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Effect of Substituents on Activation Parameters in Aliphatic S_N2 Reactions. A DFT Study

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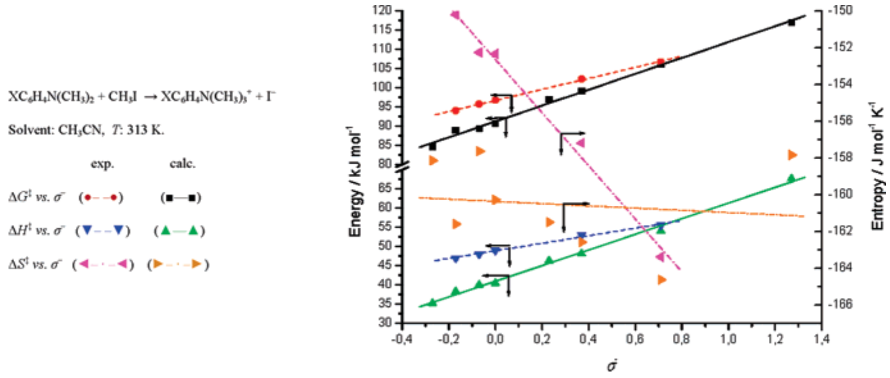

The activation parameters and optimized structures of the reactants and transition states in the S_N2 reactions of substituted pyridines and *N*,*N*-dimethylanilines with methyl iodide were computed at the DFT level in different solvents. The measured and calculated $\Delta G^\ddagger/\Delta H^\ddagger/\Delta S^\ddagger$ versus σ plots proved to be linear, and their slopes, the $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ reaction constants, were determined. The least solvent-dependent $\delta\Delta G^\ddagger$ reaction constants can be computed with acceptable accuracy. The calculated $\delta\Delta S^\ddagger$ data decrease only very slightly with the jointly increasing electron-withdrawing effect of the substituents and tightness of the transition states. The measured $\delta\Delta S^\ddagger$ values are influenced mainly by the change of solvation in the reactions, and $\delta\Delta H^\ddagger$ is also influenced by the reorganization of the solvent. Consequently, the experimental and calculated $\delta\Delta S^\ddagger$ and $\delta\Delta H^\ddagger$ reaction constants may deviate considerably from each other. In dipolar aprotic solvents the measured $\delta\Delta S^\ddagger$ was less than zero, and in protic solvents it was greater than zero. The ordering of the solvent molecules around the transition state with increasing charge is increased in the former but decreased in the latter media, as compared to the bulk of the solvents. The calculated $\Delta G_o^\ddagger$, $\Delta H_o^\ddagger$, and $\Delta S_o^\ddagger$ parameters of the unsubstituted compounds agree relatively well with the experimental data for reactions of neutral molecules in dipolar aprotic solvents (e.g., $XC_6H_4N(CH_3)_2 + CH_3I$). On the other hand, the measured and calculated activation parameters may show considerable deviations for reactions of ions (e.g., $XC_5H_4NCH_3^+ + I^-$) and for any reaction in protic solvents.

Introduction

In previous papers[1–3] the $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ reaction constants were defined (eqs 1−3) on the analogy of the Hammett equation[4,5] (eq 4).

$$\Delta G^\ddagger = \delta\Delta G^\ddagger\sigma + \Delta G_o^\ddagger \tag{1}$$

$$\Delta H^\ddagger = \delta\Delta H^\ddagger\sigma + \Delta H_o^\ddagger \tag{2}$$

$$\Delta S^\ddagger = \delta\Delta S^\ddagger\sigma + \Delta S_o^\ddagger \tag{3}$$

$$\log k = \rho\sigma + \log k_o \tag{4}$$

$\Delta G^\ddagger$, $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G_o^\ddagger$, $\Delta H_o^\ddagger$, $\Delta S_o^\ddagger$ are the activation parameters obtained for the substituted and unsubstituted compounds, respectively, and σ is the substituent constant, which gives the best correlation with the Hammett equation. The $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ reaction constants are the changes of the

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corresponding parameters per unit change of the σ constant. $\delta\Delta G^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ are given in kJ mol^{-1} σ^{-1}, but $\delta\Delta S^{\ddagger}$ is in J mol^{-1} K^{-1} σ^{-1} units. The relationships between the $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, $\delta\Delta S^{\ddagger}$, and ρ reaction constants and the temperature (T) of experiments are given in eqs 5 and 6:

$$\delta\Delta G^{\ddagger} = \delta\Delta H^{\ddagger} - T\delta\Delta S^{\ddagger} \qquad (5)$$

$$\delta\Delta G^{\ddagger} = -2.303RT\rho \qquad (6)$$

The $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, and $\delta\Delta S^{\ddagger}$ reaction constants were divided[1,3] into internal and external parts (eqs 7−9), according to the chemical reaction and the solvation process, respectively, by analogy with the theory of Heppler.[6−8]

$$\delta\Delta G^{\ddagger} = \delta\Delta G_{\text{int}}{}^{\ddagger} + \delta\Delta G_{\text{ext}}{}^{\ddagger} \qquad (7)$$

$$\delta\Delta H^{\ddagger} = \delta\Delta H_{\text{int}}{}^{\ddagger} + \delta\Delta H_{\text{ext}}{}^{\ddagger} \qquad (8)$$

$$\delta\Delta S^{\ddagger} = \delta\Delta S_{\text{int}}{}^{\ddagger} + \delta\Delta S_{\text{ext}}{}^{\ddagger} \qquad (9)$$

If remote substituents modify the structure of the transition state (TS) to only a negligible extent, i.e., the internal entropy of activation is independent of the substituents ($\delta\Delta S_{\text{int}}{}^{\ddagger} \approx 0$)[3,9] and the contribution of the solvent reorganization to the change of free energy of activation is near zero (eq 10),[10−12] eqs 7−9 can be reduced to eqs 11−13:

$$\delta\Delta G_{\text{ext}}{}^{\ddagger} = \delta\Delta H_{\text{ext}}{}^{\ddagger} - T\delta\Delta S_{\text{ext}}{}^{\ddagger} \approx 0 \qquad (10)$$

$$\delta\Delta G^{\ddagger} \approx \delta\Delta H_{\text{int}}{}^{\ddagger} \qquad (11)$$

$$\delta\Delta H^{\ddagger} \approx \delta\Delta H_{\text{int}}{}^{\ddagger} + T\delta\Delta S_{\text{ext}}{}^{\ddagger} \qquad (12)$$

$$\delta\Delta S^{\ddagger} \approx \delta\Delta S_{\text{ext}}{}^{\ddagger} \qquad (13)$$

This means that the $\delta\Delta G^{\ddagger}$ reaction constant is approximately equal to $\delta\Delta H_{\text{int}}{}^{\ddagger}$, which is the change of enthalpy of activation for the reaction, and $\delta\Delta S^{\ddagger}$ is influenced mainly by the change of the solvation with the substituents. The $\delta\Delta H^{\ddagger}$ parameter is less characteristic of the reaction as it depends both on enthalpy and entropy changes. Similarly to the Hammett equation, eqs 1−3 and 5−13 can also be used for equilibria, with $\Delta G°$, $\Delta H°$, and $\Delta S°$ instead of the activation parameters.

We intend to investigate the change of activation parameters with the substituents in aliphatic S$_N$2 reactions proceeding in different solvents by the use of nucleophiles containing a substituted aromatic ring. The mechanism of the S$_N$2 reactions was already widely studied by physical organic chemical methods and by quantum chemical calculations, both in the gas phase and in solutions. The effects of the structure of substrates, nucleophiles, leaving groups, and the media were thoroughly investigated by kinetic measurements.[13−17] Detailed calculations were performed on the energy profile of the reactions of simple substrates with different nucleophiles[16−18] and on the relationship between the structure of the TS and the kinetic isotope effect.[19,20] The solvent effect was analyzed by using the continuum model or by taking the specific interaction of solute and solvent molecules into consideration.[17,18]

We have performed DFT calculations on some reactions in which different types of electronic interactions take place between the substituted aromatic ring and the reaction center. Optimized structures and thermodynamic parameters for the reactants and TSs were computed. The calculated activation parameters were compared with the experimental data in order to support the earlier suppositions[1,3] concerning the independence of the internal part of entropy of activation on remote substituents ($\delta\Delta S_{\text{int}}{}^{\ddagger} \approx 0$) and the equivalence of the dependences of free energy and internal enthalpy of activation on substituents (eq 11). The solvents have been taken into consideration as a continuum; the calculated entropy values are practically equal for any media with those obtained for the gas phase. The entropy changes connected with the rearrangement of the solvent molecules could not be computed because of the limitations of the continuum solvent models. Earlier, the measured changes of entropy of activation with the substituents were discussed qualitatively, and the desolvation of the reactants, the solvation of the TS, and the reorganization of the solvent molecules were taken into consideration.[1,3] In aprotic solvents, the desolvation of a reactant has a positive contribution to the measured $\Delta S^{\ddagger}$, whereas the formation of the solvation shell of the TS has a negative contribution. The solvation or desolvation of dipolar or especially charged species gives rise to a high change of the orientation of solvent molecules and a great corresponding change of entropy of activation in the less polar and less ordered aprotic solvents. On the other hand, in protic solvents $\Delta S^{\ddagger}$ changed in an opposite way with the substituents as in aprotic media. The explanation offered for these observations has been that the solvent molecules in the second solvation shell of large dipolar molecules or ions are less ordered in protic media than in the bulk of the solvent.[3]

Calculation of $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, and $\delta\Delta S^{\ddagger}$ Reaction Constants from Experimental Data

The $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, and $\delta\Delta S^{\ddagger}$ reaction constants were determined[1,3] either from the dependence of the activation parameters on the substituent constants[21] (eqs 1−3) or from $\delta\Delta G^{\ddagger}$ and the β isokinetic temperature (eqs 14 and 15). The isokinetic temperature, which is the ratio of the change of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ activation parameters with the substituents[3,9] (eq 16), can be calculated from the temperature dependence of the rate con-

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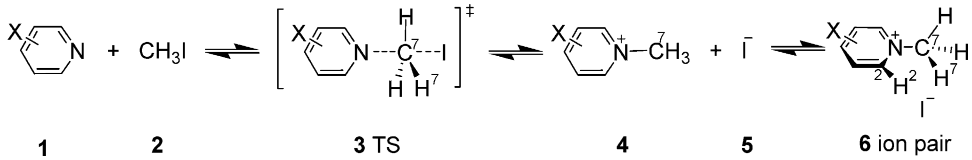
SCHEME 1. Reversible Reaction of Pyridines with Methyl Iodide



stants, by using the methods published by Exner,[9] Linert,[22,23] and Berthelot et al.[24]

$$\delta\Delta G^{\ddagger} = \delta\Delta H^{\ddagger}(\beta - T)/\beta \tag{14}$$

$$\delta\Delta G^{\ddagger} = \delta\Delta S^{\ddagger}(\beta - T) \tag{15}$$

$$\delta\Delta H^{\ddagger}/\delta\Delta S^{\ddagger} = \beta \tag{16}$$

To decrease the errors originating from the temperature dependence of activation parameters,[25,26] $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated in the same temperature range for all compounds of the reaction series and refer to the mean temperature of the measurements. In many reactions $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ showed linear dependence on the substituent constants, like the log k values in the Hammett equation. Good correlations with eqs 1−3 were obtained[1,3] when the changes of the activation parameters with the substituents were considerably greater than the experimental errors. $\Delta S^{\ddagger}$ regularly had the greatest uncertainty among the activation parameters, and often only $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ gave acceptable correlations with the substituent constants. In entropy-driven reactions. a similar situation may exist for $\Delta H^{\ddagger}$. In these cases, more correct values for $\delta\Delta S^{\ddagger}$ or $\delta\Delta H^{\ddagger}$ were calculated from eq 5 by using the $\delta\Delta G^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ or $\delta\Delta S^{\ddagger}$ constants. If the $\Delta G^{\ddagger}/\Delta H^{\ddagger}/\Delta S^{\ddagger}$ versus σ plots show a break,[3] and the $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, and $\delta\Delta S^{\ddagger}$ values change with the substituents, but the β isokinetic temperature remains constant, one may assume that wrong σ constants have been chosen for the correlations. If β is also altered at the break, the rate-determining step or the mechanism may change with the substituents.[3,5,27]

Computational Details

The geometry of each compound was fully optimized by using the Gaussian 03 software package[28] at the B3LYP level. The solvent effect was incorporated by applying the polarizable continuum model[29] in the integral equation formalism[30,31] (IEF-PCM) of the corresponding solvent. The 6-31G(d) standard basis set was used for all atoms except iodine, for which the SDD (Stuttgart/Dresden ECP) was selected with the 6D option, because the 6-31G basis set is only applicable up to Kr. All structures were characterized as energy minima or TSs by calculating the harmonic vibrational frequencies, with no or one imaginary frequency for reactants and TSs, respectively, using analytical second derivatives. The thermochemical data were obtained by the standard procedure in the framework of the harmonic approximation.[32,33]

In cases of very flat potential energy surfaces, such as complexes with explicit solvent molecules, discontinuity arising from the solvent model may prevent finding a true minimum. In such cases, the optimizations may result in oscillation or converge to higher order critical points of the not perfectly continuous potential energy surface. Even at convergence, the entropy values may not be comparable since some degrees of freedom, the normal modes corresponding to imaginary vibrational frequencies, are excluded. None of the reported data suffers from such problems, which prevented us from performing extensive studies with explicit solvent molecules.

Free energies, enthalpies, and entropies of activation were calculated from the differences of the sum of electronic and thermal free energies (G) and enthalpies (H) and from the entropies (S) of the TSs and reactants, respectively (see Table S1−S4 in Supporting Information. $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ values were multiplied by 627.51 and 4.184 in order to convert them into kJ mol^{-1} units). The entropy values, obtained by the Gaussian 03 program for a compound in different solutions and in the gas phase, are practically equal to each other. For CH_3I, CH_3CN, and CH_3OH, $S = 254.1$, 245.1, and 239.8 J mol^{-1} K^{-1} were measured[34] in the gas phase, and $S = 264$, 251 and 241 J mol^{-1} K^{-1} were calculated in CH_3CN, CH_3CN, and CH_3OH solutions, respectively, at 25 °C.

Results and Discussions

Reaction of Pyridines with Methyl Iodide. Pyridines (**1**) react with methyl iodide (**2**) in CH_3CN solution through an equilibrium reaction[35] (Scheme 1, X substituents are given in legends of Figures 1−3). The equilibrium is strongly shifted to the right side, and $\Delta G° = -49.9$ kJ mol^{-1} was obtained for the unsubstituted compound (X = H). The N-methyl pyridinium ions (**4**) and the iodide ion (**5**) form ion pairs **6** in CH_3CN solution (Scheme 1). The dissociation constant of the 4-cyano-N-ethylpyridinium iodide ion pair was found[36] to be $K_d = 0.0104$ mol^{-1}, i.e., 64% of the salt forms ion pairs, at 0.05 M

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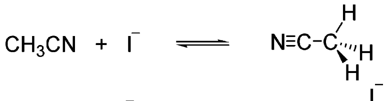
SCHEME 2. Solvation of Iodide Ion with Acetonitrile



7 **5** **8**

concentration of the salt, which was used in kinetic measurements. The reactivity of the ion pair and the free ions proved to be identical in nucleophilic substitutions.[36]

Selected data of the optimized structures obtained by DFT calculation are listed in Table S5 of Supporting Information. In the ion pairs **6** (Scheme 1), the iodide ion is near to the *ortho*-proton $\{R(\mathrm{IH}^2) \approx 3.1$ Å$\}$ and to one of the H atoms of the CH_3 group $\{R(\mathrm{IH}^7) \approx 3.2$ Å$\}$ and lies close to the plain of the pyridine ring $\{\varphi(\mathrm{IC}^7\mathrm{NC}^2) \approx -8°$, Table S5$\}$, where density of positive charge is the greatest. DFT calculations indicated that I^- forms the molecular association **8** in CH_3CN solution with a solvent molecule (Scheme 2). The I^- is in the vicinity of one of the hydrogens of the CH_3 group $\{R(\mathrm{CH}) = 3.260$ Å$\}$, and the C−H···I atoms are in a nearly linear arrangement ($\theta = 176°$).

The TS **3**, formed from both directions of the reversible reaction, exhibits a trigonal bipyramidal geometry (Scheme 1, Table S5), with collinear $\mathrm{I}\cdots\mathrm{C}^7\cdots\mathrm{N}$ atoms ($\theta = 179.8°$) and with $\mathrm{C}^7\cdots\mathrm{N}$ (∼2.2 Å) and $\mathrm{I}\cdots\mathrm{C}^7$ (∼2.6 Å) bonds, which are longer than in pyridinium salts **4** (1.48 Å) and in CH_3I (2.203 Å), respectively. The TS is reactant-like; the H atoms of the CH_3 group are bent toward the N atom $\{\theta(\mathrm{H}^7\mathrm{C}^7\mathrm{N}) < 90°, \theta(\mathrm{H}^7\mathrm{C}^7\mathrm{I}) > 90°\}$. With the increase of the electron-withdrawing (e-w) effect of the substituents in the pyridine ring, the above angles approach 90°, the $R(\mathrm{IC}^7)$ distance increases, the $R(\mathrm{C}^7\mathrm{N})$ decreases, the $Q(\mathrm{I})$ negative charge of the iodine and the positive charge of the C^7 carbon atom increase (Table S5), and the reaction coordinate of the TS is shifted toward $x = 0.5$. By accepting $\theta(\mathrm{HCI}) = 106.8°$ in CH_3I for $x = 0$ and $\theta(\mathrm{H}^7\mathrm{C}^7\mathrm{I}) = 90°$ in a TS for $x = 0.5$, reaction coordinates $x = 0.38$, 0.39, and 0.45 were calculated for the TSs of 4-CH_3O, H, and 4-NO_2 derivatives, respectively. An early TS was also proposed for the forward reaction on the basis of kinetic measurements.[35] The bond orders $n(\mathrm{N}-\mathrm{C}^7) = 0.372$ and $n(\mathrm{C}^7-\mathrm{I}) = 0.613$ were calculated for the TS of the unsubstituted compound (X = H) by using the Pauling equation[37] (eq 17):

$$R - R_o = a \ln(n) \qquad (17)$$

where R is the $\mathrm{C}^7\cdots\mathrm{N}$ or the $\mathrm{I}\cdots\mathrm{C}^7$ distance in the TSs (Table S5) and $R_o = 2.203$ Å for CH_3I and 1.481 Å for $C_5H_5NCH_3^+$. $R = 2.741$ and 1.997 Å data, calculated for the symmetric $[\mathrm{I}\cdots\mathrm{CH_3}\cdots\mathrm{I}^-]^\ddagger$ and $[\mathrm{C_5H_5N}\cdots\mathrm{CH_3}\cdots\mathrm{NC_5H_5}^+]^\ddagger$ TSs ($n = 0.5$) were used to determine the constants $a = -0.7762$ and -0.7444 in eq 17 for C−I and C−N bonds, respectively. A tighter TS is formed in the presence of e-w substituents, as is shown by the calculated sum of $\mathrm{I}\cdots\mathrm{C}^7\cdots\mathrm{N}$ distances decreasing from 4.803 to 4.790 Å in the case of 4-CH_3O and 4-NO_2 substituted compounds, respectively.

Kinetic investigations[35] on the substituent effect indicated that the forward reaction is accelerated by electron-donating (e-d) groups ($\rho = -2.27$) and the reverse reaction by e-w groups ($\rho = 5.95$). The Hammett ρ constants also support the early TS of the forward reaction. The experimental activation parameters of the methylation (Table 1, no. 1a) are in the usual range of bimolecular reactions.[38] The free energy and enthalpy of activation of the slower demethylation are much higher (Table 1, no. 2a) and the entropy of activation is positive, although this reaction is also bimolecular. The positive, unusually high entropy of activation for the bimolecular reaction may be explained by the desolvation of the ions and by the decreasing order of the solvent molecules on the formation of the TS. Experimental and calculated $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ values for the forward and reverse reactions, and the $\Delta G°$, $\Delta H°$, and $\Delta S°$ data for the equilibriums are plotted against the σ constants[21] in Figures 1−3. The $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ ($\delta\Delta G°$, $\delta\Delta H°$, and $\delta\Delta S°$ for the equilibrium) reaction constants are given in Table 1. The calculated and measured values for $\delta\Delta G^\ddagger$ and $\delta\Delta H^\ddagger$, as well as for $\delta\Delta G°$ and $\delta\Delta H°$, agree well, and the substituent effect on $\Delta G^\ddagger$ and $\Delta H^\ddagger$, as well as on $\Delta G°$ and $\Delta H°$, parameters can be calculated properly by the DFT method for the reactions investigated (Table 1, nos. 1a,b, 2a,b,c, and 3a,b,c). Good correlations were obtained for the forward reaction also with σ_o constants[21] (Table 1, nos. 1a,b, footnotes g and h) indicating that no e-d through-conjugation takes place between the π orbitals of the pyridine ring and the orbital of the $\mathrm{N}\cdots\mathrm{C}^7\cdots\mathrm{I}$ atoms of the TS, occupying orthogonal positions. Practically the same reaction constants were obtained for the separated ions **4** and **5** and the ion pair **6** in the reverse reaction (Table 1, nos. 2b,c) and in the equilibrium (nos. 3b,c). The dissociation of the ion pair **6** (Scheme 1) is not influenced significantly by the substituents of the pyridine ring; $\Delta G° = -18.5 \pm 1.0$ kJ mol^{-1}, $\Delta H° = 4.09 \pm 0.8$ kJ mol^{-1}, and $\Delta S° = 75.7 \pm 3.6$ J mol^{-1} K^{-1} were obtained on the average for compounds with different substituents.

The calculated $\Delta S^\ddagger$ and $\Delta S°$ data decrease only slightly with the increase of the e-w effect of the substituents in the forward reaction and in the equilibrium ($\delta\Delta S < 0$, Table 1, nos. 1b and 3b,c; Figures 1 and 3). The decrease of the calculated $\Delta S^\ddagger$ may also be explained by the increasing tightness of the TSs. A higher decrease of $\Delta S^\ddagger$ was observed for the same reactions evaluating the data of kinetic measurements (Table 1, nos. 1a and 3a; Figures 1 and 3). It may be assumed that the negative charge of iodine and therefore the solvation of the TS increases in the given series of compounds $\{Q(\mathrm{I}) = -0.503$ and -0.548 for 4-CH_3O and 4-NO_2 substituted compounds, respectively; see Table S5$\}$. On the other hand, $\Delta S^\ddagger$ does not show any significant dependence on substituents in the reverse reaction (Table 1, nos. 2a,b,c). The effect of X substituents on the charges and the solvation of ions **4**, **6**, and TS **3** may be similar. Correlation coefficients (r) for the $\Delta S^\ddagger$ versus σ plots are poor because the entropy changes are small, and the errors of the measured and calculated data are greater than those of the other parameters. Nevertheless the $\delta\Delta S^\ddagger$ data in Table 1 may be accepted because almost the same values can be calculated from eq 5 by using the values of $\delta\Delta G^\ddagger$ and $\delta\Delta H^\ddagger$.

The calculated $\Delta G_o{}^\ddagger$, $\Delta H_o{}^\ddagger$, and $\Delta S_o{}^\ddagger$ activation parameters of the unsubstituted compounds do not agree well with the experimental data. The forward reaction of the unsubstituted compound proceeds 1900 times more slowly, while the reverse reaction of the free ions **4** and **5** is 7200 times faster than calculated. The measured $\Delta G_o{}^\ddagger$ parameters are higher and smaller than those obtained by the DFT method for the forward and reverse reactions, respectively (Table 1, nos. 1a,b, 2a,c, Figure 1). The equilibrium is less shifted toward the right side than expected on the basis of computations, and experimental

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[37] Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542−553.

[38] Reference 27; pp 143−148.

TABLE 1. Effect of Substituents on Activation and Thermodynamic Parameters and Data for Unsubstituted Compounds in the Equilibrium Reaction of Pyridines with Methyl Iodide[a]

no.	reaction	N^b	$\delta\Delta G^{c,d}$ (r)	$\delta\Delta H^{c,d}$ (r)	$\delta\Delta S^{c,e}$ (r)	$\Delta G_o{}^{c,f}$	$\Delta H_o{}^{c,f}$	$\Delta S_o{}^{c,g}$
1a (exp)[35]	**1** + **2** ⇆ **3** TS	5	13.7[h] (0.986)	10.1[h] (0.962)	−11.9[h] (0.933)	92.6	54.2	−129
1b (calc)	**1** + **2** ⇆ **3** TS	9	16.3[i] (0.974)	14.7[i] (0.975)	−5.4[i] (0.816)	73.9	32.6	−139
2a (exp)[35]	**4** + **5** ⇆ **3** TS	5	−34.0 (0.960)	−29.2 (0.923)	∼0	143	152	31.8
2b (calc)	**6** ⇆ **3** TS	9	−31.1 (0.981)	−31.2 (0.980)	∼0	147	142	−14.3
2c (calc)	**4** + **5** ⇆ **3** TS	9	−32.0 (0.981)	−33.1 (0.985)	∼0	165	139	−86.9
2d (calc)	**4** + **8** ⇆ **3** TS + **7**	9	−32.0 (0.981)	−33.1 (0.985)	∼0	147	138	−31.0
3a (exp)[35]	**1** + **2** ⇆ **4** + **5**	5	46.0 (0.931)	51.8 (0.946)	−33.7 (0.908)	−49.9	−97.9	−161
3b (calc)	**1** + **2** ⇆ **6**	9	47.5 (0.981)	45.9 (0.980)	−5.1 (0.548)	−72.6	−110	−124
3c (calc)	**1** + **2** ⇆ **4** + **5**	9	48.3 (0.983)	47.8 (0.983)	−1.70 (0.443)	−90.7	−106	−51.7
3d (calc)	**1** + **2** + **7** ⇆ **4** + **8**	9	48.3 (0.983)	47.8 (0.983)	−1.70 (0.443)	−73.3	−105	−108

[a] Schemes 1 and 2 and eqs 18 and 19, in CH_3CN solution, at $T = 298$ K. Experimental and calculated parameters were correlated with the σ substituent constants.[21] [b] Number of compounds. [c] $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, $\delta\Delta S^\ddagger$ and $\Delta G_o{}^\ddagger$, $\Delta H_o{}^\ddagger$, $\Delta S_o{}^\ddagger$for rections nos. 1 and 2; $\delta\Delta G°$, $\delta\Delta H°$, $\delta\Delta S°$ and $\Delta G_o°$, $\Delta H_o°$, $\Delta S_o°$ for the equilibrium no 3. [d] In kJ mol^{-1} σ^{-1}. [e] In J mol^{-1} K^{-1} σ^{-1}. [f] Data for the unsubstituted compounds are given in kJ mol^{-1}. [g] Data for the unsubstituted compounds are given in J mol^{-1} K^{-1}. [h] $\delta\Delta G^\ddagger = 12.9$ kJ mol^{-1} $\sigma_o{}^{-1}$ ($r = 0.979$), $\delta\Delta H^\ddagger = 9.91$ kJ mol^{-1} $\sigma_o{}^{-1}$ ($r = 0.961$), $\delta\Delta S^\ddagger = -11.4$ J mol^{-1} K^{-1} $\sigma_o{}^{-1}$ ($r = 0.918$) were calculated with the σ_o substituent constants.[21] [i] $\delta\Delta G^\ddagger$ =17.6 kJ mol^{-1} $\sigma_o{}^{-1}$ ($r = 0.975$), $\delta\Delta H^\ddagger = 15.8$ kJ mol^{-1} $\sigma_o{}^{-1}$ ($r = 0.975$), $\delta\Delta S^\ddagger = -5.86$ J mol^{-1} K^{-1} $\sigma_o{}^{-1}$ ($r = 0.828$) were calculated with the σ_o substituent constants.[21]

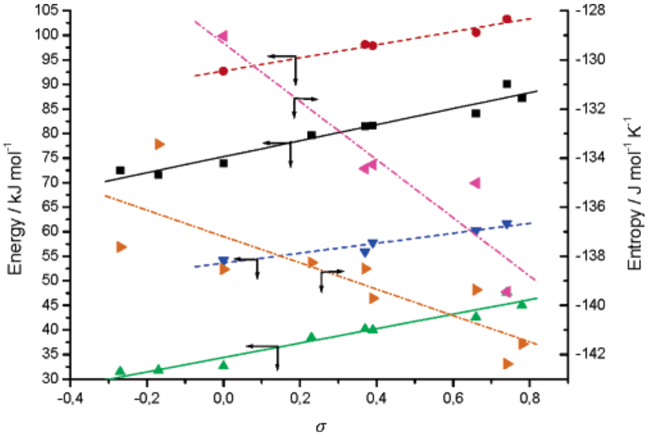


FIGURE 1. Experimental $\Delta G^\ddagger$ vs σ (red circles), $\Delta H^\ddagger$ vs σ (blue downward-facing triangles), $\Delta S^\ddagger$ vs σ (red left-facing triangles) and calculated $\Delta G^\ddagger$ vs σ (black squares), $\Delta H^\ddagger$ vs σ (green upward-facing triangles), $\Delta S^\ddagger$ vs σ (gold right-facing triangles) plots for the forward reaction of pyridines with CH_3I (**1** + **2** ⇆ **3** TS, Scheme 1), in CH_3CN solution, at 298 K. (XC_5H_4N; X = H, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2 for the experimental data, and X = 4-CH_3O, 4-CH_3, H, 4-Cl, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2, 4-NO_2 for the calculated data, in the order of the increasing values of the σ constants[21]). $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ constants are given in Table 1, nos. 1a,b.

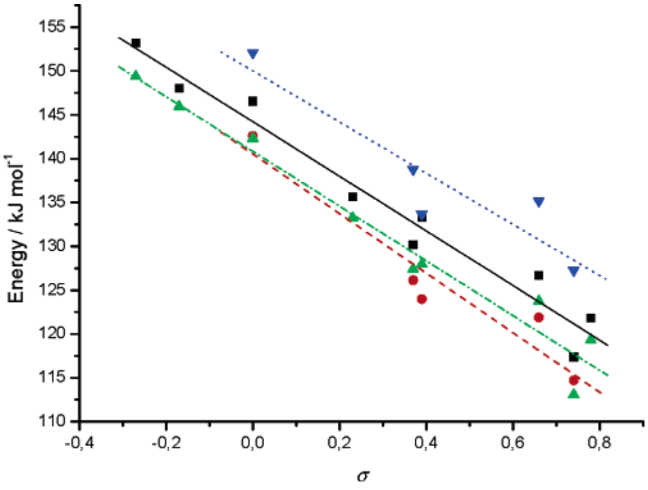
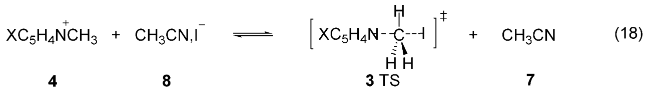


FIGURE 2. Experimental $\Delta G^\ddagger$ vs σ (red circles), $\Delta H^\ddagger$ vs σ (blue downward-facing triangles) and calculated $\Delta G^\ddagger$ vs σ (black squares), $\Delta H^\ddagger$ vs σ (green upward-facing triangles) plots for the reverse reaction of the ion pairs of *N*-methylpyridinium iodides (**6** ⇆ **3** TS, Scheme 1), in CH_3CN solution at 298 K. ($XC_5H_4NCH_3{}^+$, I^-; X = H, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2 for the experimental data, and X = 4-CH_3O, 4-CH_3, H, 4-Cl, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2, 4-NO_2 for the calculated data, in the order of the increasing values of the σ constants[21]). $\delta\Delta G^\ddagger$, $\delta\Delta H^\ddagger$, and $\delta\Delta S^\ddagger$ values are given in Table 1, nos. 2a,b.

$\Delta G_o°$ is higher than the computed one (Table 1, nos. 3a,c, Figure 3). Measured and calculated data are less different if the ion pair **6** is taken into consideration instead of the free ions **4** and **5** (Figure 2, Table 1, nos. 2a,b,c, 3a,b,c). The experimental and calculated $\Delta S^\ddagger$ values agree better in the forward reaction of neutral molecules (Table 1, nos. 1a,b, Figure 1) than in the reverse reaction (nos. 2a,c) and in the equilibrium (nos. 3a,c, Figure 3), where ions take also part in the reactions. We tried to improve the results by calculating the interactions of the reactants and the TS with one or two solvent molecules, but only the complex between I^- and one CH_3CN molecule could be computed without imaginary frequency. $\Delta G° = 17.5$ kJ mol^{-1}, $\Delta H° = 0.78$ kJ mol^{-1}. and $\Delta S° = -55.9$ J mol^{-1} K^{-1} were obtained for the equilibrium in Scheme 2. The calculated parameters of the reverse reaction and the equilibrium in Scheme 1 become only slightly better if the complex formation of I^- and CH_3CN is also taken into consideration according eqs 18 and 19 (Table 1, nos. 2a,c,d, 3a,c,d). One cannot correctly model the entropy changes with complexes containing only one solvent molecule.



$$\underset{\mathbf{4}}{XC_5H_4\overset{+}{N}CH_3} + \underset{\mathbf{8}}{CH_3CN,I^-} \rightleftharpoons \underset{\mathbf{3}\ \mathrm{TS}}{\left[XC_5H_4N\text{--}\overset{H}{\underset{H\ H}{C}}\text{--}I\right]^{\ddagger}} + \underset{\mathbf{7}}{CH_3CN} \qquad (18)$$

$$\underset{\mathbf{1}}{XC_5H_4N} + \underset{\mathbf{2}}{CH_3I} + \underset{\mathbf{7}}{CH_3CN} \rightleftharpoons \underset{\mathbf{4}}{XC_5H_4\overset{+}{N}CH_3} + \underset{\mathbf{8}}{CH_3CN,I^-} \qquad (19)$$

Reaction of *N*,*N*-Dimethylanilines with Methyl Iodide. The kinetics of the nucleophilic substitution reactions of *N*,*N*-dimethylanilines (**9**) with methyl iodide (**2**) were studied in acetone,[39] CH_3CN,[39] and CH_3OH[40,41] solutions (Scheme 3, X substituents are given in the legends of Figures 4 and 5. In CH_3-CN the same substituents were used as in acetone).

The optimized structures obtained by DFT calculations for *N*,*N*-dimethylanilines in different solvents are identical within

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(39) Matsui, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1751−1760.

(40) Evans, D. P.; Watson, H. B.; Williams, R. *J. Chem. Soc.* **1939**, 1345−1355.

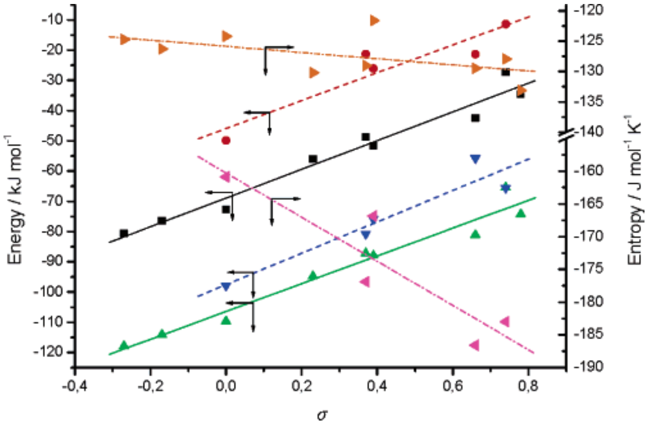

FIGURE 3. Experimental $\Delta G°$ vs σ (red circles), $\Delta H°$ vs σ (blue downward-facing triangles), $\Delta S°$ vs σ (red left-facing triangles) and calculated $\Delta G°$ vs σ (black squares), $\Delta H°$ vs σ (green upward-facing triangles), $\Delta S°$ vs σ (gold right-facing triangles) plots for the equilibriums $XC_5H_4N + CH_3I \leftrightarrows XC_5H_4NCH_3^+, I^-$ (**1** + **2** $\leftrightarrows$ **6**, Scheme 1), in CH_3CN solution, at 298 K. (X = H, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2 for the experimental, and X = 4-CH_3O, 4-CH_3, H, 4-Cl, 3-Cl, 3-Br, 4-CN, 3,5-Cl_2, 4-NO_2 for the calculated data, in the order of the increasing values of the σ constants[21]). $\delta\Delta G°$, $\delta\Delta H°$ and $\delta\Delta S°$ values are given in Table 1, nos. 3a,b.

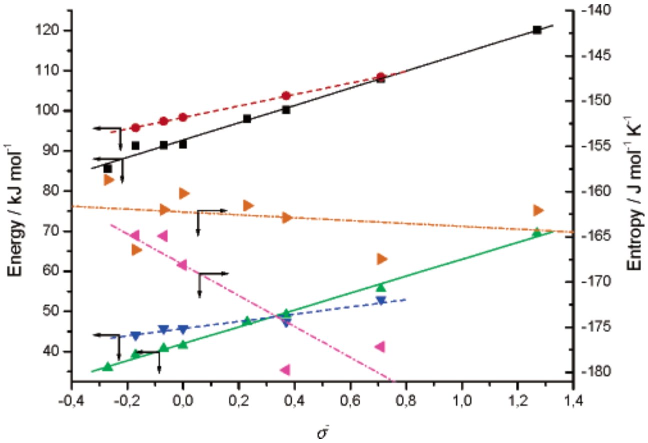

FIGURE 4. Experimental $\Delta G^‡$ vs σ^- (red circles), $\Delta H^‡$ vs σ^- (blue downward-facing triangles), $\Delta S^‡$ vs σ^- (red left-facing triangles) and calculated $\Delta G^‡$ vs σ^- (black squares), $\Delta H^‡$ vs σ^- (green upward-facing triangles), $\Delta S^‡$ vs σ^- (gold right-facing triangles) plots for the reaction of *N*,*N*-dimethylanilines with methyl iodide (**9** + **2** $\leftrightarrows$ **10** TS, Scheme 3), in acetone solution, at 313 K. ($XC_6H_4N(CH_3)_2$; X = 4-CH_3, 3-CH_3, H, 3-Cl, 3-NO_2 for the experimental, and X = 4-CH_3O, 4-CH_3, 3-CH_3, H, 4-Cl, 3-Cl, 3-NO_2, 4-NO_2 for the calculated data, in the order of the increasing values of the σ^- constants[21]). $\delta\Delta G^‡$, $\delta\Delta H^‡$, and $\delta\Delta S^‡$ values are given in Table 2, nos. 1a,b.

the errors of calculations; deviations of charges, atomic distances and angles are less than ±0.002 atomic unit, ±0.002 Å and ±0.1°, respectively. Electron-withdrawing substituents decrease the $R(C^1N)$ distance and move the N-CH_3 groups toward the plane of the aromatic ring {cf. $\varphi(C^7NC^1C^2)$ and $\varphi(C^8NC^1C^2)$ angles in Table S6}.

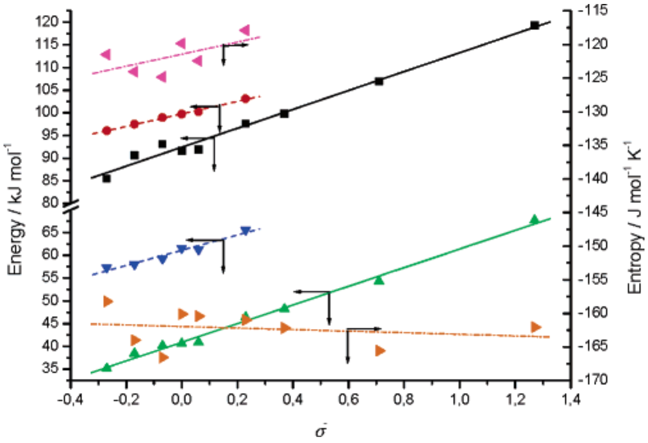

FIGURE 5. Experimental $\Delta G^‡$ vs σ^- (red circles), $\Delta H^‡$ vs σ^- (blue downward-facing triangles), $\Delta S^‡$ vs σ^- (red left-facing triangles) and calculated $\Delta G^‡$ vs σ^- (black squares), $\Delta H^‡$ vs σ^- (green upward-facing triangles), $\Delta S^‡$ vs σ^- (gold right-facing triangles) plots for the reaction of substituted *N*,*N*-dimethylanilines with methyl iodide (**9** + **2** $\leftrightarrows$ **10** TS, Scheme 3), in CH_3OH solution, at 313 K. ($XC_6H_4N(CH_3)_2$; X = 4-CH_3O, 4-CH_3, 3-CH_3, H, 4-F, 4-Cl, for the experimental, and X = 4-CH_3O, 4-CH_3, 3-CH_3, H, 4-F, 4-Cl, 3-Cl, 3-NO_2, 4-NO_2 for the calculated data, in the order of the increasing values of the σ^- constants[21]). $\delta\Delta G^‡$, $\delta\Delta H^‡$, and $\delta\Delta S^‡$ values are given in Table 4, nos. 3a,c.

The N···C^9···I atoms are collinear in the TS **10** {$\theta(NC^9I) \approx 180°$}, but their bonds are not perpendicular to the benzene ring {$\varphi(C^9NC^1C^2) \approx 65°$}. One of the N-$CH_3$ groups is in the plane of the aromatic ring, $\varphi(C^7NC^1C^2) \approx 180°$, and the $R(NC^7)$ bond distance is shorter than $R(NC^8)$. The data calculated for the TSs are practically the same, within the uncertainties of the computations in every solvents. The only exception is that the $R(C^9I)$ distances and the $\theta(NC^9H)$ angles are greater whereas the $R(C^9N)$ distances and the $\theta(IC^9H)$ angles are smaller in acetone than in the more polar CH_3CN and CH_3OH (Table S6). In the latter two solvents the structural data of the TSs were found to be the same. The TSs are reactant-like, and the H atoms of the CH_3 group are directed toward the N atom { $\theta(NC^9H) < 90°$, $\theta(IC^9H) > 90°$}. From the $\theta(IC^9H)$ angles, the reaction coordinates $x = 0.42$, 0.43, and 0.51 were calculated for the 4-CH_3O, H, and 4-NO_2 substituted derivatives in acetone, respectively, whereas $x = 0.41$, 0.43, and 0.50 were obtained for them in CH_3CN and CH_3OH solvents. Here the same procedure was followed as in the reaction of pyridines with CH_3I. Bond orders $n(C^9{-}N) = 0.396$ and $n(I{-}C^9) = 0.587$ were obtained for the TS of the unsubstituted compound from eq 17 in CH_3CN solution, by using the $R(C^9N)$ and $R(IC^9)$ distances for the TS (Table S6), $R_o = 2.203$ Å for CH_3I and $R_o = 1.515$ Å for $C_6H_5N(CH_3)_3^+$. The calculated $R = 2.741$ and 2.048 Å distances for the symmetric ($n = 0.5$) TSs $[I\cdots CH_3\cdots I^-]^‡$ and $[C_6H_5N(CH_3)_2\cdots CH_3\cdots(CH_3)_2NC_6H_5^+]^‡$ were applied to get the constants $a = -0.7762$ and -0.7650 in eq 17 for the I−C and C−N bonds, respectively. The $R(C^9I)$ distances are shorter, and the $R(C^9N)$ distances are longer in CH_3CN and CH_3OH than in the less polar acetone, indicating that slightly more reactant-like TSs are formed in the more polar solvents (cf. ref 17). The sum of the $R(IC^9)$ and $R(C^9N)$ distances (4.848 and 4.833 Å for the TSs of 4-CH_3O and 4-NO_2 substituted compounds, respectively) show that a tighter TS is formed if the nucleophile has an e-w group.

Kinetic measurements showed that the reaction is accelerated, i.e., the $\Delta G^‡$ and $\Delta H^‡$ values are decreased ($\delta\Delta G^‡ > 0$, $\delta\Delta H^‡ > 0$, Table 2) by e-d groups ($\sigma < 0$) of *N*,*N*-dimethylanilines, $\rho \approx -2.4$ was obtained in each solvent from the Hammett equation.[39−41] As electron withdrawal through conjugation

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(41) Baliah, N.; Kanagasabapathy, V. M. *Indian J. Chem. B* **1978**, *16*, 64−66.

SCHEME 3. Reaction of *N*,*N*-Dimethylanilines with Methyl Iodide

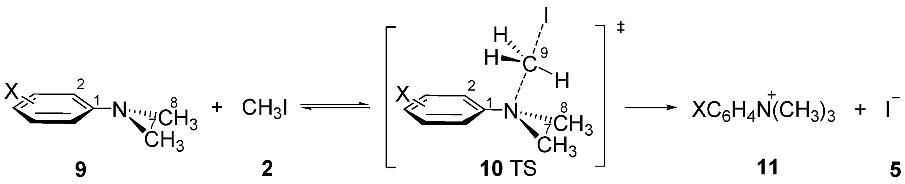

TABLE 2. Effect of Substituents and Solvents on Activation Parameters and Data for Unsubstituted Compound in the Nucleophilic Substitution of *N*,*N*-Dimethylanilines with Methyl Iodide (9 + 2 ⇆ 10 TS; Scheme 3) in Acetone, CH$_3$CN, and CH$_3$OH[a]

no.	solvent	N[b]	T (K)[c]	$\delta\Delta G^{\ddagger}$ [d] (r)	$\delta\Delta H^{\ddagger}$ [d] (r)	$\delta\Delta S^{\ddagger}$ [e] (r)	$\Delta G_o^{\ddagger}$ [f]	$\Delta H_o^{\ddagger}$ [f]	$\Delta S_o^{\ddagger}$ [g]
1a (exp)[39]	acetone	5	313	14.3 (1.000)	8.99 (0.959)	−17.1 (0.888)	98.4	45.8	−165
1b (calc)	acetone	8	313	21.6 (0.995)	21.1 (0.998)	−1.6 (0.227)	91.6	41.1	−160
2a (exp)[39]	CH$_3$CN	5	313	14.4 (0.999)	9.84 (0.996)	−14.5 (0.994)	96.7	49.0	−152
2b (calc)	CH$_3$CN	8	313	20.7 (0.997)	20.4 (0.997)	−0.6 (0.125)	90.6	40.4	−160
3a (exp)[40]	CH$_3$OH	6	318	13.8 (0.997)	16.7 (0.974)	8.95 (0.974)	99.7	61.6	−120
3b (exp)[41]	CH$_3$OH	13	318	14.7 (0.977)	19.7 (0.950)	15.5 (0.564)	99.8	60.0	−125
3c (calc)	CH$_3$OH	9	318	20.9 (0.992)	20.5 (0.996)	−1.15 (0.209)	91.6	40.7	−160

[a] Experimental and calculated data were correlated with the σ^- substituent constants.[21] [b] Number of compounds. [c] Temperature of experiments. [d] In kJ mol^{-1} σ^{-1}. [e] In J mol^{-1} K^{-1} σ^{-1}. [f] Data for the unsubstituted compound are given in kJ mol^{-1}. [g] Data for the unsubstituted compound are given in J mol^{-1} K^{-1}.

hinders the reaction, activation parameters were plotted against the σ^- constants[21] in Figures 4 and 5. In the reaction of *N*,*N*-dimethylanilines with methyl iodide, the measured $\delta\Delta G^{\ddagger}$ reaction constants are at about 14 kJ mol^{-1} σ^{-1} in each of the solvents (Table 2, nos. 1a, 2a, 3a,b). The solvents have only minor influence on this reaction constant, supporting that eq 11 can be regarded as a good approximation. The calculated values of $\delta\Delta G^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ are approximately equal and are at about 30% higher than the least solvent-dependent experimental $\delta\Delta G^{\ddagger}$ parameter (Table 2, nos. 1a,b, 2a,b, 3a,b,c).

The small negative values calculated for the $\delta\Delta S^{\ddagger}$ reaction constants in each solvent (Table 2, nos. 1b, 2b, 3c) may also be explained with the slightly increasing tightness of the TSs having e-w groups. In acetone and CH$_3$CN, the $\delta\Delta S^{\ddagger}$ values obtained experimentally are more negative than the calculated ones because they are influenced also by solvation (Figure 4, Table 2, nos. 1a, 2a). Electron-withdrawing substituents ($\sigma >$ 0) increase the Q(I) negative charge {$Q(\mathrm{I}) = -0.519$ and -0.571 for 4-CH$_3$O and 4-NO$_2$ substituted compounds, respectively, Table S6} and the solvation of the leaving iodine in the TS **10** and decrease this way $\Delta S^{\ddagger}$ in aprotic media. The $\Delta G_o^{\ddagger}$ $\Delta H_o^{\ddagger}$, and $\Delta S_o^{\ddagger}$ activation parameters of the unsubstituted compound for the reaction between *N*,*N*-dimethylanilines and methyl iodide can be calculated with good approximation in aprotic solvents (Figure 4, Table 2, nos. 1a,b, 2a,b). The experimental $\Delta G_o^{\ddagger}$ values are higher by ~7 kJ mol^{-1} compared to the calculated ones, and thus the reactions proceed at about 10 times slower than expected on the basis of the computations.

On the other hand, e-w substituents increase the entropy of activation in CH$_3$OH, the experimental $\delta\Delta S^{\ddagger} > 0$ (Figure 5, Table 2, nos. 3a,b). The value of $\Delta S^{\ddagger}$ for the unsubstituted compound is higher by at about 40 J mol^{-1} K^{-1} in CH$_3$OH than in aprotic solvents. The increase of $\Delta S^{\ddagger}$ is accompanied by that of $\Delta H^{\ddagger}$ (eq 12), whereas the experimental $\Delta G^{\ddagger}$ values are similar in each solvent (Table 2, nos. 1a, 2a, 3a,b). Analogous behavior of the activation parameters in aprotic and protic solvents were already found in the reactions of some carboxylic acid derivatives, also.[1,3]

To discuss the solvent effect, one can divide the entropy of activation into the contributions of the reaction (int) and to that of the solvation (ext) in an approximation:

$$\Delta S^{\ddagger} \approx \Delta S_{\mathrm{int}}{}^{\ddagger} + (\Delta S_{\mathrm{ext}}{}^{\ddagger})_{\mathrm{TS}} - \sum(\Delta S_{\mathrm{ext}}{}^{\ddagger})_{\mathrm{R}} \qquad (20)$$

$\Delta S_{\mathrm{int}}{}^{\ddagger}$ is the entropy change of the reaction, which may be approximately equal to the entropy of activation, calculated with the DFT method, and is about −150 J mol^{-1} K^{-1} for bimolecular reactions. The $\Delta S_{\mathrm{ext}}{}^{\ddagger}$ values are the entropy changes connected with solvation and regularly have negative values as the ordering of solvent molecules is greater in the solvation shell compared to the bulk of solvent.

The desolvation of the reactants has a positive contribution and the solvation of the TS a negative contribution to the entropy of activation, if the solvent molecules are bonded more strongly to the given species than to each other in the bulk of the solvent, e.g., in the case of apolar aprotic media. In these media, the greater the charge of the solute molecules, the greater is their solvation and the entropy change corresponding to the formation or destruction of the solvation shell. Entropy of solvation for the studied nucleophilic substitutions is determined mainly by the polarity of the TSs, because their charges are greater than those of the reactants (Tables S5, S6). In such cases, entropy of activation decreases also with the decrease of the polarity of solvents (Table 2), because the less polar solvent molecules are less ordered in the bulk of the aprotic solvent and their ordering is changed to a greater extent with the solvation of the polar TSs.[38]

In protic solvents entropy of solvation depends not only on charges of the reactants and the TS but also on the hydrogen-bonded structure of the solvent. Entropy of solvation data available mainly for water. The hydration entropy of uncharged organic molecules[42−44] is at about −90 J mol^{-1} K^{-1}, i.e., entropy of activation increases with approximately 90 J mol^{-1} K^{-1} at the desolvation of a reactant in water. The great negative value

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(42) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 2nd ed.; Verlag Chemie: Weinheim, 1988; pp 25−34.

(43) Engberts, J. B. F. N. *Pure Appl. Chem.* **1982**, *54*, 1797−1808.

(44) Schwetlick, K. *Kinetische Methoden zur Untersuchung von Reaktiosmechanismen*; Deutscher Verlag der Wissenschaften: Berlin, 1971; Chapter 4.

of $\Delta S_{\text{ext}}^{\ddagger}$ of solvation was explained with the increased water−water hydrogen bonding in the solvation shell, which surrounds the uncharged organic molecule.[44] The entropies of hydration of small ions are greater, whereas those of large ions are smaller negative values than those of uncharged molecules, e.g., $\Delta S_{\text{ext}}^{\ddagger} = -109, -50, -38, -13$ J mol^{-1} K^{-1} were obtained for F$^-$, Cl$^-$, Br$^-$ and I$^-$, respectively.[44−47] The observations were explained with the decrease of the ordering of water molecules in the second solvation shell of large ions or dipoles of low charge density compared to the bulk of solvent.[44−46] Protic organic solvents were found to have water-like behavior,[42,44,45] and also similar changes of $\Delta S_{\text{ext}}^{\ddagger}$ may be expected in these solvents. In the case of S_N2 reactions with neutral reactants and polar TSs, the desolvation of the reactants may have a large positive contribution and the solvation of the TSs a small negative contribution to the entropy of activation in protic solvents. The $\Delta S^{\ddagger}$ value is higher and changes with the substituents in the opposite way as in aprotic solvents. This may be the reason why the signs of the $\delta\Delta S^{\ddagger}$ reaction constants are different in protic and aprotic media.

Conclusions

Our aim was to calculate the dependence of the activation parameters on both substituents and solvents in selected S_N2 reactions, using the DFT method with a moderate basis set. The $\delta\Delta G^{\ddagger}$, $\delta\Delta H^{\ddagger}$, and $\delta\Delta S^{\ddagger}$ slopes of the linear $\Delta G^{\ddagger}/\Delta H^{\ddagger}/\Delta S^{\ddagger}$ versus σ plots were compared with the experimental data. The $\delta\Delta G^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ reaction constants could be calculated with acceptable accuracy. The best agreements were obtained between the least solvent-dependent experimental and the calculated $\delta\Delta G^{\ddagger}$ data. The calculated $\delta\Delta G^{\ddagger}$ and $\delta\Delta H^{\ddagger}$ values were similar because the calculated $\delta\Delta S^{\ddagger}$ values are generally small. Remote substituents change scarcely the structure of the TSs; rather e-w groups increase their tightness and so may decrease the calculated $\Delta S^{\ddagger}$ value only slightly. Because this effect is small, we could accept the former supposition[1,3] that the majority of the experimentally observed change of $\Delta S^{\ddagger}$ with the substituents is caused by the change of solvation and by the reorganization of the solvent. Since the latter effects cannot be calculated yet, the experimentally obtained and calculated $\delta\Delta S^{\ddagger}$ reaction constants deviate considerably. The experimental $\delta\Delta S^{\ddagger}$ can be explained only qualitatively by discussing the change of solvation in a reaction, where the desolvation of the reactants, the solvation of the TSs, and the reorganization of the solvent are taken into account.[3] An increasing charge of the TS and the increasing solvation may lead to a decrease of $\Delta S^{\ddagger}$ in dipolar aprotic solvents and to an increase of $\Delta S^{\ddagger}$ in highly ordered protic solvents. The sign of $\delta\Delta S^{\ddagger}$ and consequently that of the β isokinetic temperature (eq 16), as well as the temperature dependence of the selectivity in a given reaction series,[1] may change with the solvent. Because enthalpy has a contribution from the reorganization of the solvent (eqs 10 and 12), the effect of substituents on $\Delta H^{\ddagger}$ can be computed sometimes only with slight accuracy, and thus the experimental and calculated $\delta\Delta H^{\ddagger}$ values may also deviate significantly.

The $\Delta G_o^{\ddagger}$, $\Delta H_o^{\ddagger}$, and $\Delta S_o^{\ddagger}$ data for the unsubstituted compounds in a reaction series can be computed satisfactorily only if the reactions of neutral molecules are investigated in aprotic solvents. In the reactions of ions or in case of the reorganization of protic solvents by H-bond formation, the calculated and experimental data may show considerable deviations.

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Supporting Information Available: Listing of calculated electronic and thermal free energies and enthalpies, entropies of formation, dipole moments, selected atomic charges, bond distances and angles as well as Gaussian input (gjf) files to reproduce the published data for reactants and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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(46) Salomen, M. *J. Phys. Chem.* **1970**, *74*, 2519−2524.
(47) Persson, I. *Pure Appl. Chem.* **1986**, *58*, 1153−1161.