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Steric Effects in S_N2 Reactions. Determination of Transition State Structures for the Quaternization of 2-Alkylpyridines and -thiazoles by a Combined Experimental and Molecular Mechanics Procedure

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S_N2 transition-state structures for the Menschutkin reaction between 2-alkylpyridines or -thiazoles and CH_3X (X=I and SO_3F) have been calculated by the Allinger 1973 force field method. Experimentally found differences in steric energies between the quaternary iminium ions and the activated complexes are used as measures for the evaluation of the position of the transition state. Estimates of the carbon–nitrogen distance (r_{C-N}) in the transition state result in a 22±4 % extension compared to the ground state value (1.48 Å) depending upon the transition state model used. The preferred model results in r_{C-N}=1.812±0.013 Å. Consistent results were obtained with nucleophiles of different geometries (pyridines and thiazoles). A change of leaving group from iodide to fluorosulfonate leads to an extension of r_{C-N} by 0.04±0.02 Å. The results are discussed in relation to earlier work and the reactivity selectivity principle.

In the ideal case, the mechanism of a chemical reaction may be considered known if the motions of the participating atoms and the connected potential energy could be determined during the path from reactants to products. Since it is not generally possible to obtain such an intimate picture, one is reduced to obtaining information at one or more crucial stages of the reaction. The widespread use of the transition state (TS) theory has focussed the interest on the structure of the activated complex, but even this more modest purpose is not easily achieved.

Nucleophilic displacement reactions at saturated carbon have been the subject of continuous interest with respect to their mechanistic details.[1] Although numerous experimental studies have been carried out on the S_N2 reaction, little is known about the detailed geometry of the activated complexes. The experimental methods that are used are indicative rather than conclusive and give qualitative estimates of possible changes in TS structures imposed by small changes in the reactants, such as change of solvent,[2] nucleophile [3–6] and leaving group.[3,7,8] The results are often used as arguments in the ongoing controversy concerning the validity of the reactivity–selectivity principle (RSP) and related to the predictions of Hammond,[9] Thornton [10] and Harris and Kurz.[11] These approaches, however, only tell us the direction and not the magnitude of the possible changes imposed by the perturbation.

There have been several MO studies on the S_N2 reaction.[12–16] The calculations have usually been carried out on reactions with symmetrical TS of the type $[H{---}CH_3{---}H]^-$, $[F{---}CH_3{---}F]^-$ and $[H_2O{---}CH_3{---}OH_2]^+$. The CNDO [14,16] and INDO [15] methods give values of the length of the reacting bond in the TS which are 7–12 % longer than in the reactants (products) for the negatively, as well as the positively, charged TS:s. On the

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other hand, an enlargement of 29–48 % was obtained by the *ab initio* method.[12,13] The calculations were performed for reactions *in vacuo* except in one case,[14] where a small increase from 7 to 8 % was calculated for the influence of solvation (water). What we know today about the profound influence of solvation on the Menschutkin reaction (*vide infra*) gives no support to any direct comparison between gas phase data (or calculations that refer to gas phase properties) and results obtained from reaction in solution. In this work we are interested in the reaction in solution.

Recently, we proposed the use of a linear free energy relationship of the type $\log (k/k_o)_1 = \delta \log (k/k_o)_2$ to correlate steric effects with geometric parameters.[17] This idea is based upon the assumption that the steric strain might be expected to monotonously increase (or decrease) along the reaction coordinate for the reactions studied at least in the neighbourhood of the transition state. A minor perturbation, causing a shift of the position of the TS should thus imply a change of the strain, which in turn should affect the relative rate of the reaction. The utility and significance of such an approach has been demonstrated for variation in nucleophile geometries,[17] for variation in the nature of the leaving group [18] and in the study of the evaluation of the position of the TS in the Menschutkin reaction.[19] Furthermore, there is an interesting potential in this method, namely, since the geometric dependence of steric effects is approximately known, an actual estimate of distances and distance changes in the TS might be made, assuming that the proper energetics are known. This work describes an attempt to calculate, by an established force-field method, the geometries of the activated complexes for the reactions between 2-alkylpyridines or 2-alkylthiazoles and methyl substrates, using the steric parameters from Refs. 17–19 and some other work. The calculation of steric effects of alkyl groups on the rate constants for the S_N2 reaction has been the subject of several investigations since the classical work by Ingold and coworkers [20] on alkyl halides. Ingold's approach has been refined and applied to modern force-field methods.[21,22]

In this work we use the molecular mechanics method to calculate substituent strain increments in such a way that they can be related to experimental values in order to give information about the geometries of the TS. In this respect there is an obvious resemblance between our approach and those of previous work, but in this work we study non-symmetrical TS and heteroaromatic nucleophiles. We also want to emphasize that it is not attempted to be an *ad hoc* force field calculation of the S_N2 TS. Such calculations are necessarily prone to certain difficulties regarding the validity of the potential functions and of the force field for highly distorted species and regarding the problem of localization of saddle points on the potential energy surface. Furthermore, we are interested in the geometry of the TS for reaction in solution and not in gas phase. The most interesting geometrical parameters of the S_N2 TS are the bond lengths of the two bonds which are formed and broken in the reaction. They are often used as "reaction coordinates" but essentially no attempts have been reported to quantitatively estimate these values by experimental methods.

EVALUATION OF EXPERIMENTAL DATA

More than twenty years ago Brown *et al.* made extremely careful studies of the rates of reaction of 2-, 3- and 4-alkylpyridines with alkyl iodides.[23] They found that while the introduction of an alkyl group in the 3- or 4-position resulted in small increases in rate following the basicity of the nucleophiles, the introduction of such groups in the 2-position resulted in a decrease in rate being gradually more pronounced in the series methyl<ethyl<isopropyl<*t*-butyl. They proposed that this decrease in rate was due to steric strain in the activated complex and estimated this strain ($\Delta\Delta H$) to 1.7 kJ for 2-methyl-, 2.5 kJ for 2-ethyl-, 5.0 kJ for 2-isopropyl and 16.3 kJ/mol for 2-*t*-butylpyridine, in all cases related to pyridine. Furthermore, they evaluated the strain in the activated complex to amount to 65 % of the strain in the final product by considering homomorphous complexes of pyridines and Lewis acids. Our later investigations [17–19,24] are in excellent agreement with the results obtained by Brown *et al.*

In Fig. 1 a generalized energy profile for the reaction between a 2-alkylpyridine and CH_3X is shown. According to the principle of microscopic reversibility, the reverse reaction, *i.e.* the dequaternization of the pyridinium salt, should

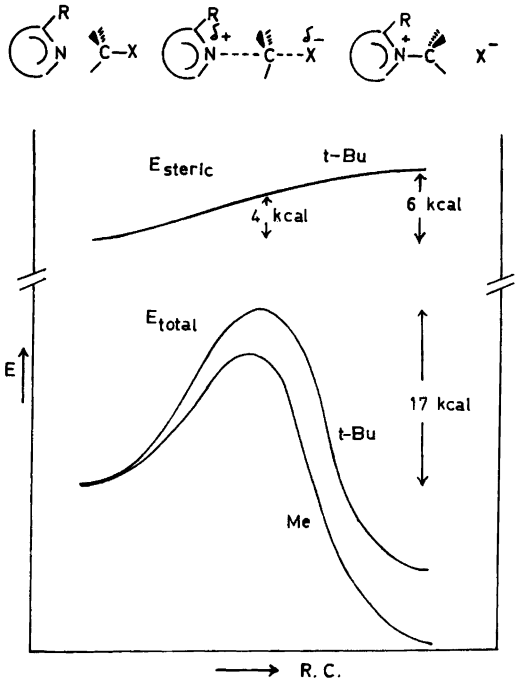
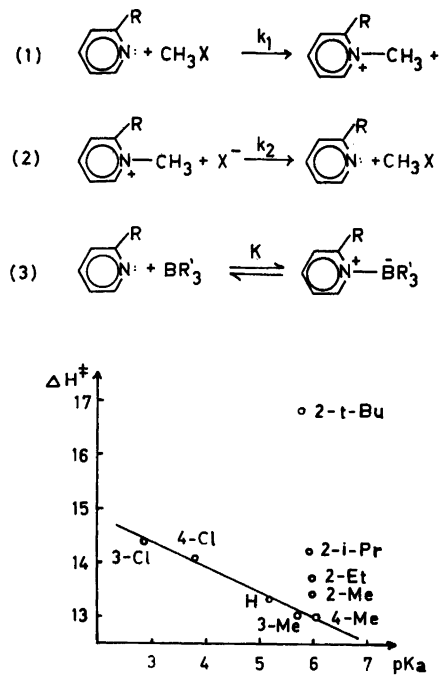


Fig. 1. A pictural potential energy profile for the quaternization of 2-methylpyridine and 2-*tert*-butylpyridine and the steric contribution to the reaction. (1 kcal=4.186 kJ).



Scheme 1. Graphical representation of the evaluation of the steric energies and the reactions for which the method was applied (1 kcal=4.186 kJ).

have the same TS and the reverse energetics as compared to the quaternization. This should also be valid for the steric part of the energy. In a recent investigation of the demethylation of 2-substituted pyridinium salts by triphenylphosphine in DMF,[19] we estimated the relief of strain in the transition state of this reaction to be 53±3 % of the steric compression in that of the methylation. This is equivalent to a strain in the activated complex amounting to 65±3 % of the strain in the salt in striking agreement with the data of Brown *et al.*[23] Experimental data are shown in Table 1. A similar quaternization/dequaternization investigation has also been carried out for 2-alkylthiazoles [25-26] (Table 2), and a strain in the activated complex amounting to 57±4 % of the strain in the salt was estimated.*

* In our earlier papers [19,25] we proposed that triphenylphosphine is the dealkylating agent. It has since been shown that the iodide counter ion is actually the nucleophile.[27] The conclusions are, however, still valid or actually reinforced by this new knowledge.

The pertinent thermodynamic parameter for comparison with calculated steric energies is the enthalpy. In the forward reaction the steric contribution of a substituent R was evaluated by the deviation from the linear relation between activation enthalpy and pK_a for 3- and 4-substituted pyridines according to eqn. (1) as illustrated in Scheme 1.

$$\Delta\Delta H_R^{\ddagger} = \Delta H_R^{\ddagger} - (\alpha \cdot pK_a + \text{const.}) \qquad (1)$$

For the reverse reaction only relative rate constants are available. We were thus forced to introduce the approximation that *the entropy of activation is constant for 2-Me, 2-Et, 2-i-Pr and 2-t-Bu pyridines in this reaction.* The observation that the relief of strain is 53 % of the compression in the methylation enables the calculation of the steric enthalpy increments of the 2-substituents in the *N*-methylpyridinium ion. Essentially the same values were obtained by Brown *et al.*[23] The experimental results for both pyridines and thiazoles are collected in Table 3.

The purpose is now to calculate the differences in strain energy (δE_s) between the pyridinium (thiazolium) ion and the TS, which reproduce the experimental data in Table 3. Furthermore, the results in Ref. 18 may be used to study the effect of a change of the leaving group on the TS geometry. We found that the strain in the TS upon methylation of 2-alkylpyridines with methyl fluorosulfonate was 69±3 % of the strain in the TS on methylation with methyl iodide. Thus, the δE_s values for methyl fluorosulfonate methylation given in Table 3 may be calculated.

METHOD OF CALCULATION AND TS MODELS

The δE_s values given in Table 3 represent differences in strain energy between the quaternary iminium salt and the activated complex.

Table 1. Kinetic data for methylation and demethylation in the pyridine series.

2-Subst.	Methylation [a] $k^{25\,°C} \cdot 10^6$ [c]	log k/k_H	$\Delta H^{\neq}$ [d]	$\Delta S^{\neq}$ [e]	Demethylation [b] log k/k_H
H	343	0	55.7	-124.7	0
Me	162	-0.32	56.1	-129.8	0.00
Et	76.4	-0.65	57.3	-131.9	0.163
i-Pr	24.5	-1.14	59.4	-134.4	0.459
t-Bu	0.080	-3.63	70.3	-144.8	1.70

[a] By CH_3I in nitrobenzene.[23a] [b] Of pyridinium iodides by Ph_3P in DMF at 153 °C.[19] [c] $M^{-1}\,s^{-1}$. [d] kJ mol^{-1}. [e] J $mol^{-1}\,K^{-1}$.

Table 2. Kinetic data for methylation and demethylation in the thiazole series.

2-Subst.	Methylation [a] $k^{25\,°C} \cdot 10^6$ [c]	log k/k_H	$\Delta H^{\neq}$ [d]	$\Delta S^{\neq}$ [e]	Demethylation [b] log k/k_H
H	3.22	0	68.6±0.8	-119.7±5.0	0
Me	4.54	0.15	66.5±1.7	-123.5±9.6	−0.22
Et	3.47	0.03	67.8±0.4	-122.6±1.2	−0.056
n-Pr	3.51	0.04	67.4±0.4	-123.5±1.2	−0.027
i-Bu	3.31	0.01	67.4±0.4	-123.9±2.9	+0.0086
neo-Pent	2.44	-0.12	68.2±0.8	-124.3±4.2	+0.20
i-Pr	1.53	-0.32	70.7±1.2	-119.3±7.1	+0.26
t-Bu	0.098	-1.52	76.6±1.7	-122.2±8.8	+1.08

[a] By CH_3OTs in nitrobenzene.[26] [b] Of thiazolium iodides by Ph_3P in DMF at 153 °C. [c] $M^{-1}\,s^{-1}$. [d] kJ mol^{-1}. [e] J $mol^{-1}\,K^{-1}$.

Table 3. Strain energies ($\Delta\Delta H$/kJ mol^{-1}) in the transition states and in the iminium ions evaluated from the methylation–demethylation data.

2-Subst.	Pyridines TS	Salt	δE_s^{I} [a]	$\delta E_s^{OSO_2F}$	Thiazoles TS	Salt	δE_s^{I} [a]
Me	1.9	2.8	0.9	1.5	0.6	1.3	0.7
Et	2.9	4.4	1.5	2.4	1.7	2.6	0.9
i-Pr	5.0	7.5	2.5	4.1	4.2	6.1	1.9
t-Bu	15.9	23.9	8.0	12.9	10.5	16.8	6.3

[a] $\delta E_s = \Delta\Delta H_{salt} - \Delta\Delta H_{TS}$.

Thus the procedure of calculation falls into two parts. In the first part the energy of the salt is calculated. This is in principle a straight-forward calculation of a molecule with ground state structure and properties. In the second part TS models are to be constructed in such a way that the difference in calculated steric energy between the salt and the activated complex reproduces experimental δE_s values. The TS models are described in detail below.

Allinger's 1973 force field [28,29] has been used throughout the calculations. The steric energy calculated by the molecular mechanic method is not the same as the experimental strain energies, but contains also contributions that depend on how the force field has been defined and on the motional restrictions that we introduce (*vide infra*). In the method to be described, differences in calculated steric energies between two species are carried out in such a way that these force-field dependent contributions cancel out.

The structures of *N*-methylthiazolium iodides with alkyl groups in the 2- and 4-positions have been determined by X-ray crystallographic methods.[30] In the pyridinium series no 2-substituted salt has been studied. Instead X-ray data on 3-substituted *N*-methylpyridinium salts make the experimental basis for the structure of the pyridinium ring in this work.[31] Since the force field is not parametrized for the pyridine and thiazole system, the ring skeleton (carbon, nitrogen and sulfur atoms) was kept rigid, and idealized geometries, taken from Refs. 30 and 31 were used (Fig. 2), the same for both salts and TS models. Apart from this restriction full relaxation was allowed, *i.e.* the ring hydrogens, the *N*-methyl and the 2-alkyl substituents were allowed to move with respect to all degrees of freedom.

The calculations satisfactorily reproduced known structures of 2-alkylpyridines and -thiazoles as well as the corresponding salts.

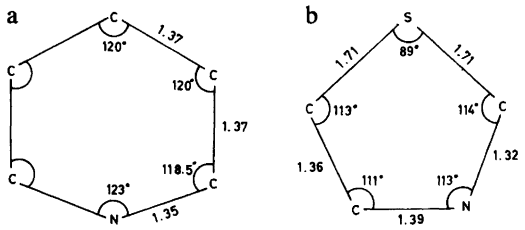


Fig. 2. Geometries for the ring skeleton, a. pyridine; b. thiazole.

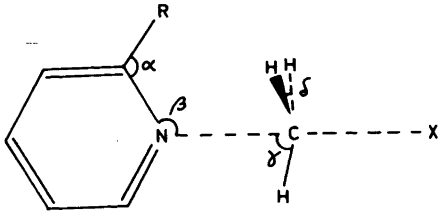


Fig. 3. Definition of the geometrical parameters of the transition state.

The TS models are defined by the internal coordinates given in Fig. 3. The main assumptions implicit in the ground state are, when possible, maintained in the TS model. The problem consists of choosing values of the angles α_o, β_o, γ_o, δ_o, the distance r_{C-N} and their corresponding force constants.*

The structures of 2-alkylpyridines or 2-alkylpyridinium salts have not been determined so that the value of α_o, the minimum energy angle, was varied within a few degrees around the one for which it symmetrically bisects the extranuclear angle. For the thiazole series α_o was chosen so as to reproduce experimental structures of the 2-alkylthiazolium salts. The same α_o was invariably used for the TS model as for the salt.

Since the bond between the central carbon and the nitrogen atom is created as the reaction progresses, the bending constant k_β is a function of the position along the reaction coordinate axis. More specifically, the value for k_β may be considered to increase from zero at the initial state to the normal value of the salt. Either of these extreme values has been used in the calculations.

The problem of choosing minimum energy values for the angles γ and δ is also connected to the degree of evaluation of the reaction at the TS. At present, there seems to be a general agreement that the TS of the Menschutkin reaction is reactant-like.[2] In the absence of detailed information we have, somewhat arbitrarily, chosen a model in which the inversion has progressed 85 % from ground-state angles to angles corresponding to a planar state (or, equivalently, to 42.5 % of the total inversion). This model was

* Subscript o, as in α_o, is denoted for minimum energy values for bond angles and bond lengths.

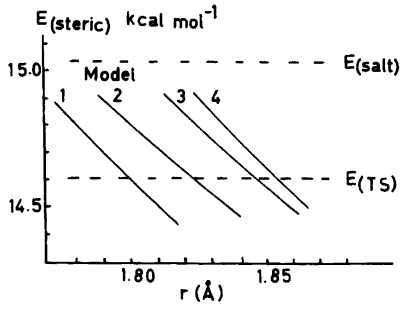


Fig. 4. Example of relations between calculated steric energy and carbon–nitrogen bond length for different transition-state models. (1 kcal=4.186 kJ).

recently used in force-field calculations on an S_N2 transition state.[32] In parallel studies, the planar model was used in order to make possible an estimation of the sensitivity of final geometries on variations in γ_o and δ_o. The bending constant k_γ was also varied from ground-state value to zero, whereas k_δ was kept at the ground-state value throughout.

The treatment of the reacting bonds in force-field calculations causes important problems, since it is highly questionable whether the normal ground-state force constants are valid for strongly distorted bonds. Moreover, it is by no means evident that the ordinary potential functions are valid in this case. Our method affords a way of getting around this problem. We perform calculations with a stiff C–N bond for varying bond lengths giving rise to an energy-bond distance relation (Fig. 4). A value of 999.9 m dyn $Å^{-1}$ was used for k_s, the stretch force constant.

The leaving group/counter ion is omitted in all calculations. Pyridinium ions form donor–acceptor complexes with iodide ions, but the latter exert little influence on the geometry of the cation,[31] so that the above approximation should cause no obvious disadvantage in the product salt calculations. In the activated complex the steric interactions between the leaving group and the rest of the atoms are obviously not negligible and these interactions are subject to strong variations during the course of the reaction. Of more importance to this investigation is, however, the difference in the development of these interactions between the 2-alkyl substituted pyridines (or thiazoles) on one hand and that of the unsubstituted heterocycles on the other hand. This difference is much smaller and if it can be neglected the leaving group may be omitted. We have made this assumption throughout the calculations. Support for this assumption was obtained in calculations on the hypothetical molecule 2-alkyl-*N*-iodopyridine with N–I bond lengths varying from 4.0 to 5.0 Å showing that the iodine atom is situated at or beyond the "van der Waals distance" between this atom and the 2-alkylpyridine moiety. Furthermore, an increase of the N–I distance was accompanied by a minimal increase in energy of 2.0 kJ $Å^{-1}$ or less.

The parameters are summarized in Tables 4 and 5.

Table 4. Force field parameters. Other parameters are found in Ref. 29.

van der Waals constants		
Atom	r^* (Å)	ε (kcal/mol)
C_{TS}	1.85	0.030
Stretching constants		
Bond	l_o (Å)	k_s (m dyn $Å^{-1}$)
C_{TS}–N	[a]	999.9
C_{TS}–H	1.09	4.6
Bending constants		
Angle	θ_o (deg)	k_b (m dyn Å rad^{-2})
$C_{sp}2$–N–$C_{sp}3$	118.5 (123.5) [b]	0.70
$C_{sp}3$–$C_{sp}2$–N	[a]	0.38
$C_{sp}3$–$C_{sp}2$–S	[a]	0.38
$C_{sp}2$–N–C_{TS}	118.5 (123.5) [b]	[a]
H–C_{TC}–H	[a]	0.19
H–C_{TS}–N	[a]	[a]

Torsional constants

Angle	V_1	V_2	V_3 (kcal/mol)
H–C_{TS}–N–$C_{sp}2$	0.0	0.0	0.0
H–$C_{sp}3$–N–$C_{sp}2$	0.0	0.0	0.0
$C_{sp}3$–$C_{sp}3$–$C_{sp}2$–N	0.0	0.0	0.30
$C_{sp}3$–$C_{sp}3$–$C_{sp}2$–S	0.0	0.0	0.30
H–$C_{sp}3$–$C_{sp}2$–N	0.0	0.0	0.0
H–$C_{sp}3$–$C_{sp}2$–S	0.0	0.0	0.0

[a] Varied in different transition state models according to Table 5. [b] Values in parentheses correspond to thiazole derivatives.

Table 5. Transition state models. Parameters are defined in Fig. 3.

Model	α_o [a]	k_α [b]	β_o [a]	k_β [b]	γ_o [a]	k_γ [b]	δ_o [a]	k_δ [b]
1	118(122) [c]	0.38	118.5(123.5)	0.70	90	0.42	120	0.19
2	118(122)	0.38	118.5(123.5)	0	90	0.42	120	0.19
3	118(122)	0.38	118.5(123.5)	0.70	87	0.42	119.25	0.19
4	118(122)	0.38	118.5(123.5)	0	87	0.42	119.25	0.19
5	120(124)	0.38	118.5(123.5)	0.70	87	0.42	119.25	0.19
6	120(124)	0.38	118.5(123.5)	0	87	0.42	119.25	0.19
7	118(122)	0.38	118.5(123.5)	0	87	0.30	119.25	0.19
8	118(122)	0.38	118.5(123.5)	0	87	0.05	119.25	0.19
9	118(122)	0.38	118.5(123.5)	0.10	87	0.20	119.25	0.19
10	118(122)	0.38	118.5(123.5)	0.20	87	0.10	119.25	0.19
11	120(124)	0.38	118.5(123.5)	0.05	87	0.25	119.25	0.19
12 [d]	120	0.38	118.5	0.04	86	0.25	119.0	0.19

[a] Degrees. [b] m dyn Å rad^{-2}. [c] Values in parentheses refer to thiazole derivatives. [d] Model for leaving group OSO_2F.

Table 6. Carbon–nitrogen bond lengths (r_{C-N}/Å) in the transition state for the models defined in Table 5.

Model	Me		Et		i-Pr		*t*-Bu	
	Pyridine	Thiazole	Pyridine	Thiazole	Pyridine	Thiazole	Pyridine	Thiazole
1	1.782	1.791	1.799	1.800	1.808	1.819	1.955	2.013
2	1.778	1.768	1.790	1.767	1.792	1.799	1.818	1.839
3	1.862	1.873	1.877	1.881	1.883	1.898	2.032	2.095
4	1.859	1.849	1.869	1.859	1.867	1.878	1.896	1.902
5	1.849	1.873	1.870	1.882	1.885	1.900	2.042	2.093
6	1.847	1.852	1.866	1.854	1.874	1.885	1.912	1.893
7	1.839	1.839	1.832	1.838	1.828	1.830	1.846	1.824
8	1.730	1.728	1.705	1.700	1.695	1.681	1.672	1.666
9	1.806	1.833	1.800	1.836	1.801	1.843	1.831	1,857
10	1.744	1.738	1.725	1.713	1.720	1.720	1.783	1.789
11	1.810	1.823	1.812	1.823	1.817	1.820	1.793	1.799

RESULTS AND DISCUSSION

Table 6 reports the carbon–nitrogen distances for 11 different TS models as defined by the force fields in Table 5. The models are chosen so as to cover different possibilities of combinations of extreme parameters as well as to make possible the choice of a "best" model as it is given by certain criteria. The total spread in r_{C-N} is 1.67–2.10 Å. Certain interesting points arise already at this level. (1) There is a striking agreement between pyridines and thiazoles throughout the series. (2) The parameters for which r_{C-N} is most sensitive are those associated with the degree of inversion around the central carbon, γ (δ) and k_γ. A variation from 35 to 50 % inversion causes a change of r_{C-N} of -0.08 ± 0.01 Å. (3) The *t*-Bu substituted compounds are much more sensitive to the parameter set than the Me, Et and i-Pr derivatives.

The question arises: can one discriminate between the models and how can that be done? We are setting up the following conditions:

(i) *The variation of* r_{C-N} *within a series Me, Et, i-Pr and* t*-Bu should not be too large.* We are here guided by the calculations for the change of leaving group from iodide to fluorosulfonate (*vide infra*). Fluorosulfonate is more reactive than iodide by a factor 10^4 whereas 2-Me-

pyridine is more reactive than 2-*t*-Bu-pyridine by a factor 10^3. Hence we anticipate that the corresponding change in r_{C-N} should not be significantly larger for a change of 2-substituent than for a change of leaving group.

(ii) *A steric perturbation in the Menschutkin reaction is associated with a change of the position of the transition state according to the Hammond postulate.* In two independent studies le Noble and coworkers claim that the most hindered and thus slowest reaction possesses the latest transition state and *vice versa.*[6,33] Their conclusion is based upon activation volume measurements [6] and kinetic isotope effects [33] for the methylation of 2,6-dialkylpyridines.

(iii) *The implications inherent in the technique of evaluating the experimental energy differences must be valid for nucleophiles with no* ortho *substituent.* Since the experimental values represent substituent strain increments the corresponding values for unsubstituted heterocycle should be zero or very close to zero for a realistic TS *i.e.* for an r_{C-N} distance fitting the pattern for the 2-alkyl derivatives. It has to be emphasized that we have no data that allow us to determine the TS structure for unsubstituted compounds in the same way as for the 2-alkyl derivatives.

Following these principles it turned out to be quite easy to determine an acceptable TS force field. Interestingly enough, this could be achieved for an essentially unique set of parameters. A limited variation of k_β from 0 to 0.10 m dyn Å rad^{-2} could be compensated by a variation of k_γ from 0.30 to 0.20 m dyn Å rad^{-2} resulting in a few equally significant models. We have chosen model 11 as the "best" model since we would like to avoid k_β=0. The r_{C-N} distances for which the energy of the iminium ion is the same as for the TS are 1.793 Å for *N*-methylpyiridinium and 1.791 Å for *N*-methylthiazolium (by model 11) which were considered to account for the condition (iii). Some interesting geometrical parameters are shown in Table 7. The conformations of the 1-methyl-2-alkyl groups are illustrated in Fig. 5.

Carbon–nitrogen distance. The length of the carbon–nitrogen bond in the TS is 1.793–1.823 Å in model 11 corresponding to an extension of the normal value (1.482–1.485 Å) by 21–23 %. It is obvious that these values are model dependent, but considering the results from calculations with extreme parameters one might estimate the extension to be 22±4 % or r_{C-N} to lie in the interval 1.75–1.87 Å including all eight compounds.

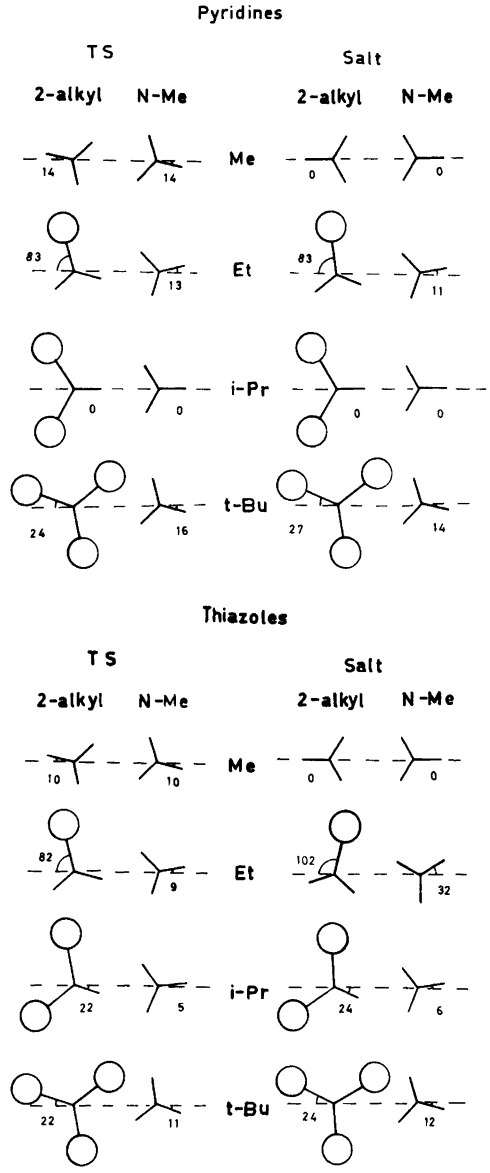


Fig. 5. Conformations of the 1-methyl-2-alkyl groups in the salt and in the transition state. The numbers indicate the dihedral angle between the sp^2-framework and the indicated bond.

In the Br^-+RBr halide exchange reactions Abraham *et al.* calculated C–Br extensions in the

Table 7. Transition state geometries according to model 11.

	Me		Et		i-Pr		*t*-Bu	
	Pyridine	Thiazole	Pyridine	Thiazole	Pyridine	Thiazole	Pyridine	Thiazole
r_{C-N}/Å	1.810	1.823	1.812	1.823	1.816	1.820	1.793	1.809
α/degrees	122.3	125.1	123.7	125.8	123.6	126.0	124.5	126.9
β/degrees	120.8	125.1	122.0	125.3	123.6	126.7	130.3	131.9
$\bar{\gamma}$/degrees [a]	93.2	92.2	93.3	92.0	93.6	93.1	95.4	94.6

[a] Mean value.

Table 8. Effects of changing the leaving group from iodide to fluorosulfonate.

Leaving group	Model		r_{C-N}			
			Me	Et	i-Pr	*t*-Bu
I^-	11		1.810	1.812	1.816	1.793
OSO_2F^-	11		1.832	1.839	1.849	1.851
		Δr_{C-N}	0.022	0.027	0.033	0.058
OSO_2F^-	12		1.851	1.849	1.850	1.858
		Δr_{C-N}	0.041	0.037	0.034	0.065

symmetrical transition state of 13–15 % [21] and De Tar *et al.* obtained 14–38 %.[22] Both of these groups allowed the C–Br bond to relax thus giving rise to energy minima. Julian and Taylor used kinetic isotope effects to evaluate transition state geometries for the reaction $PhS^- + n$-BuCl.[32] They found extensions of 10 % for the C–S distance and 2 % (!) for the C–Cl distance, the latter value not being much more than the amplitude of a normal vibration.

Effect of the leaving group. The effects of changing the substrate from methyl iodide to methyl fluorosulfonate may be treated by using the values from Table 3. Clearly all the model calculations result in an earlier TS for methyl fluorosulfonate than for methyl iodide. Adopting the same model (model 11) for both methyl iodide and methyl fluorosulfonate the change in the position of the TS, $\Delta r_{C-N} = r^F_{C-N} - r^I_{C-N}$, is 0.022 to 0.058 Å (Table 8).

It might be argued that since the position of the TS is believed to be different upon a change of leaving group, one cannot use the same parameter set. For this reason we have slightly modified the parameters, γ, k_γ and δ as shown in model 12 leading to the new Δr_{C-N} values 0.034 to 0.065 Å.

Mechanism. Recently Arnett and Reich reported a careful kinetic and thermodynamic investigation of the quaternization reaction of 3- and 4-substituted pyridines.[34] The work presents as up-to-date view of the mechanism of the Menschutkin reaction. The authors concluded that the degree of charge development in the TS is about 0.3 of that in the quaternary salt, slightly lower than the value 0.4 proposed by Abraham *et al.*[2] In geometrical terms the carbon–nitrogen bond was estimated to be about 30 % developed and the bond from the carbon to the leaving group to be nearly completely ruptured. The authors emphasized the crucial role of the solvent as manifested by the entropy parameters. The activation process for the forward reaction is determined to about 40 % by the entropy term and 60 % by the enthalpy term at room temperature. The entropy of activation has nearly the same large negative value (~ -125 J mol^{-1} K^{-1}) as for the complete reaction whereas the reverse

reaction showed a small positive entropy of activation.*

Olmstead and Brauman studied gas phase displacement reactions with anionic nucleophiles and deduced a mechanism which deviated significantly from reactions in solution.[35,36] This study also pointed at the decisive role of solvation in the S_N2 reaction.

How does our work fit with these interpretations? A question we have to consider is whether the steric effects observed in the Menschutkin reaction are actually diverse steric effects on solvation of the ground state compared to the TS. There is good reason that this is not the case.

(1) Although the rate of quaternization reactions is enormously dependent on the solvent there is virtually no dependence of the *ortho* steric effects on the solvent provided that the solvent is aprotic.[24]

(2) There is a good correlation between pK_a values and proton affinity in the gas phase also for 2-substituted pyridines.[37]

(3) Since only 2-alkylsubstituted pyridines are studied the electronic effects are virtually constant.

(4) Solvent reorganization is mainly taking place around the iodide atom [34] relatively far away from the place of substitution.

(5) The experimental steric energies are evaluated from $\Delta H^{\neq}$ values whereas solvent effects are largely reflected in $\Delta S^{\neq}$.

(6) The present calculations show that there is an increasing steric interaction between the nucleophile and the substrate when the 2-substituent is changed from methyl to *t*-butyl for any TS model tested.

Although the mechanism of Arnett and Reich is qualitatively in agreement with our TS model, there are very few details open to quantitative comparison. For example, how may their estimation that the carbon–nitrogen bond is 30 % developed in the TS be compared with ours that the bond is elongated 22±4 % in the TS?

We consider the result that the entropy changes from the TS to the products is small as a support to our approach of performing calculations on the salt and the TS.

The finding that steric effects are present as rate-retarding in the forward reaction and accelerating in the reverse reaction seems to be in line with a pentavalent TS in which the C–N bond is formed (or broken) in the rate determining step as in the classical S_N2 mechanism. Other authors have reached the same conclusion for the Menschutkin reaction.[2]

Effects of nucleophile geometry. Deady *et al.* have discussed the steric effects in the forward and reverse Menschutkin reactions of pyridines and thiazoles.[38] They noted that di-*ortho* substituted pyridines such as 2,6-lutidine did not follow the general trend observed for mono-*ortho* azines, for which the ratio of hindrance in the forward reaction to acceleration in the reverse reaction is approximately 2:1. Instead they found a ratio of 3:1 for the disubstituted compounds. Furthermore, they found no steric effect in the demethylation of thiazolium salts in contrast to our finding.[25] The reason for this discrepancy might be found in the following: Firstly, the sensitivity to steric effects is less important for thiazoles than for pyridines also in our hands. Secondly, we observed that the demethylation of the thiazolium series was less clean than the reaction in the pyridinium series and we observed a poorer correlation too.[25] Besides, Deady *et al.* studied only four thiazole compounds.

We thus face a situation where both the type of heterocyclic system and the substitution pattern influence the ratio of steric effects in the forward and reverse reactions. The trend is that the more susceptible to steric effects the system the larger this ratio, *i.e.* 2-substituted thiazoles 4:3, mono-*ortho* pyridines 2:1 and di-*ortho* pyridines 3:1.

As a check of the consistency of the calculations we have performed calculations for 2,6-lutidine. The strain in the TS of the methylation of 2,6-lutidine with methyl iodide can be evaluated to be 7.5 kJ mol^{-1}.[23b,38] A 3:1 ratio in methylation–demethylation leads to a strain in 1,2,6-trimethylpyridinium of 10.0 kJ mol^{-1}. Using model 11 an r_{C-N} distance in the transition state

* An interesting comparison may be found in a monomolecular process with similar charge developments; rotation around the carbon–carbon double bond in polarized ethylenes. Berg, U. and Sjöstrand, U. *Org. Magn. Reson. 11* (1978) 555. The rotational barrier around the formal carbon–carbon bond in two types of polarized ethylenes was studied: planar systems in which charge is created on going from ground state to TS and twisted systems with opposite charge development. Large negative entropy parameters were found on creation of charge and a small positive entropy term was found on extinction of charge and the effects were interpreted in terms of solvent reorganization. That study offers a case in which translational entropy contributions do not interfere.

of 1.863 Å was calculated. This value is somewhat high (by *ca.* 0.05 Å) but still within the interval of confidence. Assuming instead a ratio of 2:1 another r_{C-N} distance of 1.890 Å is obtained, a value which clearly falls outside the interval.

The reactivity–selectivity principle (RSP). Lately the RSP has attained remarkable interest as shown by the appearance of quite a few review articles in this domain.[39–42] The current controversy on the RSP is also illustrated by several recent papers.[43–60] The mere fact that there are so many violations to the RSP suggests that it can hardly be looked upon as a *general* principle in chemistry. In our opinion this does not mean that no information of interest can be obtained from reactivity–selectivity considerations. It is also clear that we need to know more of the reasons for adherence, or lack of it, to the RSP.

An interesting example in this connection is the important disparity between our results [18] and those of Arnett and Reich [43] on the effect of changing the leaving group from iodide to fluorosulfonate. Arnett and Reich found that 3- and 4-substituted pyridines did *not* obey the RSP in contrast to our results. Is this behaviour in agreement with our proposal that the position of the TS is changed 0.04±0.02 Å when the leaving group is changed from iodide to fluorosulfonate? If our hypothesis is correct that the selectivity is determined by steric effects in this reaction, the answer is yes. This is shown by calculations on unsubstituted pyridine. When the "fluorosulfonate model" (model 12) is compared to the "iodide model" (model 11) identical values in steric energy are obtained when r_{C-N} is 0.02 Å longer in the fluorosulfonate model. In other words, a shortening of the C–N distance by 0.02 Å is compensated by a change in pyramidalization with respect to the steric energy for pyridines unsubstituted in the *ortho* positions.

These observations lead to the question: what is the role of steric effects in reactivity–selectivity relationships? The general opinion seems to be that steric effects are the source of many violations of the RSP [51] and that they can usually not be quantified. We are not prepared at this time to speculate on the extent to which differential steric effects may influence the interpretability of reactivity–selectivity relationships in general. However, we believe that this study has shown that steric effects do not always obscure the interpretation but may be used, in certain cases, to gain information on mechanism and TS behaviour.

CONCLUSIONS

1. Kinetic data for the forward and reverse Menschutkin reaction of 2-Me-, 2-Et-, 2-i-Pr- and 2-*t*-Bu-pyridine and -thiazole may be used to evaluate the influence of *ortho* alkyl substituents on energies of the transition states (TS) and the product ions.

2. The ratio of the steric hindrance in the forward reaction to the acceleration in the reverse reaction increases with the susceptibility to steric effects of the system; this ratio being 4:3 for 2-substituted thiazoles, 2:1 for mono-*ortho* substituted pyridines and 3:1 for di-*ortho* substituted pyridines.

3. Force field (Allinger's MMI) calculations on the iminium ions and on TS models may be used to semi-quantitatively estimate the geometries of the transition state. Consistent results are obtained including all eight compounds.

4. The most interesting geometrical parameter, the carbon–nitrogen bond length, is 1.793–1.823 Å in the transition state employing the "best" model. Considering the model dependency and the various approximations introduced, an extension of 22±4 % from the ground state value seems realistic.

5. The studies are complementary to other work on the mechanism of the Menschutkin reaction and give support to the classical S_N2 mechanism operating in this reaction.

6. The effects of changing the leaving group from iodide to fluorosulfonate were treated and it was found that the carbon–nitrogen bond length in the TS was 0.04±0.02 Å longer for attack on methyl fluorosulfonate than on methyl iodide in accordance with the Hammond postulate. The magnitude of the geometrical variation with a perturbation appears to be small.

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