J. Org. Chem. **1995**, *60*, 1975−1980

Transition State Structural Variations in the Menshutkin Reaction. A Computational Study of Steric and Electronic Substituent Effects

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Received August 30, 1994®

Transition structures for the gas phase S_N2 reactions of substituted pyridines with methyl chloride, bromide, and iodide, respectively, have been localized by the AMPAC program using the AM1 Hamiltonian. The reactions are strongly endothermic ($\Delta E \approx 40-60$ kcal/mol) and have activation barriers of ca. 70 kcal/mol, and the calculated order of leaving group (X) abilities is I < Br < Cl. The carbon−nitrogen bond is longer for the more reactive leaving group. The structural parameters are relatively insensitive to substitutions in the pyridine ring. Increasing the steric strain in the *ortho* position (methyl to *tert*-butyl or 2,6-dimethyl) leads to *looser* and *earlier* transition states, whereas substitution with electron-withdrawing groups in the *para* position has very little effect on the transition structure. Solvent effects were briefly mimicked by means of a dipole placed on the N···C···X axis with the positive charge pointing toward X. This results in a decrease of the activation barrier, a less endothermic reaction, earlier transition state, and a larger negative charge on X. The consequences of steric effects in this reaction are discussed.

The structure of transition states in organic reactions is a central theme in physical organic chemistry.[2] It is so for fundamental reasons but also because several practical consequences, such as enantio- and diastereoselectivity,[3] follow from an understanding of this structure. There is no general agreement on the problem of substituent effects on the geometrical features of a given transition state. It seems that, depending upon the mechanism, substituents may have either profound or negligible influence on the geometries of the transition structures. In pericyclic reactions, for example, a concerted mechanism is associated with small substituent effects whereas reactions with diradical transition-state character show larger geometrical response to substituent variations.[4]

The quaternization reaction of tertiary amines by alkyl substrates (the Menshutkin reaction) is characterized by neutral reactants and charge separation developing during the course of the reaction. The reaction has been extensively studied in solution with respect to effects of variations in substituents, leaving group, solvent, etc., and reactivity−selectivity relations have been considered as indicators of structural variations of the transition state.[5] Experimental results suggest that substituents on the pyridine ring whose effects on the rate constants cover several orders of magnitude do not markedly change the geometry of the transition state.[6,7] These conclusions are mainly based upon linear free energy relations. The use of such relations as transition-state structure probes has, however, been questioned,[8] and Hoz has recently suggested that the LFER coefficient could reflect other characteristics of the transition state.[9]

We have proposed the use of steric effects as a monitor of transition-state structural changes. Thus, it was observed that methylation of substituted pyridines with methyl iodide and methyl fluorosulfonate follows the reactivity−selectivity principle (RSP) for 2-substituted[10] but not for 3- and 4-substituted pyridines.[7] We interpret this as being due to the extra steric contribution to the activation energy induced by a small structural change.[11] The $1/r^{12}$ dependence of the repulsive part of the van der Waals potential is an indication that steric effects are a sensitive probe of structural variations. For example, the sensitivity to steric effects in quaternization of 2-R-pyridines is 51 times larger than for 2-R-thiazoles due to the different geometries of the 6- and 5-membered rings.[12] The dichotomy of the 2- and 3,4-pyridine quaternization could thus be understood in terms of more sensitive steric monitor than Brønsted-type monitor in combination with small structural changes. That there are changes in the transition structure in the Menshutkin is suggested by the α-deuterium,[13] carbon-14,[14] and nitrogen-15[15] kinetic isotope effects (KIE).

Steric effects can be considered from two viewpoints in this connection: (i) the effect on the structure and the

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® Abstract published in *Advance ACS Abstracts*, March 15, 1995.

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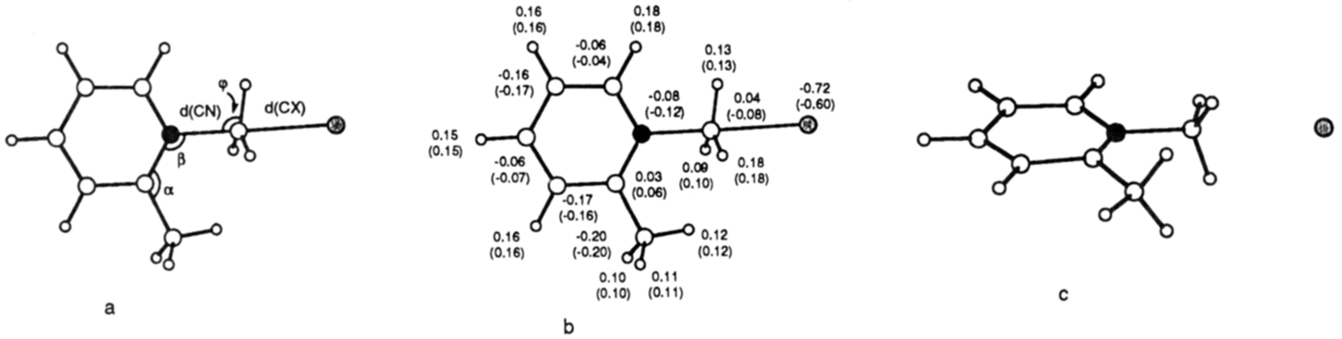

Figure 1. (a) Structural parameters of the transition state. The geometry shown is for the 2-methylpyridine–methyl chloride transition state. (b) Charge distribution in the transition state for the reaction of 2-methylpyridine with methyl chloride or methyl iodide (iodide values in parentheses). (c) Product cluster for the 2-methylpyridine–methyl chloride reaction. The carbon–chloride distance is 2.70 Å.

energy of the S_N2 transition state imposed by the *steric perturbation* and (ii) the role of nonbonded interactions in monitoring structural changes of the transition state caused by *other perturbations*. Experimentally, the first question has been addressed in two papers, both suggesting that an increase of steric strain imposed by 2- (and 6-) substituents leads to later transition states in accordance with the Hammond postulate; the activation volume of 2,6-dialkylpyridines is more negative for the bulkier substituents[16] and the chlorine KIE in reactions between methyl chloride and pyridine/2,6-dimethylpyridine,[17] a comparison which includes both electronic and steric effects though. Opposite results were found for the chlorine KIE in the reactions of quinuclidine and triethyl amine with methyl chloride.[18]

From the above it is clear that an understanding of the entanglement of steric and electronic effects in the transition state is important. The progress recently made in the molecular orbital treatment of transition states[19] should make it possible to simulate situations where both steric and electronic factors are present. Numerous computational efforts have been devoted to the S_N2 mechanism, but involve mostly anionic nucleophiles.[20,21] In the case of the Menshutkin reaction, where the reagents are neutral, the reaction between ammonia and methyl bromide was studied by Solà *et al.* using ab initio methods with special emphasis on solvent effects,[22] and the quaternization of pyridine with methylating agents was investigated by Viers *et al.*[23] Very recently, Shaik *et al.* presented computational results and an analysis in terms of the avoided crossing concept.[24] Molecular mechanics has been used to estimate transition structures in the Menshutkin reaction.[11]

We report computational results of substituent effects on the transition structure of the Menshutkin reaction: quaternization of 2-, 2,4-, and 2,6-substituted pyridines with methyl halides using the AM1 (and MNDO) semiempirical MO method of the AMPAC program. Some complementary experimental results are also presented.

Method and Explorations

The objective of this work was to localize transition states for the substitution reactions between pyridine derivatives and methyl substrates with fluoride, chloride, bromide, iodide, methanesulfonate, and triflate as the leaving group. The AMPAC program (version 2.14) employing the AM1 Hamiltonian was used.[25] The most interesting structural parameters are shown in Figure 1a. Transition state localization was performed in several steps. An initial GRID calculation gave an approximative idea of the potential energy surface, the CHAIN algorithm localized the highest transition state between given reactant and product geometries, the Powell and full Newton algorithms localized saddle points. Increased precision (PRECISE) was used in final refinements. Finally, the intrinsic reaction coordinate (IRC) algorithm was applied connecting the transition state with reactants and products by following the transition vector in both directions. Starting from the transition state the method follows a reaction path tangential to the force in weighted Cartesian coordinates. In contrast with gas phase S_N2 reactions of anionic nucleophiles the reactant clusters are simply van der Waals complexes of neutral molecules. An example of the structure of a product cluster is shown in Figure 1c.

The following observations were made: the reaction with fluoride as leaving group did not follow the S_N2 pathway but gave transition states on the way to elimination reactions according to Scheme 1, and fluoride was abandoned in the work.[26] This behavior is consistent with the strong basicity of a "naked" fluoride.[27] Since there was a tendency also with, e.g., chloride to associate with a hydrogen atom on the way to elimination products we introduced the single constraint that nitrogen–central

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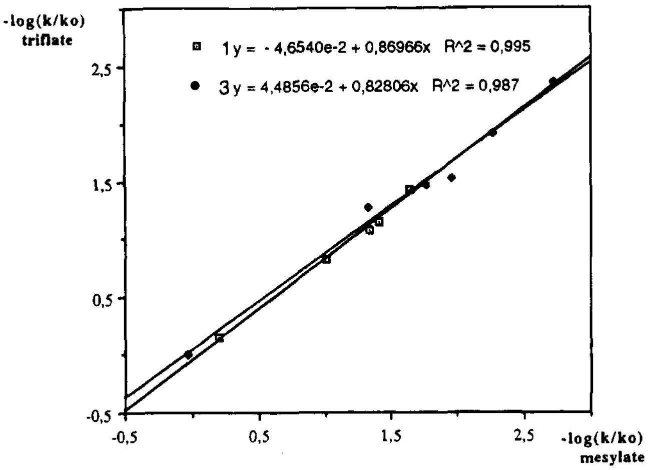
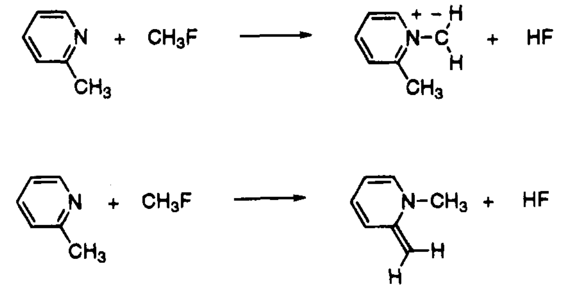


Figure 2. Comparison of experimental rate data for quaternization of 2-substituted pyridines in water/acetonitrile (60/40, ⊡) and acetonitrile (◆) at 25 °C. Substituents are 2,4-dimethy, 2-methoxy, 2-chloro, 2,6-dimethyl, 2-cyano, and 2-phenyl (only acetonitrile).

Scheme 1



carbon—leaving group lie on a line. In most cases this led to true first-order saddle points. In a few cases a second negative eigenvalue was observed some 2 orders of magnitude smaller than the first one. It is difficult to assess exactly the relevance of the second negative eigenvalue caused by the geometry constraint, but an analysis shows that it only affects the dummy atom used to define the linear transition state. Transition states with only one negative eigenvalue and less basic halogenide, such as iodide, remained linear (N—C—X angle 178.3°) when the restriction was removed.

Results

An Experimental Addendum. The capricious behavior that 2-substituted pyridines follow RSP, and 3- and 4-substituted do not, was interpreted by us in terms of steric effects.[6,9] It has, however, been questioned as being due to artificial reaction conditions since different solvents were used in the reactions with iodide and fluorosulfonate as leaving group.[5,6] We therefore have repeated the experiments using the same solvent in reactions with the two different leaving groups. We also used a new set of leaving groups, methanesulfonate (mesylate) and trifluoromethanesulfonate (triflate), in order to minimize differences such as variational solvation around developing anionic leaving group in the transition state. The reaction was followed in two different solvents: water and acetonitrile/water (60/40). The results are summarized in Figure 2. A slope of 0.85 ± 0.04 was found if the results from both reaction series are combined. We consider this result as significant and to be a strong support to our earlier finding.[10]

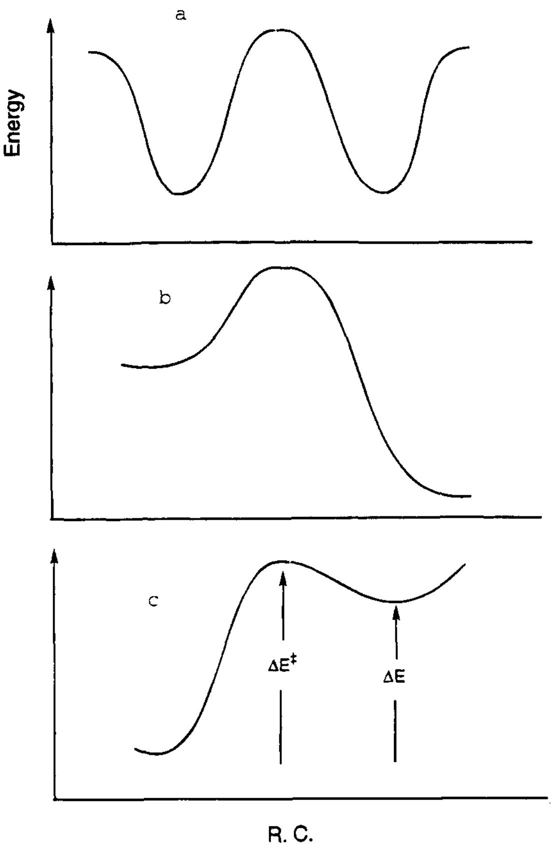


Figure 3. Schematic energy profiles for the S_N2 reaction: (a) halogen exchange identity reaction in the gas phase, (b) reaction in solution, (c) Menshutkin reaction in the gas phase.

General Features of the Reaction. The halogen exchange reactions in the gas phase differ substantially from reactions in solution. Gas-phase reactions are characterized by the formation of strong ion—molecule complexes,[28,29] the stabilization energy of which dominates the reaction energy profile. The energy of the transition state is not much higher than uncomplexed reactants due to the high energy of isolated ions in the gas phase (Figure 3a), thus illustrating the importance of solvation particularly in ionic reactions. S_N2 reactions in solution have the well-known energy profile shown in Figure 3b. This is also the case for the Menshutkin reaction, but this reaction has been much less studied in the gas phase both experimentally and computationally. As a matter of fact this reaction has only been observed in the gas phase in crossed-beam studies for reactants of very high translational energy.[30]

The general energy profile for the quaternization reaction of the pyridine derivatives studied here is shown in Figure 3c. The stabilization of the van der Waals cluster of the reactants is less pronounced but the energy of the product ion-pair cluster is high, primarily due to charge separation. Consequently, the reaction is endothermic (endoergic). The structure of a representative product cluster is shown in Figure 1c. Further separation of the ions is accompanied by increase in energy. Thus, the product side of the reaction shows resemblance

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Table 1. Calculated Energies (in kcal mol^{-1}) for the S$_N$2 Reaction between Pyridine Derivatives and Methyl Substrates Obtained by AMPAC AM1 Calculations

R	X	$\Delta H_f^{\ddagger a}$	ΔE^b	$\Delta E^{\ddagger b}$
2-Me	Cl	75.6	43.7	68.7
2-Me	Br	90.5	48.5	70.9
2-Me	I	96.7	54.6	74.3
2-*t*-Bu	Cl	69.4	46.2	73.2
2-*t*-Bu	Br	82.8	51.9	73.9
2-*t*-Bu	I	98.4	58.8	77.6
2,6-diMe	Cl	70.0	43.0	69.4
2,6-diMe	Br	84.7	46.6	71.3
2,6-diMe	I	100.0	53.2	74.8
2-Me-4-NH$_2$	Br	85.4	45.0	68.7
2-Me-4-Cl	Br	85.0	48.9	72.2
2-Me-4-F	Br	46.9	49.1	72.4
2-Me-4-CN	Br	125.8	49.6	73.5
+AMPAC sparkles^c				
2-Me	Cl	74.8	31.4	58.9
2-Me	Br	90.3	36.7	60.7
2-Me	I	106.6	43.3	64.2
MNDO parameters				
2-Me	Cl	73.1	57.7	75.5
2-Me	Br	87.1	*d*	77.3
2-*t*-Bu	Cl	81.0	73.2	83.8
2-*t*-Bu	Br	96.0	*d*	86.6

[a] Heat of formation of the transition state. [b] ΔE and $\Delta E^{\ddagger}$ are defined in Figure 3. [c] Sparkles positioned as described in the text. [d] MNDO did not minimize properly to product cluster for leaving bromide.

with the ionic halogen exchange reactions. Calculated energies are shown in Table 1. The activation barriers are calculated as the difference between transition state and reactant heats of formation. The absolute heights of the barriers are three to four times higher in the gas phase than in solution, reflecting the development of charge in this reaction and the importance of the solvation of the transition state. Zero point energy corrections were performed in some cases and did not change the reactivity difference induced by either steric (Me → *t*-Bu, $\Delta E^{\ddagger}_{\mathrm{ZPE}} = 1.0$ kcal/mol for both substituents) or leaving group (Cl → Br, $\Delta E^{\ddagger}_{\mathrm{ZPE}} = 0.1-0.2$ kcal/mol for both leaving groups) perturbation.

Transition-State Properties. The most important transition state characteristics are summarized in Table 2. Generally speaking, AM1 gives tight transition states. Particularly the C−N bond is strikingly short. Looseness index, $\%L^{\ddagger}$, defined by eq 1,[21] where $d^{\ddagger}$ and d_o are bond

$$\%L^{\ddagger} = 100\Sigma(d^{\ddagger} - d_o)/d_o \qquad (1)$$

lengths in the transition state and ground state, is given in Table 2. It shows that a change of leaving group has a large influence on the looseness index, whereas both steric and electronic effects from substitution in the pyridine ring have only minor influence on $\%L^{\ddagger}$. Still the differences in barrier heights are about the same. The steric effect imposed by substituting 2-methyl with 2-*tert*-butyl is calculated to give a barrier increase similar to the experimental value, $\Delta\Delta E^{\ddagger}$ (Table 1). $\Delta\Delta E^{\ddagger}$ and $\Delta\Delta H^{\ddagger 11}$ are both 3.3 kcal/mol for leaving iodide. Substitution of 2-methyl by 2,6-dimethyl gives $\Delta\Delta E^{\ddagger} = 0.4$ compared to experimental $\Delta\Delta H^{\ddagger} = 1.3$ kcal/mol.[11] The *tert*-butyl and 2,6-dimethyl transition states are *looser* than the methyl transition state, emanating mainly from nitrogen−carbon bond loosening.

Reaction asymmetry $\%AS^{\ddagger}$ can be estimated by eq 2,[21] and the the values are reported in Table 2. An increase of the steric strain with concomitant higher barrier results in slightly less asymmetric transition state.

$$\%AS^{\ddagger} = 100[[(d^{\ddagger} - d_o)/d_o]_{\mathrm{C-X}} - [(d^{\ddagger} - d_o)/d_o]_{\mathrm{N-C}}] \qquad (2)$$

Leaving group variation gives the barrier order Cl < Br < I, which is *opposite* to that observed in solution and to gas phase identity reactions. The more reactive leaving group (chloride) has the looser transition state. Judging by the asymmetry indices, $\%AS^{\ddagger}$, a more reactive leaving group has a later transition state, whereas the more directly comparable changes in C−N bond length show the opposite trend. The important asymmetry index variation, representing the larger relative variation in leaving group breaking compared to C−N bond formation, illustrates the inadequacy of using this index as a measure of transition state variation when different leaving groups (or nucleophiles) are used.

Substitution in the 4-position of the pyridine ring covers a barrier range of 4.8 kcal/mol but has very little effect on the transition structure.

Inversion around the central carbon atom, as measured by the sum of the N−C−H angles, $\Sigma\varphi$, indicates rather late transition states.[31] There is, however, a large spread in the individual angles. In the 2-methyl series one hydrogen has $\varphi = 102-103°$, it is placed close to the ring plane and points away from the 2-methyl group (see Figure 1a). The conformation with geared methyl groups[32] (as depicted in Figure 1a) is ca. 1.8 kcal/mol more stable than the gear clashed conformation in contrast to molecular mechanics predictions. In the 2-*tert*-butylpyridine transition states two methyl groups are straddling the central methyl which has one hydrogen pointing toward the *tert*-butyl group.

A charge distribution analysis (Figure 1b) reveals that the variation of the charges on the different leaving halogenides is nearly entirely compensated by the charge on the central carbon atom and, to a lesser degree, on the nitrogen atom, which is slightly negative.

Solvent Effects. In this study the solvent was simply represented by a pair of AMPAC sparkles placed on the N−C−X axis and with the positive charge facing the leaving group. The distance between the two sparkles was chosen as 0.9 Å (μ = 4.3 D) which gives zero contribution to the heat of formation from the dipole since there is a cutoff if the intersparkle separation is less than 1.0 Å. The distance *a* in the transition state was varied and the value in Table 2 chosen as 3 Å. It turned out that at this distance the transition state heat of formation ($\Delta H_f^{\ddagger}$) was the same as without sparkles for leaving bromide.

$$\mathrm{C}\text{- - - -}\mathrm{Br}\underset{a}{\text{- - - - -}}+\underset{0.9\ \text{Å}}{\text{- - - - - -}}-$$

The geometrical parameters are summarized in Table 2. Several interesting effects were found. The barrier decreases by 10 kcal/mol. A longer C−N and slightly shorter C−X distance indicates an *earlier* transition state. The same effects were found in ab initio 3-21G computations of the reaction between ammonia and methyl bromide, in which the solvent was represented either by two discrete solvent water molecules or by an electrostatic continuum model.[22] The charge at the leaving group increases, though, an effect that may be due to the simple solvent model.

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Table 2. Transition-State Properties for the S_N2 Reaction between Pyridine Derivatives and Methyl Substrates Obtained by AMPAC AM1 Calculations[a]

R	X	$d_{(C-N)}^{\ddagger}$ (%CN)[c]	$d_{(C-X)}^{\ddagger}$ (%CX)[d]	$\Sigma\varphi$[e]	α[e]	β[e]	charge X[b]	$\%L^{\ddagger}$	$\%AS^{\ddagger}$
2-Me									
	Cl	1.700 (15)	2.275 (29)	284	123	123	−0.72	43	14
	Br	1.662 (12)	2.380 (23)	288	123	122	−0.67	35	12
	I	1.644 (11)	2.493 (13)	290	123	121	−0.60	24	2
2-t-Bu									
	Cl	1.742 (18)	2.283 (29)	286	121	129	−0.72	46	12
	Br	1.680 (14)	2.370 (22)	289	127	126	−0.67	36	10
	I	1.657 (12)	2.495 (13)	291	123	125	−0.61	25	1
2,6-diMe									
	Cl	1.733 (17)	2.258 (28)	283	122	119	−0.71	45	11
	Br	1.682 (14)	2.365 (22)	287	122	119	−0.66	36	10
	I	1.655 (12)	2.490 (13)	290	124	119	−0.60	25	1
2-Me	Br								
4-NH_2		1.668	2.381	286	123	122	−0.69	35	12
4-Cl		1.658	2.379	288	123	122	−0.66	35	12
4-F		1.658	2.381	289	123	122	−0.66	35	12
4-CN		1.656	2.373	289	123	121	−0.64	34	12
+AMPAC Sparkles									
2-Me	Cl	1.752	2.251	279	118	122	−0.74	43	10
2-Me	Br	1.676	2.378	285	123	122	−0.73	36	11
2-Me	I	1.668	2.490	285	117	122	−0.68	25	0
MNDO-parameters									
2-Me	Cl	1.697	2.435	287	120	126	−0.85	52	23
2-Me	Br	1.735	2.497	290	121	124	−0.81	46	13
2-t-Bu	Cl	1.786	2.437	288	123	128	−0.84	59	17
2-t-Bu	Br	1.750	2.502	292	123	128	−0.81	47	12

[a] The following reference bond lengths were used: C−N 1.480 Å; C−Cl 1.767 Å; C−Br 1.938 Å; C−I 2.207 Å. [b] X = leaving group. [c] %CN = 100[($CN^{\ddagger}$ − CN)/CN]. [d] %CX = 100[($CX^{\ddagger}$ − CX)/CX]. [e] See Figure 1a.

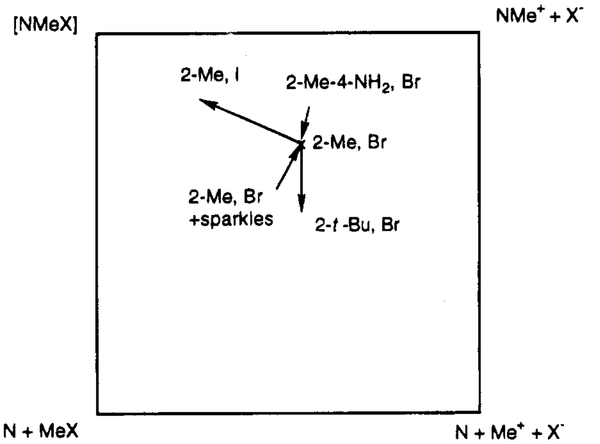

Figure 4. Schematic More O'Ferrall−Jencks diagram showing the trends with changing leaving group, 2-alkyl and 4-substituent, and "solvent". The arrows indicate the direction in which the calculated barriers increase and their lengths show the relative magnitude of the geometrical changes. (Perpendicular movements are defined as displacements towards the upper left or lower right corners.)

Comparison with the MNDO Method. A few calculations were also performed by the MNDO method. The results are given in Tables 1 and 2. The transition structures are significantly looser than with AM1. The structural effect on changing the steric requirements of the 2-substituent is in the same direction in the two methods as is the leaving group abilities.

A summary of the different effects is shown in the More O'Ferrall−Jencks diagram[33] in Figure 4. Both steric and electronic perturbations in the pyridine ring show behavior opposite to the Hammond postulate, whereas change of leaving group is accompanied by important perpendicular displacements.

Discussion

The most striking result from these calculations is the difference in direction and magnitude of the various perturbations. Substitution in the pyridine ring, by strongly activating or deactivating groups as well as by sterically perturbing groups, leads to only minor changes in the transition structure, $\delta\%L \leq 3$, $\delta\%AS \leq 2$. A change of leaving group, on the other hand, has a profound influence on the transition structure, $\delta\%L \approx 10-20$, $\delta\%AS \approx 6$. The variations in barrier, though, are of the same order of magnitude and acceptably reproduce the experimental variations despite the huge difference in calculated gas phase barrier and experimental barrier in solution, and the change from exoergic reaction in solution to highly endoergic reaction in gas phase. We are currently investigating whether the important leaving group effects are preserved when the leaving atom is the same, as it is in mesylate and triflate.

A remarkable result in these calculations is the order of leaving halogen ability: Cl > Br > I. Considering the level of calculation and the small differences observed too much attention should not be put on these results, but the trend is maintained in all calculations. Experimentally, S_N2 reactions, in the gas phase as well as in solution, usually show the opposite trend ($\Delta G^{\ddagger}$ as well as $\Delta H^{\ddagger}$). This behavior does not reflect a larger charge separation for the heavier halide due to longer C··X distance, since the charge separation is smaller such that the dipole moments of the transition state are 12.4, 11.8, and 11.1 D for Cl, Br, and I, respectively. Halogenide ion solvation energies are $I^- < Br^- < Cl^-$ in solvents as different as water and benzene and thus do not help to

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[33] (a) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705. (b) More O'Ferrall, R. A. In *The Chemistry of Carbon-Halogen Bond*; Patai, S., Ed.; Wiley: New York, 1973; Vol. 2, p 609.

explain the calculated reactivity order. Shaik *et al.* calculated the reactivity trend Br $\geq$ I > Cl for the reaction NH_3/CH_3X using various *ab initio* methods.[24] Thus, the unexpected reactivity order does not seem to be simply due to deficiencies in the semiempirical methods. It may originate in the intrinsic stabilities of the halides, which are increasing according to $I^-(g) < Br^-(g) < Cl^-(g)$,[34] and are "remembered" in the transition state. The leaving group effect is difficult to interpret in terms of movements along the reaction coordinate, but so much more straightforward in the perpendicular direction—the more reactive leaving group gives the looser transition state (Figure 4).

Our primitive solvent model, using a single pair of charges, seems to give results in good agreement with the more sophisticated solvent representation in terms of dielectric continuum[22] or the surface-constrained all-atom solvent model.[35] The main characteristics, less endoergic reaction, lower barrier, and earlier transition state, illustrate the difference between the Menshutkin reaction and a type 1 S_N2 reaction which is accompanied by charge migration instead of charge separation. The increased negative charge on the leaving group is unexpected and may be the result of the solvent model with a strong pulling positive charge close to the leaving group. The largest structural change is obtained for the C–N bond, while the C–X bond is very little influenced as is the experimentally found leaving group KIE.[36] However, the bizarre reactivity order for the leaving group is maintained.

A relatively pure steric effect is considered to result if the 2-methyl group is replaced by a 2-*tert*-butyl group.[9,10] The more hindered nucleophile has, according to our calculations, a slightly looser and earlier transition state and, thus, such a perturbation exhibits a component opposite to the Hammond postulate. This is also opposite to the interpretation of le Noble and co-workers of the activation volume variations[17] and to our earlier suggestion.[10,11] Primary $^{35}Cl/^{37}Cl$ kinetic isotope effects (KIE) are ambiguous on this point. Reactions of methyl chloride with pyridine and 2,6-dimethylpyridine give KIE's of 1.00355 and 1.00384, respectively, in agreement with the Hammond postulate.[17] An opposite result was, however, obtained by Swain and Hershey for reaction of methyl chloride with triethylamine and quinuclidine, two amines with similar pK_a values but very different reactivity due to steric hindrance in the triethylamine reaction.[18] Preliminary results of the primary $^{11}C/^{14}C$ KIE for the reaction of methyl iodide and 2,4-dimethyl- and 2,6-dimethylpyridine give 1.189 ± 0.012 and 1.220 ± 0.009, respectively, values which are in agreement with a looser transition state for the more hindered 2,6-derivative, provided that the reaction has an early transition state.[37]

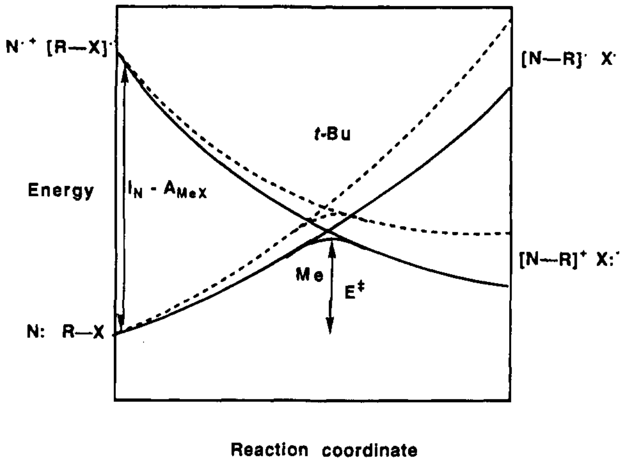

Figure 5. Schematic SCD diagram showing the steric perturbation of changing the 2-alkyl substituent (Me = —; *t*-Bu = – –) in the Menshutkin reactions with CH_3X.

S_N2 reactions have been analysed in terms of the state correlation diagram (SCD) method of Shaik and coworkers[21,24] in which the barrier is determined by the gas phase ionization potential I_N, the gas phase vertical electron affinity, A_{RX}, a bond coupling delay index f, and the avoided crossing B, according to eq 3.

$$\Delta E^{\ddagger} = f(I_N - A_{RX}) - B \tag{3}$$

The steric effects have been only briefly mentioned in connection with the SCD model such that increased hindrance will increase f and thus the shallowness of the curves.[21,38] An analysis of the effects of substituting methyl by *tert*-butyl in the 2-position of pyridine leads to the diagram shown in Figure 5. Anchoring the reactants in the same point, we also get coincident charge transfer reactant state since the ionization potentials are very similar (calculated values for 2-methyl- and 2-*tert*-butylpyridine are 9.63 and 9.65 eV, respectively). The difference in reaction ergicity ($\Delta\Delta H$) in several solvents is 5.0 kcal/mol,[11] a value that we extrapolate to the gas phase. The same difference has also been chosen for the product charge transfer state, assuming the same electron affinity for the two 2-alkylpyridinium ions. Furthermore, the steric contribution appears to be smoothly increasing from reactant to product, at least in the neighbourhood of the transition state.[11,39] Such an analysis reproduces the increase in barrier height, but does not indicate any important movement along the reaction coordinate.

In summary, these calculations indicate that the introduction of steric strain in the transition state of the Menshutkin reaction results in a looser transition state, and give no support to the idea that an increase in steric strain should lead to enhanced selectivity. The rather low level of calculation in this work, motivated by the complexity of the systems studied, certainly requires further investigation. The results presented here will be tested in these and other reactions by both experimental and computational methods.

Acknowledgment. We thank CNRS of France and NFR of Sweden for financial support. We acknowledge Dr. José-Luis M. Abboud, Madrid, for valuable suggestions. U.B. is grateful to the Université d'Aix-Marseille for a guest professorship and to Dr. W. P. Jencks, Brandeis University, for discussions and for generously putting his laboratory at our disposal for some experimental work.

JO941502W

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