

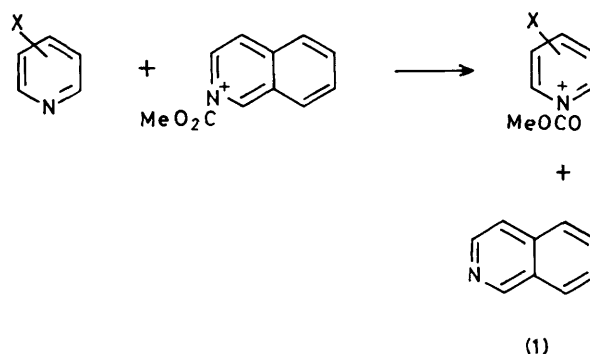
Brønsted Exponents and Activated-complex Structure: An AM1 SCF-MO Theoretical Simulation of a Rate–Equilibrium Correlation for Transfer of the Methoxycarbonyl Group between Isoquinoline and Substituted Pyridines

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The AM1 SCF-MO method has been applied to simulate the transfer of a methoxycarbonyl group between isoquinoline and a range of substituted pyridines in the gas phase. The nucleophiles and leaving group were mimicked by ammonia molecules whose gas-phase basicities were modulated by suitably located dipoles of varying size. Linear rate–equilibrium correlations were obtained for reaction series involving activated complexes of variable structure. The meaning of the Brønsted exponents is discussed in regard to charge development, bond order, and a simple model of intersecting energy curves. It is concluded that linear rate–equilibrium relationships are not incompatible with the Leffler principle and Hammond postulate, and that Brønsted exponents do not measure activated-complex structure directly but do reflect the Morse curvature of the bond being made with the nucleophile.

To probe the nature of activated-complex structure is an important quest in view of the fundamental rôle of the activated complex within the transition-state theory of chemical reactivity.¹ Linear free-energy relationships (LFER) provide useful tools for this purpose but interpretation of the slope of, say, a linear Brønsted correlation is problematic. The existence of a LFER seems to imply that the activated complex has a constant structure at the site of reaction as the rate and equilibrium constants are varied by changing a substituent at a remote position. On the other hand, the Leffler principle² and Hammond postulate³ suggest that changing the reaction energetics should cause variation in activated-complex structure incompatible with a *linear* LFER. Theoretical chemistry may contribute to resolving this apparent paradox and so may assist the interpretation of experimental LFERs.⁴ The reactions of a series of substituted compounds may be examined computationally, with the geometries, force constants, and free energies of reagents, activated complexes, and products being determined in each case by location and characterisation of the appropriate critical points on the respective potential-energy surfaces. In principle rate–equilibrium relationships may then be constructed from plots of calculated ΔG^{\ddagger} vs. ΔG° . The advantage of the theoretical approach is that the activated-complex structural features deduced indirectly from these simulated free-energy relationships may then be compared with those determined directly.

In this paper we report a theoretical (gas-phase) simulation of a rate–equilibrium correlation for methoxycarbonyl group transfer between isoquinoline (IQ) and a range of substituted-pyridine nucleophiles [equation (1)], preliminary results of which were communicated elsewhere.⁴ An experimental Brønsted correlation for this reaction series in aqueous solution has recently been published.⁵ The presence of a linear correlation between $\log k_2$ and pK_a (of the conjugate acid of the nucleophile) over a wide range of basicity, and the absence of a break at the pK_a of IQ, were taken as evidence that the methoxycarbonyl transfer proceeds in a concerted fashion rather than by the usual stepwise addition–elimination mechanism for acyl transfer. The question we wish to address here is this: in what manner are Brønsted exponents β_N related to actual activated-complex structures?

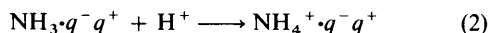


Methods

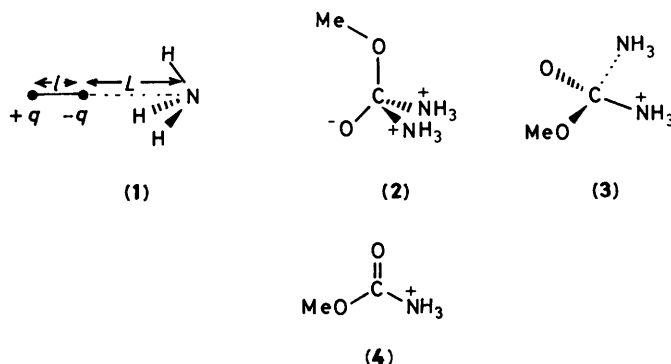
The AMPAC program⁶ was used to perform semiempirical RHF molecular orbital calculations with the AM1 hamiltonian and parameters for H, C, N, and O.⁷ We chose to simulate *only* the polar effect of substituents X modifying the gas-phase basicity of the nucleophiles in equation (1), and to consider only 4-substituted pyridines as nucleophiles. It was assumed that the contributions from entropy and from the steric component of the enthalpy to the standard free energies of activation ΔG^{\ddagger} and the standard free energies of reaction ΔG° throughout this series would be essentially constant and would not sensibly affect the *relative* values of ΔH^{\ddagger} and ΔH as determined directly from the AM1 calculated heats of formation of the reagent, activated complexes and products. This allowed two important simplifications to be made. First, the rate–equilibrium correlation was constructed as a plot of ΔH^{\ddagger} vs. ΔH only. Second, the pyridine nucleophiles and IQ leaving group were *mimicked* by ammonia molecules whose proton affinities were modulated to reproduce the experimental proton affinity (PA) of each base relative to that of ammonia; this enabled the computations to be performed economically by avoiding repetitious and uninformative calculation upon the large and constant aromatic-ring portions of the nitrogen bases.

The mimicking was accomplished by placing a pair of oppositely charged AMPAC 'sparkles' (constituting a dipole) on the three-fold axis of ammonia, on the same side as the hydrogens, with the negative charge a constant distance $L =$

5.0 Å from the nitrogen atom, as shown in (1). By adjustment of the charge ($|q| = 1$ or 2) and dipolar separation l (in the range 0.2–1.7 Å), the basicity of the ammonia could be suitably tuned. A sparkle is an integral charge at the centre of a spherical repulsive potential;⁶ if the separation between oppositely charged sparkles is less than 1.0 Å, the energy due to the dipole on its own is subtracted from the total energy. PAs were calculated as negative heats of reaction (2), where $q^- \cdot q^+$ indicates a pair of sparkles whose dipole moment and location were the same in reagent and product species. The geometries of the NH_3 and NH_4^+ moieties were frozen at the values optimised for isolated ammonia molecule and ammonium cation, respectively.



The tetrahedral intermediate (2) for degenerate methoxy-carbonyl transfer between identical ammonia molecules, without sparkles, was located by complete geometry optimisation of the C_s -symmetrical structure. A force-constant calculation and vibrational analysis confirmed this species to be a true intermediate. The activated complex for formation (or breakdown) of this symmetrical intermediate was located as follows. Energy



minimisation of a species (3) corresponding to nucleophilic attack of ammonia on the carbonyl group of the methoxy-carbonylammonium cation (4), with the making $\text{N} \cdots \text{C}$ bond length constrained at 1.9 Å, yielded a structure which was then subjected to SIGMA gradient-norm minimisation⁸ without constraints; this optimisation converged to a saddle point, characterised by a force-constant calculation and vibrational analysis as having a single imaginary frequency corresponding to the expected reaction co-ordinate. The geometry and energy of an activated complex (3) containing NH_3 moieties frozen in their optimised geometries for isolated ammonia, and similarly located using SIGMA, differed only negligibly from those of the fully optimised structure. The asymmetrical intermediate and the distinct activated complexes for its formation and breakdown in the case of each of the mimicked substituted-pyridine nucleophiles and the mimicked IQ leaving group were located using the optimised geometries of (2) and (3) as starting points. The alternative, slow but sure, NLLSQ routine was employed when SIGMA failed to converge. Force-constant calculations were not performed for the species with sparkles, owing to the presence of constraints; it was verified that each activated complex reverted to the intermediate (or to reagents or products) upon energy minimisation following a small displacement in the making and breaking $\text{C} \cdots \text{N}$ bonds.

Results and Discussion

Proton Affinities.—In common with MINDO/3⁹ and MNDO,¹⁰ AM1¹¹ gives a very poor estimate for the heat of formation of the proton (calculated 314.92 kcal mol⁻¹,* experimental 367.19 kcal mol⁻¹¹²). All AM1-calculated PAs would therefore contain a systematic error of 52 kcal mol⁻¹ unless the experimental heat of formation of H^+ were used in equation (2); the latter option was followed in this work, in line with previous authors.^{9–11} Table 1 contains a comparison of calculated and experimental PAs for three of the bases pertinent to this study; the average error is 5.5 kcal mol⁻¹, similar to that reported for a much larger sample of bases.¹¹ MNDO PAs have larger errors, particularly for nitrogen bases; e.g. -10.5 kcal mol⁻¹ for ammonia and -14.0 kcal mol⁻¹ for pyridine.¹⁰

The charges q and dipolar separations l for the sparkles used to mimic the 4-substituted pyridines and IQ are given in Table 2; these were adjusted to reproduce the experimental PAs^{13,14} relative to that of ammonia.¹⁵ (At the outset the experimental PA of pyridine was mis-read as 220 instead of 222 kcal mol⁻¹,¹³ since the PAs of the substituted pyridines¹⁴ relative to that of pyridine itself were used, the resulting PAs relative to ammonia were in error by 2 kcal mol⁻¹. This was of no consequence except that, in effect, different bases were employed in the simulated Brønsted correlations from those stated.)

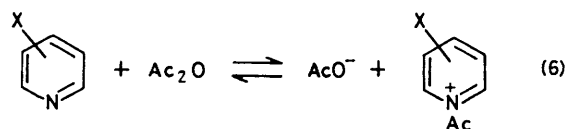
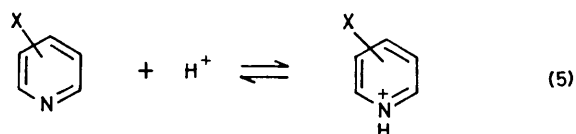
The energetics of proton transfer in gaseous and aqueous phases are not generally related.¹⁶ However, Arnett *et al.*¹⁴ reported a linear relationship between the relative proton affinities of 3- and 4-substituted pyridines and the corresponding relative enthalpies of ionisation in aqueous solution, with $\Delta H(\text{aq}) \approx 0.4 \delta \text{PA}$; this special case is due to the limited nature of the structural variation permitted in the series of bases. There is also a good linear correlation ($r = 0.977$) between the (corrected) absolute proton affinities of the six bases considered in the present study and their aqueous pK_a s at 25 °C:¹⁷

$$\text{pK}_a = 0.30 \text{ PA} - 60.8 \text{ kcal mol}^{-1} \quad (3)$$

Brønsted Correlation for Equilibria.—The AM1 heats of reaction ΔH_p for methoxycarbonyl transfer (1) (Table 2) correlate linearly ($r = 0.99998$) with the proton affinities of the nucleophiles relative to ammonia:

$$\Delta H_p = 19.5 - 0.95 \Delta \text{PA kcal mol}^{-1} \quad (4)$$

The nucleophiles considered span a wide range of basicity; for the four nucleophiles less basic than the IQ leaving group the transfer is endothermic whereas for 4-dimethylaminopyridine (4-NMe₂py), which is more basic than IQ, the transfer is exothermic. The slope of the correlation for the six points, $\beta_p = 0.95$, is the sensitivity of $-\Delta H_p$ to variation in PA due to the changing substituent. If, by definition, the substituent experiences a charge change on the nucleophile/base of +1 in the protonation equilibrium (5), then it 'sees' an effective charge¹⁸ change of 0.95 in the methoxycarbonyl transfer equilibrium (1); in the *gas phase* the methoxycarbonyl group has a *smaller* effective elec-



* 1 kcal mol⁻¹ = 4.184 kJ mol⁻¹.

Table 1. Calculated heats of formation and calculated and experimental proton affinities for some nitrogen bases

Base	AM1 heat of formation/ kcal mol ⁻¹		Proton affinity/ kcal mol ⁻¹	
	B	BH ⁺	AM1	Expt.
Ammonia	-7.28	150.58	209.3	207 ^a
Pyridine	32.04	184.17	215.1	222.0 ^b
Isoquinoline	50.18	197.82	219.6	227.5 ^b

^a Ref. 15. ^b Ref. 13.**Table 2.** Dipolar charges and separations, proton affinities relative to ammonia, AM1-calculated enthalpies for activated complexes **f** and **b**, intermediate **i**, and products **p** relative to isolated reagents, and AM1-calculated ionisation energies for various mimicked substituted-pyridine nucleophiles involved in simulated methoxycarbonyl-group transfer from isoquinoline^a

Nucleophile	q	l/Å	ΔPA	ΔH _f [‡]	ΔH _i	ΔH _b [‡]	ΔH _p	I
4-CN	1	0.245	2.5	0.0	-0.5	2.5	17.1	237.4
4-Cl	2	0.503	9.9	-4.7	-5.8	-3.0	10.2	229.2
4-H	2	0.678	13.0	-6.6	-8.0	-5.7	7.2	225.8
4-Me	2	0.919	17.0	-9.2	-11.1	-8.7	3.4	221.4
IQ	2	1.147	20.5	-11.5	-13.7	-11.5	0.0	217.5
4-NMe ₂	2	1.657	27.6	-16.1	-19.1	-17.1	-6.7	209.7

^a All energies in kcal mol⁻¹.

tronegativity than the proton. A Brønsted plot of logarithmic equilibrium constraints against pK_a for reaction (6) of substituted pyridines with acetic anhydride in water¹⁹ has a slope of 1.58, implying a *greater* effective electronegativity for the acetyl group than for the proton in the *aqueous phase*; the methoxycarbonyl and acetyl groups are considered to be similar in this regard.⁵ The gas-phase and aqueous-phase Brønsted exponents may not be compared directly since the former is calculated as $-\delta\Delta H_p(g)/\delta PA$ and the latter is determined as $\delta\log K(aq)/\delta pK_a$.

The aqueous-phase Brønsted correlation for acyl transfer may be expressed as

$$-\delta\Delta G_p(aq) = 2.303RT \times \beta_p(aq) \times \delta pK_a \quad (7)$$

Assuming that $\delta\Delta G(aq) \approx \delta\Delta H(aq)$, and differentiating equation (3), leads to

$$-\delta\Delta H_p(aq) \approx 0.30 \times 2.303RT \times \beta_p(aq) \times \delta PA \quad (8)$$

Arnett *et al.*¹⁴ reported an aqueous solvent attenuation factor of 2.5 for proton transfer, *i.e.* $\delta\Delta H(aq) \approx \delta\Delta H(g)/2.5$; if this factor were the same for acyl transfer then the following relationship would result implying that $\beta_p(g) \approx \beta_p(aq)$ at

$$-\delta\Delta H_p(g) \approx 2.5 \times 0.30 \times 2.303RT \times \beta_p(aq) \times \delta PA \quad (9)$$

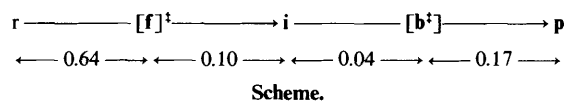
25 °C. However, there is no reason to suppose that the aqueous solvent attenuation factors for proton and acyl transfer are actually the same. The solvation of the products is quite different, for pyridinium is a hydrogen-bond donor^{14,20} but acylpyridinium is not. A solvent attenuation factor of 1.5 for acyl transfer would imply $\beta_p(g) \approx 0.61 \beta_p(aq)$ at 25 °C, and would reconcile the two values mentioned above. It has been pointed out¹⁸ that experimental effective charges refer to solvated reagents and products in the standard and calibrating equilibrium. Effective charges or effective electronegativities have no *absolute* significance.

Brønsted Correlations and Reactivity.—Unconstrained approach of ammonia to methoxycarbonylammonium was predicted by AM1 to be accompanied by proton transfer leading to an ion-molecule complex, between ammonium and methyl carbamate, 17 kcal mol⁻¹ lower in energy than the isolated reagents. The symmetric intermediate (**2**) lies 2 kcal mol⁻¹ lower than the reagents, and the activated complexes (**3**) for its formation and breakdown are just 1.2 kcal mol⁻¹ higher than this, *i.e.* $\Delta H_f^\ddagger = \Delta H_b^\ddagger = -0.8$ kcal mol⁻¹. Freezing the geometry of the NH₃ moiety of the mimicked nucleophiles prevented proton transfer from occurring but nonetheless the initial approach of each of these nucleophiles to the carbonyl group was predicted to lead exothermically to formation of a hydrogen-bonded ion-molecule complex whose structure and energy were not germane to a simulation of nucleophilic attack by pyridine nucleophiles. The calculated enthalpies of the activated complexes **f** and **b** for formation and breakdown of the intermediate **i** for methoxycarbonyl transfer (1) were consistently lower than those of the isolated reagents or products **p** (Figure 1), as is evident from the data presented in Table 2.

In Figure 2 are plotted the negatives of the AM1 heats of activation for formation and breakdown of **i** against the relative PAs of the nucleophiles. There are two straight lines intersecting at the PA of IQ. For nucleophiles less basic than IQ, $\Delta H_f^\ddagger < \Delta H_b^\ddagger$ and breakdown of the intermediate would be rate limiting. The Brønsted exponent $-\delta\Delta H_b^\ddagger/\delta PA = \beta_b = 0.78$. For nucleophiles more basic than IQ, $\Delta H_f^\ddagger > \Delta H_b^\ddagger$ and formation of the intermediate would be rate limiting. The Brønsted exponent $-\delta\Delta H_f^\ddagger/\delta PA = 0.64$. A similar correlation for the enthalpy change $-\Delta H_i$ vs. relative PA yields $\beta_i = 0.74$.

If, for each nucleophile, only the *higher* (less negative) of the activation enthalpies ΔH_f^\ddagger and ΔH_b^\ddagger were plotted against relative PA, the resulting plot would comprise two linear portions with a break in slope at the PA of IQ; for less basic nucleophiles the slope would be 0.78 and for more basic nucleophiles it would be 0.64. The presence of a break in slope between two linear portions of a free-energy relationship is regarded as evidence for the existence of an intermediate in a stepwise mechanism.²¹ The curvature observed in a Brønsted plot for pyridinolysis of methyl chloroformate was thus attributed to a change in the rate-determining step.²² The absence of such a break in a Brønsted plot for pyridinolysis of *N*-methoxycarbonylisoquinolinium (NMCIQ) has recently been interpreted as being consistent with a concerted mechanism involving a single activated complex.⁵ While this interpretation may indeed be correct for the reaction in aqueous solution, it is of interest to note that the six calculated points corresponding only to the rate-limiting activated complexes of the simulated gas-phase reaction (*i.e.* only the lower limbs of Figure 2) may be well correlated by a single straight line ($r = 0.999$) of slope 0.75! More extensive data would be required to justify a break in slope at the PA of IQ were it not that the theoretical simulation reveals both ΔH_f^\ddagger and ΔH_b^\ddagger for each nucleophile. By the same token it may be extremely hard to distinguish between stepwise and concerted mechanisms if the difference in slope $\Delta\beta$ between putative linear portions of a Brønsted correlation is small.⁵

Charge Development.—The series of Brønsted exponents 0.64, 0.74, 0.78, and 0.95 may quite plausibly be interpreted as manifesting the increasing effective charge on the nucleophile in **f**, **i**, **b**, and **p**, respectively. The charge changes on the nucleophile, occurring between the critical structures along the reaction path, may then be summarised by the Scheme.



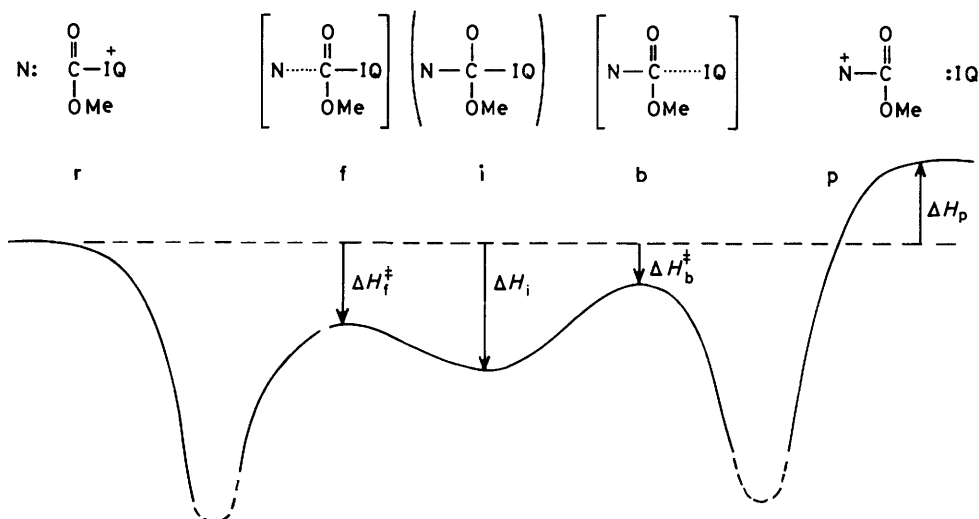


Figure 1. Energy profile for methoxycarbonyl transfer between isoquinoline and substituted-pyridine nucleophiles, showing critical structures along the reaction co-ordinate

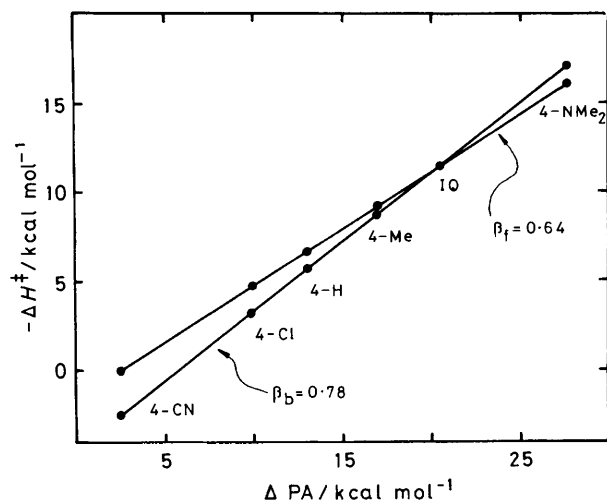


Figure 2. Brønsted plot of AM1 heats of activation for formation ($-\Delta H_f^\ddagger$) and breakdown ($-\Delta H_b^\ddagger$) of the intermediate *vs.* relative proton affinity of the nucleophile

Table 3. AM1 total net charges Q_{nuc} on the nucleophilic moiety of critical structures along the reaction co-ordinate

Nucleophile	f	i	b	p
4-CN	0.350	0.505	0.636	0.738
4-Cl	0.332	0.532	0.647	0.751
4-H	0.239	0.550	0.653	0.756
4-Me	0.318	0.561	0.659	0.762
IQ	0.312	0.568	0.665	0.767
4-NMe ₂	0.301	0.589	0.675	0.778

The greatest change, as sensed by the polar substituent on the nucleophile, occurs during the initial act of bond making leading to activated complex **f**; smaller changes occur subsequently. These effective charge changes measured by the Brønsted exponents may be compared with the charge changes determined from the AM1 calculated atomic charges. The total net charge Q_{nuc} on each of the nucleophiles as it changes along the reaction path is given in Table 3. For each critical structure **f**,

i, **b**, or **p**, note that Q_{nuc} varies with the nucleophile; it is not independent of the nucleophile as implied by the effective-charge interpretation of the Brønsted exponents. As the mimicked nucleophile becomes more basic (*i.e.* the dipole of sparkles becomes more capable of stabilising a positive charge) so Q_{nuc} becomes more positive in **i**, **b**, and **p**. Conversely the value of Q_{nuc} in activated complex **f** decreases with increasing basicity of the nucleophile: this reflects Hammond postulate³ behaviour (see below). The ranges of values for Q_{nuc} for each critical structure do not agree with the respective Brønsted exponents β_f , β_i , β_b , and β_p .

Bond Lengths and Bond Orders.—The AM1-optimised lengths for the making and breaking carbon-nitrogen bonds in the critical structures along the reaction path are presented in Table 4. As the basicity of the nucleophile increases, so the making bond length $C \cdots N_{\text{nuc}}$ decreases in **i**, **b**, and **p** but increases in **f** (*cf.* the behaviour of Q_{nuc} discussed above). Considering the intermediates **i**, it is obvious that $C \cdots N_{\text{nuc}}$ should equal $C \cdots N_{\text{ig}}$ for the symmetrical reaction with IQ as the nucleophile and the leaving group. Increasing the basicity of the nucleophile causes $C \cdots N_{\text{nuc}}$ to decrease, as more positive charge is carried by the nucleophile, and causes $C \cdots N_{\text{ig}}$ to increase as less positive charge is carried by the leaving group. The relative heights of the barriers either side of **i** change with the basicity of the nucleophile (Table 2). The barrier for the back reaction *via* **f** increases from only 0.5 kcal mol⁻¹ for 4-CNpy to 3.0 kcal mol⁻¹ for 4-NMe₂py. According to the Hammond postulate,³ it would be expected that the structural resemblance between **i** and **f** would be greatest for 4-CNpy and least for 4-NMe₂py. Similarly, since the barrier for the forward reaction *via* **b** decreases from 3.0 kcal mol⁻¹ for 4-CNpy to 2.0 kcal mol⁻¹ for 4-NMe₂py, the expectation would be that the structural resemblance between **i** and **b** would be greater for the more basic nucleophiles. These expectations are borne out by the trends in the bond lengths $C \cdots N_{\text{nuc}}$ and $C \cdots N_{\text{ig}}$ for **f** and **b** relative to those for **i**.

The bond order n of a bond of length $R(n)$ is defined by Pauling's rule²³ to be

$$n = \exp\{[R(1) - R(n)]/c\} \quad (10)$$

where $R(1)$ is the length (in Å) corresponding to unit bond order and c is a constant for a particular type of bonding,

Table 4. AM1 Optimised bond lengths (Å) for making and breaking C...N bonds in critical structures along the reaction co-ordinate

Nucleophile	f		i		b		p C-N
	C...N _{nuc}	C...N _{lg}	C...N _{nuc}	C...N _{lg}	C...N _{nuc}	C...N _{lg}	
4-CN	1.820	1.554	1.650	1.594	1.550	1.918	1.503
4-Cl	1.854	1.549	1.631	1.602	1.548	1.908	1.500
4-H	1.865	1.547	1.622	1.607	1.546	1.903	1.499
4-Me	1.882	1.545	1.617	1.609	1.544	1.898	1.498
IQ	1.895	1.543	1.612	1.612	1.543	1.895	1.496
4-NMe ₂	1.920	1.540	1.602	1.617	1.540	1.887	1.494

Table 5. Normalised charge changes \hat{Q} and C...N_{nuc} bond orders n calculated for critical structures along the reaction co-ordinate. (Values in italics constrained to be equal. Normalisation with respect to products p)

Nucleophile	\hat{Q}_f	n_f	\hat{Q}_i	n_i	\hat{Q}_b	n_b
4-CN	0.47	0.43	0.68	0.67	0.86	0.87
4-Cl	0.44	0.39	0.71	0.70	0.86	0.87
4-H	0.44	0.38	0.73	0.72	0.86	0.88
4-Me	0.42	0.37	0.74	0.73	0.86	0.88
IQ	0.41	0.35	0.74	0.74	0.87	0.89
4-NMe ₂	0.39	0.33	0.76	0.76	0.87	0.89

commonly set equal to 0.3.²⁴ It is reasonable to suppose that the charge development on the nucleophile is mirrored in some way by the bond order of the making C...N_{nuc} bond. Normalised charge changes \hat{Q} on the nucleophilic moieties may be obtained by expressing Q_{nuc} for f, i, or b as a fraction of its value in p. If it is assumed that the value of \hat{Q}_i for the symmetrical intermediate in the identity reaction with IQ as the nucleophile is equal to the bond order n_i of the making and breaking C...N bonds, and the $n_p = 1$ for NMCIQ, then $\hat{Q}_i = n_i = 0.74$ and equation (10) yields a value of $c = 0.385$. Analysis of *ab initio* RHF/6-31G*⁻ optimised carbon-nitrogen bond lengths²⁵ for MeNH₂, CH₂=NH, and HC≡N (assuming respective bond orders of 1, 2, and 3) leads to $c = 0.29$, whereas a similar analysis for MeNH₃⁺, CH₂=NH₂⁺, and HC≡NH⁺ gives $c = 0.35$. The proposed value of $c = 0.385$ for C...N⁺ bonds therefore seems quite reasonable. Table 5 contains values of \hat{Q} and n calculated in this manner from the data in Table 3 and 4. The similarity of these pairs of values for f, i, and b is immediately obvious: bond order and charge development do seem to be closely related.

Brønsted Exponents and Activated-complex Structure.—If it is assumed that the properties of an activated complex are intermediate to those of the reagents and products, then the value of those properties depends upon the degree of resemblance of the activated complex to the reagents and products. In particular the free-energy response δG^{\ddagger} of the activated complex to a substituent change may be modelled by the corresponding free-energy responses δG_r° of the reagents and δG_p° of the products according to (9), where α is a parameter (having limits of 0 and 1) which measures the resemblance to the products.² Hence the rate-equilibrium relationship (12) is obtained between the change in free energy of activation and the change in free energy of reaction caused by a substituent.

$$\delta G^{\ddagger} = \alpha \delta G_p^\circ + (1 - \alpha) \delta G_r^\circ \quad (11)$$

$$\delta \Delta G^{\ddagger} = \alpha \delta \Delta G^\circ \quad (12)$$

The parameter α (sometimes known as the Leffler transition-state index²⁶) corresponds to the slope of a plot of $\log k$ vs. $\log K$

for the *same* reaction and 'should be at least approximately equal to the fractional displacement of the transition state along the reaction co-ordinate from reagents to products'.^{2b} It is important to note that this identification of α with activated-complex structure is intuitive rather than rigorous and rests upon the assumption, embodied in equation (11), that activated-complex properties may be modelled as a linear combination of reagent and product properties. However, it is commonly accepted that Brønsted exponents for proton-transfer reactions are indicative of activated-complex structure.²⁷

A corollary to the Leffler principle [equation (12)] is that as the activated complex bears the greater resemblance to the less stable of the species in a chemical equilibrium (*cf.* the Hammond postulate³), so α will be greater than one-half if ΔG° is positive and will approach unity as ΔG° becomes large; conversely α will be less than one-half if ΔG° is negative and will approach zero as ΔG° becomes highly negative.^{2b} It follows that α will be constant only for small changes in structure; substituent variations which effect large changes in ΔG° will cause changes in α (*i.e.* a non-linear free-energy relationship) and, by implication, variation in activated-complex structure.^{2a} However, free-energy relationships are often remarkably linear over wide ranges of reactivity involving large changes in the free energy of reaction.²⁸ Apparently there is a paradox: the existence of a linear free energy relationship seems to imply *constant* activated-complex structure as the rate of reaction is varied by a substituent effect, but the Leffler principle and Hammond postulate (or, more generally, the canon of ideas codified as the 'Bema Hapothle'²⁹) suggest *variation* of activated-complex structure with reaction energetics.

The present theoretical simulation of a Brønsted correlation sheds some light on this apparent paradox. For the sake of this discussion it is convenient to focus attention upon the initial step of the acyl transfer, *i.e.* formation of **i** *via* activated-complex **f**. The quantity corresponding to the Leffler index is the normalised Brønsted exponent $\delta \Delta H_f^\ddagger / \delta \Delta H_i = \beta_f / \beta_i = 0.86$, equivalent to a correlation of rate and equilibrium constants for the same reaction $\mathbf{r} \rightleftharpoons \mathbf{i}$. Is it valid to interpret this value as meaning that the activated complex **f** lies 86% of the way along the reaction co-ordinate towards **i**? Or that **f** bears 0.86 resemblance to **i** and 0.14 resemblance to **r**?

Table 6 contains fractional charge changes and bond-order changes describing structural features of **f** relative to **i**. As the basicity of the nucleophile increases, the stability ΔH_i of **i** relative to **r** increases (Table 2) and the values of both \hat{Q}_f / \hat{Q}_i and n_f / n_i decrease, since the activated complex **f** bears a diminishing resemblance to the product **i** of this reaction step. Clearly there is variation in the structure of the activated-complex. Table 6 also contains a quantity θ_r / θ_i which expresses the fractional change in the sum of the three angles about carbon in the mimicked NMCIQ moiety. ($\theta_r = 0$ for the trigonal reagent and θ_i would be equal to unity for a perfectly tetrahedral intermediate; actual values for θ_i are in the range 0.72 to 0.82, and θ_r varies between 0.38 and 0.49.) This *angular* variable decreases with increasing nucleophile basicity in remarkably

Table 6. Normalised charge changes, C...N_{nuc} bond orders, and angular changes for activated complexes **f** for formation of intermediate **i** (normalisation with respect to **i**)

Nucleophile	\hat{Q}_f/\hat{Q}_i	n_f/n_i	θ_f/θ_i
4-CN	0.69	0.64	0.67
4-Cl	0.62	0.56	0.59
4-H	0.60	0.53	0.54
4-Me	0.57	0.51	0.52
IQ	0.55	0.47	0.51
4-NMe ₂	0.51	0.43	0.48

similar fashion to the changes in the bond-order and charge-development variables. The three indices given in Table 6 present a coherent picture of variable activated-complex structure accompanying changes in reaction energetics arising in response to changes in a remote polar substituent, in complete accord with the tenets of the Bema Hypothesis. However, there is also a linear rate-equilibrium relationship describing the same reaction step, characterised by the slope $\beta_f/\beta_i = 0.86$; this value is quite different from the range of values of \hat{Q}_f/\hat{Q}_i , n_f/n_i and θ_f/θ_i . Two points should be noted: first, a linear rate-equilibrium relationship is not incompatible with the Leffler principle and Hammond postulate; second, the slope of such a correlation is not a direct measure of activated-complex structure as understood in terms of simple geometrical and charge changes.

The Meaning of the Brønsted Exponent.—The immediate significance of a (normalised) Brønsted exponent is as an energetic descriptor of the activated complex, since it is a measure of the effect of substituents on the energy of this species as compared with the effect of the same substituents on the energy of the products for the particular reaction step. Arnett has espoused a sceptical viewpoint regarding the use of rate-equilibrium energy correlations to elucidate activated-complex structures, by asserting that 'transition-state theory has provided a theatre for untestable speculation about an inherently elusive entity (the transition state) which has scarcely had a parallel since the close of medieval scholasticism. The danger in such speculations is that they suggest to the unwary that we have detailed knowledge about the structure of the transition state when in fact for many cases . . . it is only feasible to make gross energetic comparisons with other clearly defined states such as reactants or products.'³⁰ More optimistically we would suggest that the beauty of the present theoretical approach is that it yields both rate-equilibrium correlations and activated-complex structures at the same time. In principle the properties of these constructs may then be analysed (within the context of the model) to examine the nature of their inter-relationship.

Simple theoretical models based on intersecting parabolic energy curves³¹⁻³⁴ permit identification of the Leffler index with the fractional displacement of the point of intersection along the reaction co-ordinate (*i.e.* the structure of the activated complex) provided that the curvatures of the reagent and product parabolae are equal. This condition is satisfied for proton transfers, and approximately linear Brønsted correlations may be predicted over wide ranges of reactivity, provided also that the intrinsic barrier (the value of ΔG^{\ddagger} when $\Delta G^\circ = 0$) is high.³²⁻³⁵ However, the Brønsted exponent (Leffler index) ceases to be a measure of the position of the activated complex along the reaction co-ordinate if the intrinsic barrier varies with ΔG° or if the reagent and product parabolae have different curvatures.^{33,34} Similarly, the lack of identity between the Leffler index and the position of the maximum in general quartic reaction-profile function³⁶ also corresponds

with different curvatures at the reagent and product minima. It should be appreciated that the notion of an *identity* between the Leffler index and the activated-complex location along a reaction co-ordinate arises indirectly from the use of over-simple functional forms to represent reaction profiles rather than directly from the Leffler principle and Hammond postulate.

The barrier to formation of a tetrahedral intermediate in acyl transfer may be regarded⁴ as the result of an avoided crossing between the ground state and an excited (charge-transfer) state of the reagents as they are distorted towards the geometry of the intermediate.³⁷ A simple intersecting-curves model corresponding to this qualitative picture may be developed as follows. The energy E_r of the valence-bond configuration for the reagent ground state may be described by a repulsive potential of inverse exponential form

$$E_r(R) = B \exp[-\gamma(R - R_i)/c] \quad (13)$$

where R is the nucleophile-carbonyl separation, R_i is its value in the intermediate and c is the constant which appears in equation (10) defining the bond order. This reagent-like potential may be simply expressed as a function of bond order.

$$E_r(n) = B n^\gamma \quad (14)$$

The intermediate-like potential E_i may be described by a Morse curve which may also be simply rewritten as a function of bond order.

$$E_i(R) = D\{1 - \exp[\kappa(R - R_i)/c]\}^2 \quad (15)$$

$$E_i(n) = D(1 - n^{\kappa})^2 \quad (16)$$

Dissociation of the intermediate C-N⁺ yields the fragments C⁻ and N⁺ corresponding to a charge-transfer configuration of the reagents with energy I - A, where I is the vertical ionisation potential of the nucleophile and A is the electron affinity of the carbonyl compound. Changing a polar substituent on the nucleophile should cause variation in I and in the dissociation energy D, but should not affect A, B, γ , or κ . Note that if $\delta D/\delta I = 0$, $\gamma = 2$, $\kappa = 1$, and $B = D$, this model reduces to that of intersecting identical parabolae,³²⁻³⁴ except that the potentials are quadratic in bond order rather than in bond length; transformation to bond-length co-ordinates yields Bell's model of intersecting identical Morse curves.³⁸

Figure 3 shows a plot of $E_r(n)/D$ with $B/D = 1.5$ and $\gamma = 2$, together with a series of curves $E_i(n)/D$, each with $\kappa = 1$, chosen such that $\delta D/\delta I = 1/3$. It is clear that $\delta \Delta H_i = \delta I - \delta D$ and therefore $\delta \Delta H_i/\delta I = 2/3$ for this example. The energies at the points of intersection of the curves $E_r(n)$ and $E_i(n)$ are the activation energies ΔH_i^\ddagger . A Brønsted plot of ΔH_i^\ddagger vs. ΔH_i for this example gives a straight line of slope 0.74. Excellent linear correlations ($r \geq 0.9999$) are also obtained for other choices of γ , κ , and B/D . Decreasing the value of the Morse curvature parameter κ leads to an increase in the value of the Brønsted exponent, and *vice versa*; however, since κ is likely to be a constant for a series of similar nucleophiles of varying basicity, so the Brønsted exponent remains constant also. The structure of the activated complex, as measured by the bond order at the point of intersection of the curves, also correlates linearly with ΔH_i^\ddagger ($r = 0.981$).

Further consideration of the AM1-calculated energetics for addition of mimicked substituted-pyridine nucleophiles to NMCIQ (Table 2) reveals linear correlations with the vertical ionisation potential of the nucleophile, similar to those assumed for the intersecting-curves model. Thus $\delta \Delta H_i^\ddagger = 0.58 \delta I$ and $\delta \Delta H_i = 0.67 \delta I$, and the ratio of these slopes is, of course, the

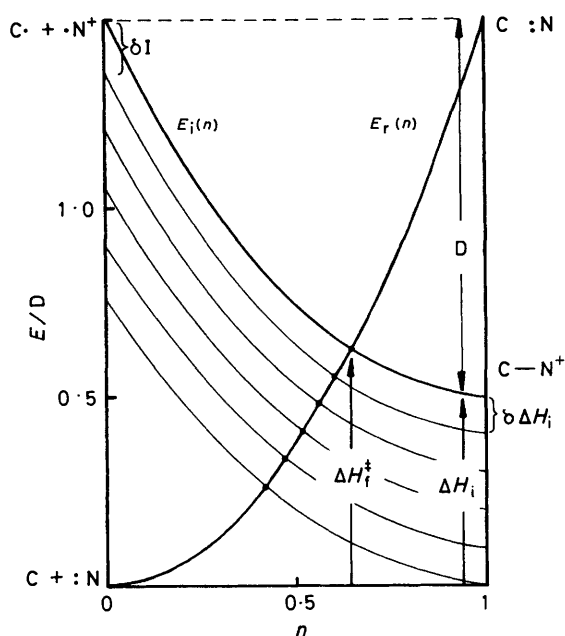


Figure 3. Intersecting reagent-like energy curve $E_r(n)$ and intermediate-like energy curves $E_i(n)$ for reactions of a range of nucleophiles with $\delta D/\delta I = 1/3$

Brönsted exponent $\delta\Delta H_i^\ddagger/\delta\Delta H_i = 0.58/0.67 = 0.86$. It follows that there is also a linear relationship between PA and I:

$$PA = 427 - 0.91 I \text{ kcal mol}^{-1} \quad (17)$$

The model suggests that the value of the Brönsted exponent is determined by two characteristics of the bond being made between the nucleophile and the carbonyl compound: (i) The sensitivity $\delta D/\delta I$ of its dissociation energy to changes in the ionisation potential of the nucleophile (related to basicity changes) and (ii) the curvature parameter κ of the Morse potential.

Concluding Remarks

The results of a recent experimental study of methoxycarbonyl transfer between IQ and substituted pyridines in aqueous solution were interpreted as being consistent with a concerted mechanism.⁵ The present theoretical study predicts a stepwise mechanism for this process in the gas phase; the barriers either side of the intermediate vary in height between 0.5 and 3.0 kcal mol⁻¹ depending on the nucleophile. The primary objective of this paper is to consider in general terms the significance of Brönsted exponents in regard to activated-complex structure, using this reaction as a convenient example, rather than specifically to perform an accurate simulation of the mechanism of this particular reaction. Nonetheless it is of interest to inquire whether the involvement of an intermediate in the predicted gas-phase mechanism is merely an artefact of the model or is a true reflection of reality. AM1 calculations for the identity reaction of pyridine with *N*-methoxycarbonylpyridinium, in which all atoms were treated explicitly, have also predicted⁴ a stepwise mechanism, with a symmetrical intermediate lying in a well only 0.5 kcal mol⁻¹ deep (*cf.* 2.0 kcal mol⁻¹ for the simulated symmetrical intermediate with IQ as nucleophile and leaving group). It would appear that steric effects (neglected by the present simulation) serve to destabilise the two activated complexes and the intermediate between them, and to diminish the well-depth of the latter. Conceivably, the greater steric bulk of IQ as the leaving group (if treated explicitly) might cause

these three critical structures to coalesce into a single activated complex; differential solvation along the reaction co-ordinate might achieve this also. However, since 0.5 kcal mol⁻¹ is less than kT at room temperature, an intermediate in a well as shallow as this would have a very short lifetime anyway, and might not be detected experimentally; instead, a Brönsted correlation might probe the properties of a virtual transition state.³⁹

The main conclusions of this theoretical study of methoxycarbonyl transfer are as follows.

(i) Variation in the gas-phase basicity of the nucleophile leads to variation in the structure of the activated complex.

(ii) Linear rate-equilibrium correlations may be obtained for processes involving activated-complexes of variable structure.

(iii) Charge development and changes in bond-order and angular co-ordinates occur in concert and do provide a coherent picture of changes in activated-complex structure.

(iv) Brönsted exponents do not provide a direct measure of activated-complex structure, nor do effective charges directly reflect actual charge changes.

(v) The value of the Brönsted exponent for formation of the tetrahedral intermediate is determined by the Morse curvature parameter characterising the bond being made with the nucleophile.

Years ago, Jaffé⁴⁰ summarised the factors determining the value of a Hammett reaction constant ρ as being: (i) the transmission of electronic effects to the reaction site; (ii) the susceptibility of the reaction to changes of electron density at the reaction site; (iii) the effect of reaction conditions. Similar factors are likely to determine the value of a Brönsted exponent β_N . Commonly these are interpreted in terms of charge development in the activated complex [factor (ii)]. The discussion above of Brönsted correlations for equilibria points to the importance of solvation [factor (iii)]. The analogue of factor (i) may be the role of the curvature parameter for the new bond being formed.

Finally, these conclusions as yet apply only to the present example of an acyl-transfer process. Work is in hand in this laboratory to investigate the meaning of Brönsted exponents for other types of reaction, including proton transfer and methyl transfer, by means of theoretical simulation. It is our contention that theoretical modelling can in this manner provide a bridge between empirical probes of activated-complex structure and actual features of energy surfaces describing chemical reactivity, and can thereby serve as a valuable tool to assist the interpretation of experimental results.

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