Short Communications

The Relevance of Base Catalysis in Aromatic Nucleophilic Substitution to C—X Bond Cleavage

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Lamm and Lammert¹ have recently criticized the "absence of element effect" criterion for assessing whether or not bond-breaking occurs during the rate-determining step of nucleophilic substitution reactions. According to this criterion, originated by Bunnett, Garbisch and Pruitt² and initially applied to S_NAr reactions, if several substrates whose leaving group first atoms represent different elements react with a common nucleophilic reagent at nearly the same rate, scission of the bond to the leaving group does not occur during the rate-determining step. (A proviso, however, is that if rate-determining scission of the C—X bond had made little progress at the transition state, a sameness of rate might nevertheless result.)

Bernasconi and Zollinger³ reported in 1966 that the reaction of 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene solution is strongly catalyzed by DABCO (1,4-diaza[2.2.2]bicyclo-octane). The rate law has a prominent third-order term, first order in substrate, first order in anisidine and first order in DABCO. Lamm and Lammert extended study of that process to embrace also the leaving groups Br, $PhSO_2$, and $MeSO_2$. Among these four, whose first atoms represent three elements, the maximum difference in the third-order rate constants was 9-fold, rather greater than the maximum difference of 1.3-fold for reactions of the same

substrates (excepting the methylsulfonyl compound) with piperidine in methanol,² but nevertheless a small difference.

After Bernasconi and Zollinger, Lamm and Lammert took the third-order term to represent base catalysis. They accepted base catalysis as evidence that the rate-determining step is, in their words, "the second reaction step, involving cleavage of the C—X bond." From their results they drew the inference that a small element effect is of limited validity as a criterion of mechanism in the sense mentioned.

The reservations of Lamm and Lammert, if well grounded, would have important implications regarding the question of whether nucleophilic aromatic substitution and the analogous nucleophilic vinylic substitution⁴ are one- or multi-step processes. Thus, in vinylic substitutions⁴ retention of stereochemistry argues for a concerted process⁵ while the near absence of a leaving group element effect indicates a multi-step mechanism. It is important to know whether the element effect criterion has general validity.

The work of Lamm and Lammert unfortunately does not constitute a definitive test of the criterion. The crucial point is that although a valid third-order term in the rate law, as described, does indicate the presence of a DABCO molecule in the rate-determining transition state, it does not indicate the structure of the transition state or the function of the DABCO molecule in it. There are at least two reasonable structures for the transition state which do not involve scission of the C—X bond.

First, it is conceivable that the initial (k_1) step is rate-limiting, with DABCO present in the transition state interacting by hydrogen-bonding with a rather acidic hydrogen of the anisidine amino moiety. In the transition state (V), one of the amino hydrogens would hydrogen-bond intramolecularly to the *o*-nitro

group⁶ and the other to a DABCO molecule. The feasibility of this model depends on the relative magnitudes of the decreases in $T\Delta S^\ddagger$ and in $\Delta H^\ddagger$ implied by incorporation of a DABCO molecule. The loss in $T\Delta S^\ddagger$ is likely to be about 5 kcal⁷ and the strength of the hydrogen bond might well be of similar or greater magnitude; DABCO is quite basic, the amino hydrogens are likely to be quite acidic (because the transition state is probably attained late in the attachment of anisidine nitrogen to aromatic carbon) and the hydrogen bond is expected to be a strong one. (The fact that the reaction of I (X = Cl) with butylamine in benzene is merely second order,⁸ which might seem to contradict this model, could be rationalized by postulating for a primary amine of high nucleophilicity an early transition state, in which the amine hydrogens would not be very acidic.)

A second alternative takes account of good evidence⁹ that S_NAr reactions of amine nucleophiles may involve three steps: Initial formation of zwitterionic σ -complex II, deprotonation of II by a base to form anionic σ -complex III, and finally leaving group expulsion. Lamm and Lammert discussed it, however, as a two-step process. It is possible that formation of II is a mobile equilibrium and that the deprotonation (k_3) step is rate-limiting. The DABCO molecule would be present in the rate-determining transition state, taking the proton, but there would be no scission of the C-X bond. This model would require that expulsion of the leaving group from III be much faster than reprotonation to II.

There are now known several examples of relatively slow reactions, in water solution, that have rate-determining proton transfer steps.¹⁰ Rate-determining proton transfer steps are even more likely in benzene because hydrogen-bonded networks of solvent to acidic or basic sites, which expedite proton transfer,¹¹ are not possible.

Because there are plausible alternative interpretations of the results of Lamm and Lammert, they do not constitute a serious challenge to the validity of the element effect as a criterion of mechanism.

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A Novel Fragmentation in the Mass Spectra of Some 3-(2-Hydroxyphenyl)-4-oxo-3,4-dihydroquinazolines

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In our current study on metabolites of the hypnotic drug methaqualone [2-methyl-4-oxo-3-(2-tolyl)-3,4-dihydroquinazoline] we reported the mass spectra of its monohydroxy derivatives.¹ We found that the fragmentation of these compounds was dominated by loss of the

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