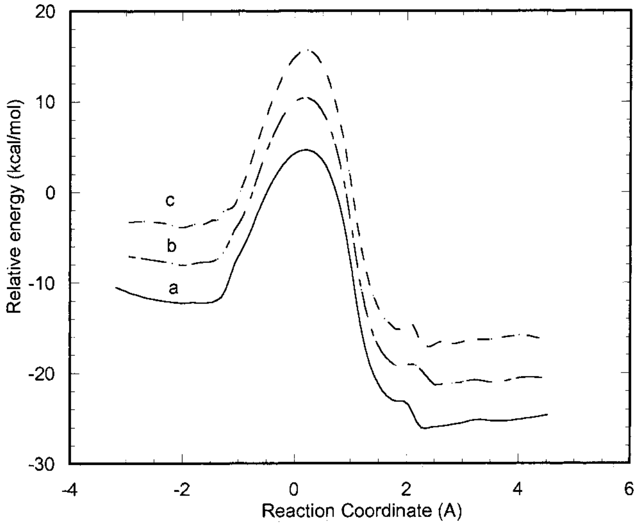

Figure 3. Reaction paths for the reactions of trimethylsulfonium ion with pyridine in the gas phase (a), in cyclohexane (b), and in DMSO (c).

Table 2. Critical Points in the Energy Profile for the Reaction of Trimethylsulfonium with Ammonia and with Pyridine in Cyclohexane[a]

entity	r(C−N)	r(S−C)	∠(HCS)	E_{rel}	% BS[b]	CT[c]
		$NH_3-(CH_3)_3S^+$				
reactants		1.822	108	0.0	0.0	0.000
ion−dipole complex	3.595	1.823	108	−6.1		0.015
second complex	3.104	1.827	109	−3.7	0.3	0.040
transition state	2.097	2.351	91	12.6	29.0	0.431
third complex	1.504	3.959		−16.3		0.682
products	1.510			−6.6		0.778
		Pyridine$-(CH_3)_3S^+$				
reactants		1.822	108	0.0	0.0	0.000
ion−dipole complex	3.627	1.824	108	−6.8		0.011
second complex	3.144	1.826	109	−4.9	0.2	0.032
transition state	2.090	2.319	92	10.6	27.3	0.421
third complex	1.486	4.009		−19.5		0.737
products	1.485			−15.2		0.781

[a] Bond distances in angstroms, bond angles in degrees, and energy in kilocalories per mole. The E_{rel} include the zero point energies. [b] Percent of the S−C bond stretching. [c] Charge transferred to the B:CH_3 moiety for B = ammonia, pyridine.

Here, the concentration of the charge onto a smaller ion (i.e., methylammmonium ion) facilitates the solvation process.

In the case of pyridine, the solvation of the products is not as effective because of the larger size of the pyridinium ion and its more diffuse charge density. Thus, the whole energy profile is shifted upward. The differential solvation between ionic species of different sizes is even reflected in the energies of the transition states for the two reactions. In the reaction with ammonia, the energy of the transition state is raised by 2.8 kcal/mol on going to cyclohexane solution, while in the reaction with pyridine, whose transition state is larger with a more diffuse charge, the energy increases by 5.7 kcal/mol.

The dielectric constant of cyclohexane is not large enough to either alter the path of the reaction or overcome the strong stabilizing effect of pyridine on the products, which is the reason the pyridine reaction exhibits the same exothermicity in the gas phase and in cyclohexane.

Table 3. Critical Points in the Energy Profile for the Reaction of Trimethylsulfonium with Ammonia and with Pyridine in Dimethyl Sulfoxide[a]

entity	r(C−N)	r(S−C)	∠(HCS)	E_{rel}	% BS[b]	CT[c]
		$NH_3-(CH_3)_3S^+$				
reactants		1.821	108	0.0	0.0	0.000
ion−dipole complex	3.571	1.822	108	−2.1		0.016
transition state	2.130	2.297	93	15.7	26.1	0.422
third complex	1.504	3.959		−17.6		0.685
products	1.501			−13.4		0.779
		Pyridine$-(CH_3)_3S^+$				
reactants		1.821	108	0.0	0.0	0.000
transition state	2.102	2.331	92	16.0	28.0	0.431
products	1.484			−12.8		0.783

[a] Bond distances in angstroms, bond angles in degrees, and energy in kilocalories per mole. The E_{rel} include the zero point energies. [b] Percent of the S−C bond stretching. [c] Charge transferred to the B:CH_3 moiety for B = ammonia, pyridine.

Figures 2 and 3 show the energy profile for the reaction with ammonia and pyridine in dimethyl sulfoxide. The relative energies of the critical points along the reaction path are shown in Table 3. The polarity of the solvent is now large enough to alter the reaction path. Almost all the intermediates found in cyclohexane solution have disappeared. Only the initial ion−dipole complex and the hydrogen-bonded complex (third complex) for the reaction with ammonia survive with energies −2.1 and −17.6 kcal/mol, respectively, below the reactants.

The transition states for both reactions have been destabilized with respect to the reactants. The destabilization is again larger in the pyridine reaction. The energies of the transition states have been increased by 11.1 and 5.4 kcal/mol with respect to that in the gas phase and cyclohexane, respectively. This is larger than the increments of 5.9 and 3.1 kcal/mol for the transition states for the reaction of ammonia in the same solvents.

The energy barrier is the same for the two reactions in dimethyl sulfoxide. This is again a result of the differential solvation of the two transition states.

(b) Water as the Solvent. The reaction field model would lead to the expectation that the solvent effects of DMSO and water would be essentially the same since in both cases $(\epsilon - 1)/(2\epsilon + 1)$ is close to the maximum value of 0.5. However, in many cases, these solvents give different solvent effects.[15] One of the more satisfactory ways of treating aqueous solutions is to make use of an explicit representation of the solvent that will better account for the interaction of water with the solute. Thus, we have chosen to use the free energy perturbation method of Jorgensen, which has been shown to reproduce experimental results for many reactions.[16]

A full characterization of the energy profile in the 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 in intervals of 0.05 Å in the C−N distance. This procedure produces essentially a movie of the reaction between the two critical points on the potential energy surface. ChelpG charges[17] were obtained for each of the structures along the path. 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 at a higher theoretical level.[18] 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 using the gas-phase reaction coordinate. Starting at the gas-phase transition-state geometry and moving

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Table 4. Reaction and Activation Free Energies in Gas Phase and Solution, 25 °C

	$\Delta G^{\ddagger}$			ΔG_r	
	ammonia	pyridine		ammonia	pyridine
phase	calc	calc	obs[a]	calc	calc
gas phase	17.1	13.3		−1.0	−18.0
cyclohexane	19.9	19.0		−8.0	−16.3
DMSO	23.0	24.4	(27.8)[b]	−14.8	−13.9
water	26.5	25.9	29.6	−12.1	−13.4

[a] Corrected to 25 °C using the calculated entropies of activation. [b] Measured value in acetone or acetonitrile at 55 °C.. The DMSO value would be expected to be the same.

Table 5. Position of the Transition States

	base	
medium	NH_3	pyridine
gas phase	0.337	0.219
cyclohexane	0.254	0.229
DMSO	0.167	0.229
water	0.188	0.219

Table 6. Transition-State Structures from Aqueous Solution BOSS Simulations

base	r(C−N)	r(C−S)	∠(HCS) (deg)
NH_3	2.193	2.381	92.2
pyridine	2.102	2.321	91.6

toward reactants, the free energy first increases, and after the new transition-state location is reached, it begins to decrease.

Table 4 shows the activation free energy and the reaction free energy for both reactions in all media, including water. The calculated activation free energies of the two reactions in water were only slightly larger than those in dimethyl sulfoxide. One might have expected a larger effect since the amines are stabilized by hydrogen bonding in aqueous solution, and this will be lost during the reaction. The destabilization trend as the solvent polarity increases is, however, observed, as the activation free energies are higher in this solvent. The reaction free energies here also follow the same trend as in the other solvents. Namely, it becomes more negative than in cyclohexane and gas phase for the reaction of ammonia and less negative for the pyridine reaction.

Table 5 shows the position of the transition state along the reaction path using the difference between the C−N and S−C bond distances as the reaction coordinate. For the ammonia reaction, the transition state is shifted to an earlier stage of the reaction as the polarity of the solvent increases. In contrast, no significant shift is observed in the position of the transition states for the pyridine reaction. Table 6 shows the structural parameters for the transition states obtained in the BOSS simulations. Despite the small effect of solvent polarity on the position of the transition state for the pyridine reaction, the values of the H−C−S angles suggest that both reactions have early transition states in water.

The relative energies given in Table 1 must be converted to free energies in order to compare them with the experimental data given below. This was done using the calculated entropy terms and zero-point energies derived from vibrational frequencies calculated at the B3LYP/6-31+G* level.[5] It has been found that vibrational frequencies are changed relatively little on going from the gas phase to a solution.[19] The relative energies in Tables 2 and 3 derived from the SCI-PCM calculations contain the energies of the species and the free energies of solvation. To convert these values to free energies, it was assumed that the entropy change would be the same in the gas phase and in solution. In at least one well-studied case, this has been shown to be the case.[20] It also was assumed that the changes in the cavity formation and dispersion terms along the reaction path will approximately cancel. There is evidence that this is an appropriate approximation.[21]

Table 7. Kinetics of the Reaction of Pyridine with Trimethylsulfonium Triflate at 55.0 °C

solvent	[pyridine] (M)	k_2 (L mol^{-1} s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
acetone	0.03−0.06	$(9.2 \pm 0.1) \times 10^{-7}$	28.3
acetonitrile	0.03−0.07	$(1.19 \pm 0.03) \times 10^{-6}$	28.1
D_2O	0.03−0.07	$(7.06 \pm 0.03) \times 10^{-8}$	30.0
D_2O[a]	0.03−0.07	$(3.64 \pm 0.03) \times 10^{-7}$	28.9

[a] Using trimethylsulfonium iodide.

Experimental Studies

The rate of reaction between pyridine and trimethylsulfonium triflate was studied in acetone, acetonitrile, and aqueous solutions at 55 °C. Pseudo-first-order kinetics were studied using pyridine as the limiting reagent, and the concentration of pyridine as a function of time was determined via ^{1}H NMR spectroscopy. The reaction was studied through one half-life, and linear plots of ln[pyridine] vs time were obtained. The resulting second-order rate constants and the free energies of activation are shown in Table 7. The free energies of activation in acetone and acetonitrile were essentially the same, as expected from the reaction field model, and they are in satisfactory agreement with the calculated value for DMSO, which also should give the same activation parameter. The small deviation between experiment and theory is not unexpected. The assumption that the change in activation entropy is the same in the gas phase and in solution is one potential source of the difference.

Although the calculated difference in activation free energy on going from DMSO to water as the solvent is relatively small (1.5 kcal/mol), it does agree very well with the experimental observation (1.8 kcal/mol).

When the reaction with pyridine in water was carried out using trimethylsulfonium iodide, the reaction occurred at a significantly faster rate. It seems likely that iodide ion initially reacts with the sulfonium salt to form methyl iodide,[22] which would rapidly react with pyridine to form the product.

Conclusions

The rather convoluted reaction path for the reaction of trimethylsulfonium with ammonia and with pyridine in gas phase is greatly simplified on going to a polar solvent. The activation free energy increases with the increasing polarity of the solvent as a consequence of the differential solvation between the compact ionic reactants and the transition states with a diffuse charge distribution. The spreading of the charge that stabilizes the transition state for pyridine, compared to ammonia, hinders its solvation leading to a larger increase of the activation free energy with the increase of the solvent's polarity. Differential solvation is also responsible for the

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opposite effect of the polarity of the solvent on the reaction free energy of both reactions. In the case of ammonia, the products are stabilized with respect to the reactants, increasing the exothermicity of the reaction, while with pyridine, the better solvation of the reactants leads to a much less exothermic reaction in solution than in gas phase.

The small change in the position of the transition state for the reaction with pyridine on going from one medium to another is remarkable and probably results from the dispersal of charge into the pyridine ring, making the medium effect on the position of the transition state relatively small.

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Supporting Information Available: A table of point groups, energies, zero-point energies, and Cartesian coordinates of the compounds in this study. This information is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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