Entropy of Activation for Reactions in the Condensed Phase: A Theoretical Study of the S_N2 Alkylation of Amines

Carlo Canepa,*[a] Marco Mosso,[a] Andrea Maranzana,[a] and Glauco Tonachini[a]

Keywords: Alkylation / Amines / Entropy of activation / Eyring equation / Solvation

A theoretical model for the evaluation of the entropy of activation for organic reactions in the condensed phase is proposed. The required partition functions for solutes are computed taking into account the hindered translation and rotation in the solvent cavity. The activation parameters for the alkylation of 3-bromopyridine by iodomethane in acetonitrile were obtained by regression of experimentally determined rate constants to the Eyring equation with different reference volumes. While the gas-phase reference volume affords an entropy of activation of $-40.7\ \mathrm{cal\,mol^{-1}\,K^{-1}}$, the corresponding calculated quantity at the MPW1K/CRENBL•6-311(+)G(d) level of theory is $-34.9\ \mathrm{cal\,mol^{-1}\,K^{-1}}$. The condensed-phase reference volume gives $\Delta S^{\neq} = -24.1\ \mathrm{cal\,mol^{-1}\,K^{-1}}$, in better agreement with the computed value of $-22.6\ \mathrm{cal\,mol^{-1}\,K^{-1}}$. Regressions with all reference volumes give an enthalpy of activation of around $13\ \mathrm{kcal\,mol^{-1}}$, while the computed potential-energy barriers lie between 16.8 and $18.4\ \mathrm{kcal\,mol^{-1}}$. Transition-state theory, making use of calculated potential-energy barriers and either gas-phase or condensed-phase partition functions, affords second-order rate constants for the reaction of CH_3I with 3-bromopyridine at least three orders of magnitude below the experimentally observed value. This discrepancy does not appear to be a consequence of a lack of accuracy of the pre-exponential factor, but might be caused by either overestimated calculated potential-energy barriers or the functional form of the Eyring equation.

Introduction

Statistical theories characterize the potential-energy difference between the transition structure and reactants associated with a chemical process as the most sensitive parameter in regulating reaction rates. Among these theories, the transition state theory (TST) in its classical[1] and variational (VTST)[2] formulation is the most popular, and its thermodynamic interpretation represents a framework for mechanistic considerations on most of the organic reactions that take place in the gas and condensed phases. Equation (1) gives the rate constant according to TST, once a suitable definition of the transition structure has been provided.

$$k_r(T) = \sigma \frac{kT}{h} \frac{z^{\neq}}{z^{A} z^{B}} V e^{-\beta \Delta E^{\neq}} \tag{1}$$

In Equation (1), σ represents the symmetry number, z the partition functions of the reactants and transition structure, $V = N{\cdot}v^{A}v^{B}/v^{\neq}$ (the ratio of the molar volumes), $\Delta E^{\neq}$ is the potential-energy barrier, and $\beta = (kT)^{-1}$. In the gas phase all molar volumes are equal and we have $V = RT/P$. Considerable effort has been expended in the evaluation of the potential-energy barrier ($\Delta E^{\neq}$) from electronic structure theory (both by ab initio and density functional methods) for a wide variety of reactions. While a widely accepted formulation for the volume and the partition functions in the gas phase is available within the rigid rotor–harmonic oscillator approximation, the corresponding quantities in the condensed phase do not benefit from the same standardization for the calculation of thermodynamic functions. In their theoretical and experimental study of four paradigmic Menschutkin reactions, Wiberg and co-workers[3] have pointed out the lack of a satisfactory theoretical treatment of reactions in solution in the literature. This work aims to calculate activation parameters in the condensed phase from the accurate partition functions for solutes, as exploited in a previous study.[4] The proposed method is general, computationally affordable, and applicable to most organic reactions in solution. The procedure will be exemplified using the widely studied S_N2 alkylation of amines, a reaction that has attracted interest since its discovery in 1890 because of the dramatic dependence of its rate on the polarity of the solvent. Consequently, the Menschutkin reaction has been extensively studied both from the experimental and theoretical points of view. A number of papers have appeared concerning the potential-energy and free-energy profiles of the Menschutkin reaction in various environments.[3,5–9] The paradigm methods for theoretical calculations in the condensed phase rely on either the polariz-

---

[a] Dipartimento di Chimica Generale e Organica Applicata, Università di Torino,
Corso Massimo d'Azeglio 48, 10125 Torino, Italy

DOI: 10.1002/ejoc.200500063

able continuum models (SCRF) developed over the years by Onsager, Tomasi, and Barone, where the solute is embedded in a cavity with a specified dielectric constant and shape, or dynamics simulations. The free energy of activation calculated in ref.[3] by Monte Carlo simulations in various solvents is in good agreement with the SCRF model. The high dipole moment of the transition structure for the alkylation of amines is thought to motivate the high degree of sensibility of rates on the polarity and polarizability of the medium. This behavior suggests this reaction as a particularly suitable test for a model of processes in the condensed phase. Gordon and co-workers[6] have studied the effect of water molecules on the energy profile of the alkylation of ammonia by methyl bromide both by explicit ab initio treatment of solvent molecules in a supermolecule approach and by the effective fragment potential (EFP) method. Both methods agree on a dramatic reduction of the reaction barrier induced by interactions with the solvent with respect to the gas-phase process. Amovilli and co-workers[7] have incorporated the polarizable continuum model into the CASSCF framework to obtain solvation and activation free energies that are in good agreement with experimental values and other ab initio and density-functional methods. Another example of how the environment affects the activation parameters of the Menschutkin reaction comes from Schlegel and co-workers,[8]who studied the simple alkylation of ammonia by methyl chloride in a carbon nanotube, finding a significant reduction in the potential-energy barrier with respect to the gas-phase process. The extensive experimental study of the Menschutkin reaction by Arnett and co-workers[9] is the basis for the present study. Individual rate constants at various temperatures, which are indispensable quantities in order to be able to test partition functions alternative to the conventional gas-phase formulation, are made available in this study.

Results and Discussion

Model for the Condensed Phase

Calculations of the thermodynamic and kinetic properties of polyatomic molecules in the condensed phase were carried out with accurate partition functions with translational and rotational components corrected for the specific interactions between the solute and the solvent cavity. The electronic and vibrational parts are assumed to be identical in the gas and the condensed phase. While we refer to ref.[4] for the detailed form of the various contributions to the total molecular partition function z, we briefly outline here the contribution of the condensed-phase partition function, which is responsible for the largest correction with respect to the gas phase, that is the definition of a free volume of translation according to the Lennard-Jones–Devonshire theory of liquids.[10] The free volume of translation replaces the perfect gas expression RT/P_0 and is calculated as

$$v = 4\pi \int_0^x dr\, r^2 e^{-\beta u(r,x)} \tag{2}$$

where the function $u(r,x)$ in Equation (2) gives the potential of the particle at a distance r from the equilibrium position in a cavity of radius x. The partition functions for four common liquids were used in ref.[4] to calculate molar enthalpies and entropies of vaporization and heat capacities. While the molar enthalpies and entropies of vaporization were found to reproduce well the experimental values, the corresponding molar heat capacities were affected by a larger relative error as a consequence of their dependence on the second derivative of z with respect to the temperature.

Parameters of Activation

Regressions of experimental data at various temperatures to the expression for the bimolecular rate constant are usually carried out making use of the thermodynamic interpretation of the Eyring equation (see Atkins[11] and McQuarrie[12])

$$k_r = \frac{kT}{h\rho_0} e^{\Delta S^{\neq}/k} e^{-\beta \Delta H^{\neq}} \tag{3}$$

by optimizing the two parameters of activation $\Delta S^{\neq}$ (entropy) and $\Delta H^{\neq}$ (enthalpy). However, as pointed out by Abraham,[13] different reference concentrations (ρ_0) give widely different values for the entropy of activation of the Menschutkin reaction. In order to compare the activation parameters calculated according to the condensed-phase partition functions and the corresponding experimental values, the enthalpy and entropy of activation for the reaction of CH_3I with 3-bromopyridine in acetonitrile were obtained by fitting the experimental rate constants to Equation (3) with consistent reference volumes.

The values relative to the standard states ($1/\rho_0$) 1 L mol^{-1}, RT/P_0 (24.5 L mol^{-1} at 1 bar and 298 K), and $N{\cdot}v^A v^B/v^{\neq}$ are summarized in Table 1. The quantity v^X represents the volume in the condensed phase corresponding to a free translation of species X, and is given by Equation (2). For each regression, the relative standard deviation, σ, of the calculated values $k_r(T_i)$ with respect to the experimental points $\bar{k}_r(T_i)$ is also reported.

$$\sigma = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left[1 - \frac{\bar{k}(T_i)}{k_r(T_i)}\right]^2} \tag{4}$$

In Equation (4) the sum is over the number, n, of experimental points.

While all standard states afford similar values for the enthalpy of activation, the corresponding entropy is more sensitive to the particular choice of V. Table 2 reports the po-

Table 1. Activation parameters for the reaction of CH_3I with 3-bromopyridine in acetonitrile. The values were obtained by regression of experimental rate constants at various temperatures to Equation (3). The ratio $\nu^A\nu^B/\nu^{\neq}$ was calculated at the MPW1K and the B3LYP (in parentheses) levels of theory.

Reference volume	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [cal mol^{-1} K^{-1}]	σ
RT/P_0	13.16	–40.656	1.495×10^{-2}
1 L mol^{-1}	13.75	–32.335	1.421×10^{-2}
1 L mol^{-1}[a]	13.82	–32.090	1.439×10^{-2}
$N\cdot\nu^A\nu^B/\nu^{\neq}$	12.88 (12.83)	–24.125 (–26.841)	1.533×10^{-2} (1.549×10^{-2})

[a] Taken from ref.[9]

tential-energy barriers obtained by regression of the experimental rate constants to Equation (1), with $\Delta E^{\neq}$ as the only variable. The additional constraint of making the dependence of the factor $z^{\neq}V/(z^Az^B)$ on temperature explicit affords slightly higher values of the relative standard deviation with respect to the regressions reported in Table 1, where the temperature dependence of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is neglected. It is worth stressing the fact that the regression to Equation (1) does not rely on this approximation, as Equation (3) does, and is therefore physically more sound. Notably, the value of σ for the condensed-phase reference volume in Table 2 is one order of magnitude lower than the ideal-gas value, which is an indication that the volume defined by Equation (2) is more adequate to the description of processes in solution.

Table 2. Potential-energy barrier for the reaction of CH_3I with 3-bromopyridine in acetonitrile. The values were obtained by regression of experimental rate constants at various temperatures to Equation (1). The partition functions z and reference volumes V were calculated at the MPW1K and the B3LYP (in parentheses) levels of theory.

Reference volume	$\Delta E^{\neq}$ [kcal mol^{-1}]	σ
RT/P_0	13.69 (13.86)	1.412×10^{-1} (1.506×10^{-1})
$N\cdot\nu^A\nu^B/\nu^{\neq}$	14.42 (14.65)	4.354×10^{-2} (5.862×10^{-2})

Figure 1 reports the geometries and relative energies of iodomethane (**1**), 3-bromopyridine (**2**), and the transition structure for the methyl transfer (TS-**3**). The gas-phase potential-energy barrier of 26.60 kcal mol^{-1} at the MPW1K/CRENBL·6-311(+)G(d) level of theory points out that specific modeling of the solvent is in order for this reaction. In fact, the interaction with one molecule of acetonitrile per molecule of reagent is sufficient to lower the potential-energy barrier to 17.99 kcal mol^{-1} at the same level of theory (structures **4**, **5**, and TS-**6** in Figure 2). Reoptimizing both the gas-phase and the solvated structures with the B3LYP functional and the same basis set does not significantly alter the energy profile. Both the supermolecule approach of Figure 2 and the corresponding COSMO calculation afford earlier transition structures with respect to the gas phase. Table 3 lists the parameters used to construct the partition functions in the condensed phase. The vibrational frequencies and force constants for the solute in the cavity were obtained by computing the analytical second derivatives of the potential energy of the structures in Figure 2. Cavity radii and energies of interaction between the solutes and the cavity were obtained from SCRF calculations within the COSMO approximation.

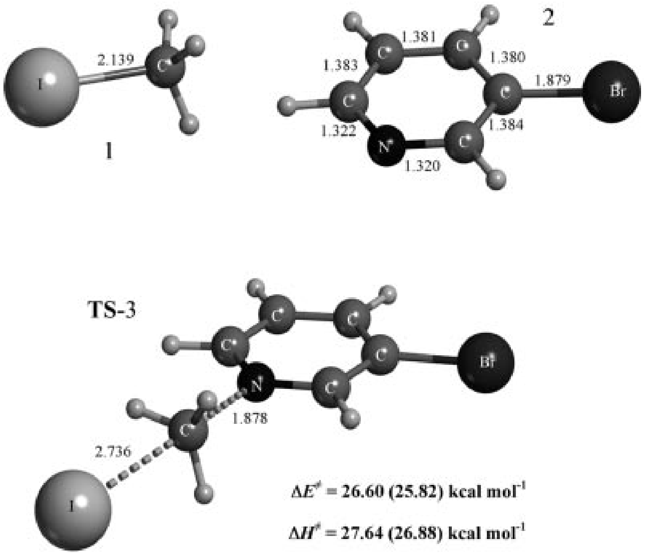

Figure 1. Potential-energy barrier ($\Delta E^{\neq}$) and enthalpy of activation at 298 K ($\Delta H^{\neq}$) for the gas-phase alkylation of 3-bromopyridine by iodomethane at the MPW1K/CRENBL·6-311(+)G(d) and the B3LYP/CRENBL·6-311(+)G(d) (in parentheses) levels of theory. Geometries are fully optimized at both levels; the reported MPW1K/CRENBL·6-311(+)G(d) distances are given in Å.

Although most of the parameters needed by the theory may easily be obtained either by explicit solvation by a lim-

Table 3. Parameters used for the evaluation of the partition functions of the solvated structures at the MPW1K and B3LYP (in parentheses) levels of theory. The frequencies of intermolecular modes were obtained with the supermolecule approach, and the CPCM approximation affords the remaining parameters.

Parameter	CH_3I	3-Br-pyridine	TS
Frequencies [cm^{-1}]	59.6616 (35.5058)	40.5105 (39.9482)	61.7699 (60.1722)
Force constants [Nw m^{-1}]	0.81 (0.41)	0.93 (0.78)	1.97 (1.87)
Interaction energies [kcal mol^{-1}]	1.95 (2.01)	2.87 (2.99)	5.23 (5.48)
Cavity radius [Å]	3.67 (3.90)	4.23 (4.54)	5.03 (5.34)

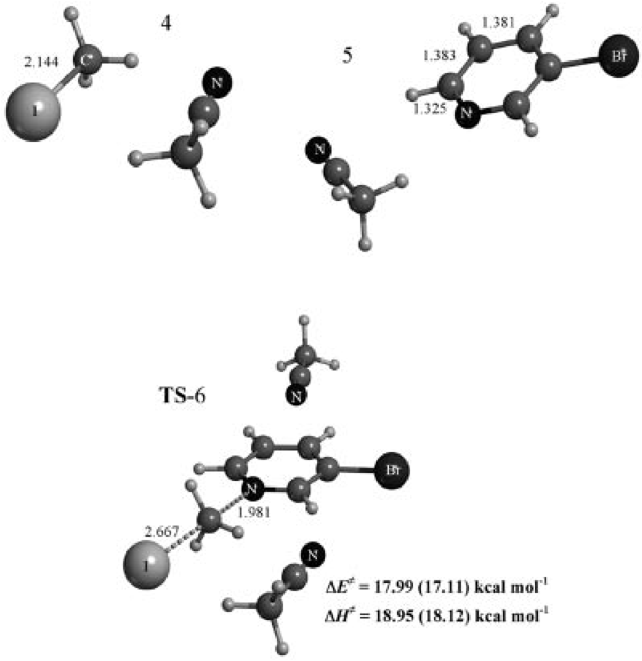

Figure 2. Potential-energy barrier ($\Delta E^{\neq}$) and enthalpy of activation at 298 K ($\Delta H^{\neq}$) for the alkylation of solvated 3-bromopyridine by iodomethane. Geometries are optimized at the MPW1K/CRENBL·6-311(+)G(d) level; distances are in Å. Values at the B3LYP/CRENBL·6-311(+)G(d) level of theory are reported in parentheses.

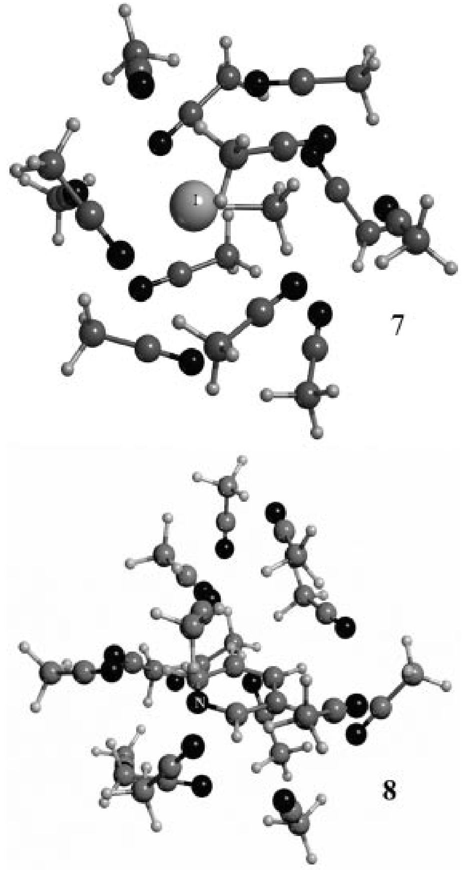

Figure 3. Structures of the fully solvated reagents for the alkylation of pyridine by iodomethane ($CH_3I{\cdot}12CH_3CN$, $C_5H_5N{\cdot}15CH_3CN$). Geometries are optimized at the MPW1K/CRENBL·6-311(+)G(d)·STO-3G level.

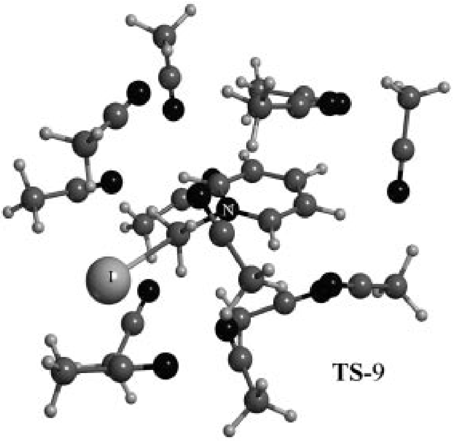

Figure 4. Structure of the fully solvated transition structure for the alkylation of pyridine by iodomethane ($TS{\cdot}13CH_3CN$). The geometry is optimized at the MPW1K/CRENBL·6-311(+)G(d)·STO-3G level with the N–C and C–I distances constrained to the corresponding gas-phase values.

ited number of solvent molecules or by SCRF-based approximations, explicit consideration of a relatively large number of solvent molecules is necessary to calculate the number of molecules directly interacting with the solute, a parameter involved in the definition of the free volume of translation given by Equation (2) through the potential energy term $u(r,x)$. To this purpose, clusters **7** and **8** of solvated iodomethane (12 acetonitrile molecules), pyridine (15 acetonitrile molecules), and the transition structure for the methyl transfer TS-**9** (13 acetonitrile molecules) were optimized with mixed basis-sets for solute and solvent (Figures 3 and 4). The largest components of the transition eigenvector (i.e. the N–C and C–I distances) were fixed at the gas-phase-optimized values, subsequently optimizing and adding acetonitrile molecules until a whole first shell of solvation was in evidence. Although the solvated structures **7**, **8**, and TS-**9** might not be absolute minima, it is very likely that the coordination number would be fairly constant if other energetically close minima or other values of the N–C and C–I distances were considered.

Table 4 gives the calculated factors $(kT/h){\cdot}z^{\neq}{\cdot}V/(z^{A}z^{B})$ at 298 K; the potential-energy barriers are reported for the Menschutkin reaction. The corresponding values obtained by regression of the experimental rate constants to the equation $k_r = \alpha{\cdot}e^{-\beta\Delta E^{\neq}}$ (with α and $\Delta E^{\neq}$ treated as parameters) are 1.43×10^{3} m^3 mol^{-1} s^{-1} and 14.34 kcal mol^{-1}, respectively. While the computed value of the parameter α, including both molecular partition functions and the molar volume, is affected by a larger absolute relative error (61% on average) with respect to the potential-energy barrier, the error in the latter (28% averaged on the condensed-phase methods) is more responsible for the poor reproduction of the experimental rate constants (Table 5). The above quantities have been evaluated making use of the MPW1K/

Table 4. Calculated gas-phase partition functions, pre-exponential factor $a = (kT/h)\cdot z^{\neq}\cdot V/(z^{A}z^{B})$ [$m^3\,mol^{-1}\,s^{-1}$] at 298 K, and potential-energy barrier [$kcal\,mol^{-1}$] for the species involved in the Menschutkin reaction. A regression of the experimental rate constants for the reaction of CH_3I with 3-bromopyridine in acetonitrile to the expression $k_r = a\cdot e^{-\beta\Delta E^{\ddagger}}$ affords values of $1.4346\times10^{3}\,m^3\,mol^{-1}\,s^{-1}$ and 14.34 $kcal\,mol^{-1}$ for a and $\Delta E^{\neq}$, respectively.

Level of theory	CH_3I	3-Br-pyridine	TS	a	$\Delta E^{\neq}$
MPW1K	1.8007×10^{18}	3.7352	4.5872×10^{-14}	6.2392×10^{2}	26.60
B3LYP	6.4017×10^{18}	81.0104	4.6141×10^{-12}	8.1396×10^{2}	25.82
MPW1K CPCM[a]	1.9140×10^{18}	3.4679	3.4189×10^{-14}	4.7121×10^{2}	18.42
B3LYP CPCM[a]	6.6429×10^{18}	69.4111	3.1618×10^{-12}	6.2734×10^{2}	16.84
MPW1K CPCM[b]	1.6813×10^{13}	1.2853×10^{-5}	2.5722×10^{-20}	9.7132×10^{2}	18.42
B3LYP CPCM[b]	1.6082×10^{14}	3.0724×10^{-4}	2.3949×10^{-18}	2.3973×10^{3}	16.84
MPW1K SM[a]	3.3072×10^{2}	5.0439×10^{-17}	2.7813×10^{-47}	1.5253×10^{2}	17.99
B3LYP SM[a]	4.8791×10^{3}	5.2866×10^{-15}	3.3216×10^{-44}	1.1781×10^{2}	17.11

[a] Computed with the gas-phase volume RT/P_0. [b] Computed with the condensed-phase volume $N\cdot v^{A}v^{B}/v^{\neq}$.

CRENBL·6-311(+)G(d) and B3LYP/CRENBL·6-311(+)G(d) levels of theory both in the gas phase and with two approximations modeling the potential-energy barrier in the condensed phase, i.e. the CPCM and the supermolecule (SM) approach. The COSMO approximation of the structures in Figure 1 yields a potential-energy barrier very close to the corresponding barrier of the explicitly solvated solutes in Figure 2 (Table 4). The potential-energy barriers calculated in the gas phase appear to be overestimated by both the MPW1K and B3LYP functionals. The solvation method based on the polarizable continuum model affords lower values, although they are still in excess of the experimental value by around 3 $kcal\,mol^{-1}$. The quality of both calculated partition functions and the potential-energy barrier may also be determined by computing absolute rate constants according to the Eyring equation [Equation (1)]. The ratios of calculated rate constants with various levels of theory and reference volumes with the observed value are at least three orders of magnitude too small (Table 5). This fact, given the good quality of the pre-exponential factors, has either to be attributed to an overestimated potential-energy barrier or to the inability of Equation (1) to reproduce observed rate constants. Table 6 reports the calculated values of the entropy of activation for the reaction of CH_3I with 3-bromopyridine. While entropies of activation calculated with gas-phase partition functions range from –38.3 to –34.3 $cal\,mol^{-1}\,K^{-1}$, the corresponding values computed with the condensed-phase partition functions range from –24.9 to –22.6 $cal\,mol^{-1}\,K^{-1}$. While Equation (3) has its limitations due to the different standard states in the gas and the liquid phase, it is the elected procedure to obtain the entropy of activation experimentally. The relative error of the computed entropy of activation at 298 K for the reference volume RT/P_0 at the MPW1K-CPCM level, with respect to the value obtained by regression to Equation (3) (Table 1), is 12.99%. For comparison, the corresponding error for the condensed-phase reference volume $N\cdot v^{A}v^{B}/v^{\neq}$ is lowered to 6.12%. Also, the data in Table 2 provide evidence to the effect that the condensed-phase reference volume defined in Equation (2) gives a better description of the observed rate constants. Making use of this volume, we obtain an entropy of activation of 25.5 $cal\,mol^{-1}\,K^{-1}$ as an average of the MPW1K and B3LYP methods for the evaluation of the volumes in Table 1. This result is consistent with the first-principle average value of 23.8 $cal\,mol^{-1}\,K^{-1}$ of Table 6.

Table 5. Ratios of the rate constants, calculated at 298 K according to Equation (1), to the corresponding experimental value at the same temperature ($3.59\times10^{-4}\,L\,mol^{-1}\,s^{-1}$). The two columns give data obtained with the gas-phase and condensed-phase reference volumes and partition functions.

Method	$V = RT/P_0$	$V = N\cdot v^{A}v^{B}/v^{\neq}$
MPW1K CPCM	4.12×10^{-5}	8.52×10^{-5}
B3LYP CPCM	7.91×10^{-4}	3.04×10^{-3}
MPW1K SM	2.76×10^{-5}	–
B3LYP SM	9.42×10^{-5}	–

Conclusions

The rate constants at different temperatures for the reaction of CH_3I with 3-bromopyridine in acetonitrile have been used for regression to the Eyring equation with various reference volumes. The obtained energy barriers are similar in all cases, while the entropy of activation exhibits

Table 6. Calculated absolute and relative entropies [$cal\,mol^{-1}\,K^{-1}$] of structures **1**, **2**, and TS-**3** at 298 K.

Level of theory	Partition function	$S_{(MeI)}$	$S_{(3\text{-Br–pyridine})}$	$S_{(TS)}$	$\Delta S^{\neq}$
MPW1K	gas phase	62.671	78.181	105.992	–34.860
B3LYP	gas phase	62.913	78.806	107.456	–34.263
MPW1K CPCM	gas phase	62.674	78.235	105.533	–35.376
B3LYP CPCM	gas phase	62.921	78.769	106.677	–35.013
MPW1K SM	gas phase	102.789	113.397	178.213	–37.973
B3LYP SM	gas phase	103.088	114.397	179.160	–38.325
MPW1K CPCM	condensed phase	45.411	58.805	81.567	–22.649
B3LYP CPCM	condensed phase	47.907	59.629	82.672	–24.864

a marked sensitivity to the particular choice of the reference volume.

The partition functions for the condensed phase devised by restricting free translation and rotation have been used to compute the entropies of activation for the Menschutkin reaction, obtaining significantly lower values with respect to the corresponding quantity calculated with the gas-phase partition functions.

Both the gas-phase and condensed-phase approaches afford absolute rate constants that are underestimated by a few orders of magnitudes with respect to the observed value. This discrepancy remains unresolved at this point, but it might be due either to a systematic error of quantum calculations in estimating the potential-energy barrier or the inability of Equation (1) to accurately describe the dependency of rate constants from $\Delta E^{\neq}$.

Computational Methods

Quantum chemistry calculations were carried out using the GAUSSIAN 98 suite of programs,[14] utilizing redundant internal coordinate-geometry optimization.[15] All structures were fully optimized at the MPW1K[16] and B3LYP[17] levels of theory. Throughout this study the CRENBL[18] basis set was used for the iodine atom and the 6-311G(d) set for the other atoms of the substrates CH_3I and 3-bromopyridine. A set of diffuse functions with exponent 0.0639 was also added to the nitrogen atom of pyridine. This combination of basis sets is designated CRENBL·6-311(+)-G(d). For clusters with more than two molecules of CH_3CN, the atoms in the solvent molecules were assigned the STO-3G basis set. This combination of basis sets is named CRENBL·6-311(+)G(d)·STO-3G. Vibrational-frequency calculations were used to characterize the stationary points as either minima or first-order saddle points at the level indicated. Thermodynamic quantities in the gas phase were evaluated at 298 K and 1 bar within the rigid rotor-harmonic oscillator approximation.[19] Solvation calculations based on continuum models were carried out with the conductor solvation (COSMO) method.[20] Molecular graphics were obtained with the program Moldraw.[21]

Acknowledgments

The authors are thankful to Prof. Piero Ugliengo for many helpful discussions on this subject.

---

[1] S. C. Tucker, D. G. Truhlar, *New Theoretical Concepts for Understanding Organic Reactions* (Eds.: J. Bertran, I. G. Csizmadia), Kluwer Academic Publishers, Dordrecht, **1989**, pp. 291–346.

[2] a) D. G. Truhlar, B. C. Garret, *Acc. Chem. Res.* **1980**, *13*, 440–448; b) G. Gershinsky, E. Pollak, *J. Chem. Phys.* **1995**, *103*, 8501–8512; c) W.-P. Hu, Y.-P. Liu, D. G. Truhlar, *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1715–1725; d) D. G. Truhlar, B. C. Garrett, S. J. Klippenstein, *J. Phys. Chem.* **1996**, *100*, 12771–12800.

[3] H. Castejon, K. B. Wiberg, *J. Am. Chem. Soc.* **1999**, *121*, 2139–2146.

[4] C. Canepa, *J. Chem. Phys.* **2001**, *115*, 7592–7598.

[5] a) M. Solà, A. Lledós, M. Duran, J. Bertrán, J.-L. M. Abboud, *J. Am. Chem. Soc.* **1991**, *113*, 2873–2879; b) T. Mineva, N. Russo, E. Sicilia, *J. Comput. Chem.* **1998**, *19*, 290–299; c) K. Jug, C. Kölle, F. Neumann, *J. Comput. Chem.* **1999**, *20*, 301–304.

[6] S. P. Webb, M. S. Gordon, *J. Phys. Chem. A* **1999**, *103*, 1265–1273.

[7] C. Amovilli, B. Mennucci, F. M. Floris, *J. Phys. Chem. B* **1998**, *102*, 3023–3028.

[8] M. D. Halls, H. B. Schlegel, *J. Phys. Chem. B* **2002**, *106*, 1921–1925.

[9] E. M. Arnett, R. Reich, *J. Am. Chem. Soc.* **1980**, *102*, 5892–5902.

[10] a) J. E. Lennard-Jones, A. F. Devonshire, *Proc. R. Soc. London, Ser. A* **1937**, *163*, 53–70; b) J. E. Lennard-Jones, A. F. Devonshire, *Proc. R. Soc. London, Ser. A* **1938**, *165*, 1–11; c) J. E. Lennard-Jones, A. F. Devonshire, *Proc. R. Soc. London, Ser. A* **1939**, *169*, 317–338.

[11] P. Atkins, J. de Paula, *Physical Chemistry*, Oxford University Press Inc., New York, **2002**.

[12] D. A. McQuarrie, J. D. Simon, *Physical Chemistry, A Molecular Approach*, University Science Books, Sausalito, CA, **1997**.

[13] M. H. Abraham, A. Nasehzadeh, *J. Chem. Soc., Chem. Commun.* **1981**, 905–906.

[14] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Jr., Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian*, Gaussian, Inc., Pittsburgh PA, **1998**.

[15] C. Peng, P. Y. Ayala, H. B. Schlegel, M. J. Frisch, *J. Comput. Chem.* **1996**, *17*, 49–56.

[16] a) B. J. Lynch, P. L. Fast, M. Harris, D. G. Truhlar, *J. Phys. Chem. A* **2000**, *104*, 4811–4815; b) B. J. Lynch, D. G. Truhlar, *J. Phys. Chem. A* **2001**, *105*, 2936–2941.

[17] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) P. J. Stevens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[18] M. M. Hurley, *J. Chem. Phys.* **1986**, *84*, 6840–6853.

[19] D. A. McQuarrie, *Statistical Thermodynamics*, University Science Books, Mill Valley, CA, **1973**.

[20] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995–2001.

[21] a) P. Ugliengo, D. Viterbo, G. Borzani, *J. Appl. Crystallogr.* **1988**, *21*, 75–75; b) P. Ugliengo, D. Viterbo, G. Chiari, *Z. Crystallogr.* **1993**, *207*, 9–23.

Received: January 26, 2005