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TRANSITION STATE FLEXIBILITY IN NUCLEOPHILIC ATTACK ON CARBON

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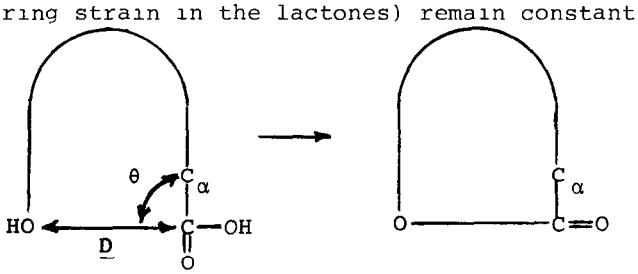
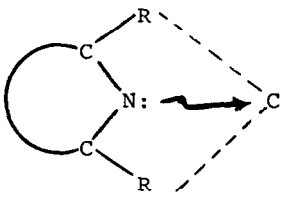
Summary: Multi-directional transition state theory qualitatively explains steric effects with hindered nucleophiles.

We recently advanced the hypothesis that reactions do not occur by means of single definable transition states[1]. Instead, there exist "cones" of trajectories; each trajectory is associated with a particular degree of bond formation and cleavage. Support for the notion of "reaction windows" comes from a study of lactonization rates with rigid hydroxyacids[2]. Compounds were constructed for which angles θ differ by as much as 10° whereas other factors (such as OH/C=O distances D and the ring strain in the lactones) remain constant We found that



lactonization rates do not depend on the angularity differences; carbonyl addition must have, therefore, a reaction window of at least 10° (and perhaps much larger) Wide reaction windows suggest, among other things, that an isotope effect or a Brönsted coefficient represents a composite derived from a multitude of geometries

In the present Note we examine nucleophilic attack on sp^2 and sp^3 carbon by nitrogen bases (pyridine and imidazole) having zero, one, or two methyl groups adjacent to the nitrogen. These methyls enter the reaction window as the nitrogen forms a partial bond to carbon in the transition state:



R = H or CH_3

Inasmuch as the methyl groups engage in non-bonded interactions with the substrate, the reaction is impeded. Multi-directional transition state theory[1] leads to the following postulates:

1. If the reaction window is narrow (a single trajectory in the extreme), then the effects of the methyl groups should be roughly additive. In other words the ratio of $k_{H,H}$ to $k_{Me,H}$ should approximate the ratio of $k_{Me,H}$ to $k_{Me,Me}$. This presupposes little shortening of the N/C partial bond with methyl substitution; work by Arnett[3] and by Johnson[4] on the alkylation of pyridine supports such bond-length invariability in the transition state.

2. If the reaction window is wide, a single methyl group should induce a relatively minor rate retardation because the nucleophile can "tilt" to direct the methyl group outwardly and thus minimize non-bonded interactions A second methyl group should, however, cause more severe rate perturbations because rotating one methyl away from the substrate brings the other one closer.

In Table I we list relative rate constants for the acylation of three imidazoles with p-nitrophenyl acetate in water at 25.0°. Tables II and III present literature data for the alkylation of three imidazoles by ethyl methylsulfonate in water[5] and for the alkylation of three pyridines by methyl iodide in acetonitrile[6]. It is seen from Table I that, consistent with a wide reaction window, a second methyl in proximity to the nitrogen has a much more profound effect than the first. The same is true in Table III for the pyridine nucleophiles. This cannot be attributed to basicity because the pK_a values increase uniformly with methyl substitution. Since the effects of the methyl groups are definitely not additive, a single trajectory mechanism seems unlikely. Note from Table I that the rate differences arise mainly from changes in ΔH^* (not ΔS^*) suggesting that non-bonded interactions as opposed to solvation effects govern the behavior.

Table I. Activation Parameters and Relative Rates at 25 0° for the Acylation of Imidazole Bases with p-Nitrophenyl Acetate in Water.

Nucleophile	pK_a[a]	ΔH* (kcal)	ΔS* (eu)	k_{rel}
Imidazole	6.95	7 5	-35	151[b]
2-Methylimidazole	7.86	9.0	-33	34
2,4,5-Trimethylimidazole	8.86	10.9	-33	1

[a] Taken from Ref. 3. [b] Second-order rate constant for this reaction equals 0.513 $M^{-1}sec^{-1}$

Table II. Relative Rates[a] for the Alkylation of Imidazole Bases with Ethyl Methanesulfonate in Water at 35°.

Nucleophile	pK_a	k_{rel}
Imidazole	6.95	1
2-Methylimidazole	7.86	2.1
2,4,5-Trimethylimidazole	8.86	4.9

[a] Data taken from Ref 3.

Table III. Relative Rates[a] for the Reaction of Pyridine Bases with Methyl Iodide in Acetonitrile at 25.0°

Nucleophile	pK_a	k_{rel}
Pyridine	5 17	25
2-Picoline	5.97	11
2,6-Lutidine	6.77	1

[a] Data taken from Ref. 4

Methyl substituents actually increases the reaction rates in Table II. Apparently, the N/C bond is weakly formed in the transition state as might be expected for a borderline S_N1/S_N2 mechanism in water[7]. Thus, non-bonded interactions with the methyl groups are minimized, and the rate increases reflect the larger pK_a values for the methylated nucleophiles. In general, the longer the N/C partial bond, for a given reaction type, the larger the volume available to the nucleophile within the reaction cone, the smaller the effect of the second methyl group over and beyond that of the first.

In summary, multi-directional transition state theory can qualitatively explain the steric effects among the alkylated nucleophiles. A more quantitative assessment of the theory requires our examining bifunctional molecules whose two interactive groups have varying but measurable dispositions in space (as with the hydroxyacids mentioned above). Further work along these lines will be reported later. It should be mentioned here, however, that the Dunitz solid state approach to reaction trajectories[8] does not (despite its great interest) provide the necessary information X-ray structures give an optimum trajectory but tell nothing about other concurrent trajectories and how they compare with the optimum. Collectively, an array of non-optimal geometries could well dominate a reaction pathway (similar to intermolecular hydrogen bonding where greater than half the population deviates by 20^{o} or more from linearity[9]).

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