Tetrahedron Letters No. 13, pp. 1041-1044, 1970. Pergamon Press. Printed in Great Britain.

ON THE SEARCH FOR AN ADDITION-INTERMEDIATE ALONG THE REACTION PATH OF NUCLEOPHILIC AROMATIC SUBSTITUTION

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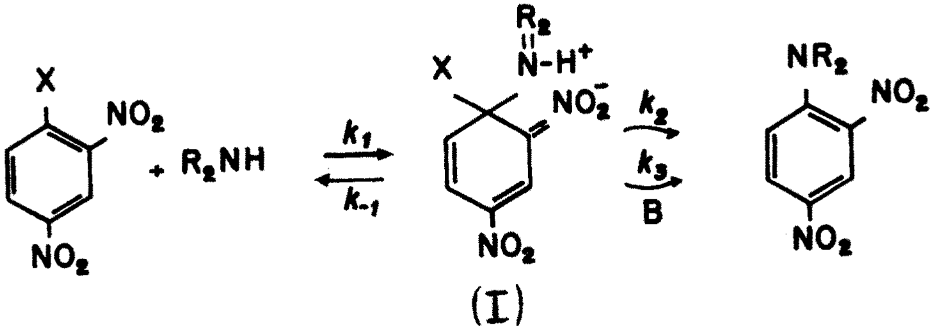
(Received in UK 2 February 1970; accepted for publication 12 February 1970)

So far the strongest evidence for the addition-elimination mechanism of nucleophilic aromatic substitution[1] has come from studies of the occurrence and form of base catalysis in reactions in which the nucleophile is a primary or a secondary amine.[1] Such a mechanism may be sketched as in eq.(1) for the case of a 2,4-dinitro-activated substrate and a secondary amine, and, if the steady-state treatment applies, it gives the rate equation (2), where B represents a general base, including the reacting amine itself, and k the second-order rate coefficient (Rate/ $[ArX][R_2NH]$).[1]



(1)

A few such reactions have been found to undergo base catalysis in such a way that k

$$k = (k_1k_2 + k_1k_3\ [B])/(k_{-1} + k_2 + k_3\ [B]) \qquad (2)$$

increases less than linearly with increasing catalyst concentration.[1] This trend has been unequivocally attributed to a change of the rate-limiting step with increasing catalyst concentration.[1] Therefore, at least one intermediate, such as (I), must be present along the reaction path in such cases. In terms of the mechanism of eq.(1) this corresponds to $k_{-1} \approx k_2 + k_3\ [B]$.[1]

More commonly, base catalysis of reactions of the type shown in eq. (1) results in a linear increase of k with catalyst concentration, an observation compatible with both the mechanism of eq.(1) (when $k_{-1} \gg k_2 + k_3[B]$) and other mechanisms as well.[2]

Finally, the great majority of reactions of the type in eq.(1), notably those in which a good leaving-group is displaced, are slightly accelerated by the reacting amine but fail to be further accelerated by the addition of stronger bases. [3] Such mild rate accelerations by the reacting amine have been attributed by various authors to a stabilisation of the transition state by a common solvent effect or, alternatively, to a more specific effect of unclear origin which, however, cannot be base catalysis in the sense commonly agreed for this terminology.[1,3]

However, other authors[4,5,6] did not agree with the above interpretation and definitely attributed such rate accelerations to base catalysis of the removal of a proton from type (I) intermediates. In one such case, that of the reaction of piperidine with 4-chloro-3-nitrobenzotrifluoride in benzene at 35°C, the evidence seemed to be compelling. In fact, as required by eq.(2) in the instance that $k_{-1} \approx k_2 + k_3[B]$, both a less than linear increase of k with piperidine concentration (in the amine concentration range from 0.05 to 0.6 M) and a linear 1/k versus 1/[piperidine] plot were reported.[4] Moreover, change to [$1-^2H$] piperidine was reported[4] to give lower rates and the isotope effect $k_{3(H)}/k_{3(D)}$ for the proton abstraction step was calculated[4] to be 2.1, a figure probably much too high to be accounted for in terms of a secondary isotope effect.[7]

However, at 25°C, under otherwise identical conditions, these experiments[4] could not be reproduced in another laboratory.[8] Rather, a very mild (linear) acceleration by piperidine and no measurable isotope effect (within the 4% uncertainty of the experimental error) were found.[8]

It has been now reported that in the reaction of piperidine with 1-chloro-2-nitrobenzene in benzene the second-order rate coefficient increases very mildly with increasing piperidine concentration, the trend being linear at 75°C but less than linear at 100°C.[9] Such results have been interpreted[9] in terms of the mechanism of eq.(1) with $k_{-1} \gg k_2 + k_3[B]$ at the lower and $k_{-1} \approx k_2 + k_3[B]$ at the higher temperature. A similar change of the rate-limiting step is also suggested[9] as the origin of the above discussed disagreement of experimental results for the reaction of piperidine with 4-chloro-3-nitrobenzotrifluoride.

This report[9] seems again to require a rather drastic revision of the mechanisms for both nucleophilic aromatic substitution and proton transfer reactions. Therefore, we report here the results of a kinetic re-investigation of the reaction of piperidine or [$1-^2H$]piperidine (90% deuteriated) with 4-chloro-3-nitrobenzotrifluoride in benzene at 34.8°C. Purification of chemicals, product analysis and kinetic procedure are as already described[8] for the work at 25°C the rate data of which prove to be nicely reproducible.

The rate data (average of at least two runs with less than 4% uncertainty of the experimental error) are collected in the Table, and it can be seen that they are nicely fitted by eq.(3), where PIP stands for piperidine or [$1-^2H$]piperidine. This can be appreciated even better from the

$$k = k_o + k_{PIP}[PIP] \tag{3}$$

Figure. Linear regression analysis gives $k_o = 1.06 \times 10^{-3}$ mole^{-1} l.sec.$^{-1}$ and $k_{PIP} = 3.77 \times 10^{-4}$ mole^{-2} l.^{2}sec.$^{-1}$. Therefore we obtain $k_{PIP}/k_o = 0.36$ mole l.$^{-1}$ which compares well with the value 0.38 mole^{-1} l. previously obtained[8] at 25°C. (Table 2 of ref.8 contains a misprint: k_o and k_{PIP} values for the reaction of 4-chloro-3-nitrobenzotrifluoride have to be interchanged).

TABLE. Second-order rate coefficient (k) for the reaction of piperidine with 4-chloro-3-nitrobenzotrifluoride (initial conc. 1.56×10^{-4} M) in benzene at 34.8°C.

10^2 [$C_5H_{10}NH$] (M)	2.37	4.75	10.2	15.8		34.2	52.8	-	79.3
10^2 [$C_5H_{10}ND$] (M)	-	-	-	-	32.2	-	-	64.4	-
10^3k	1.07	1.08	1.09	1.12	1.19	1.19	1.26	1.31	1.35

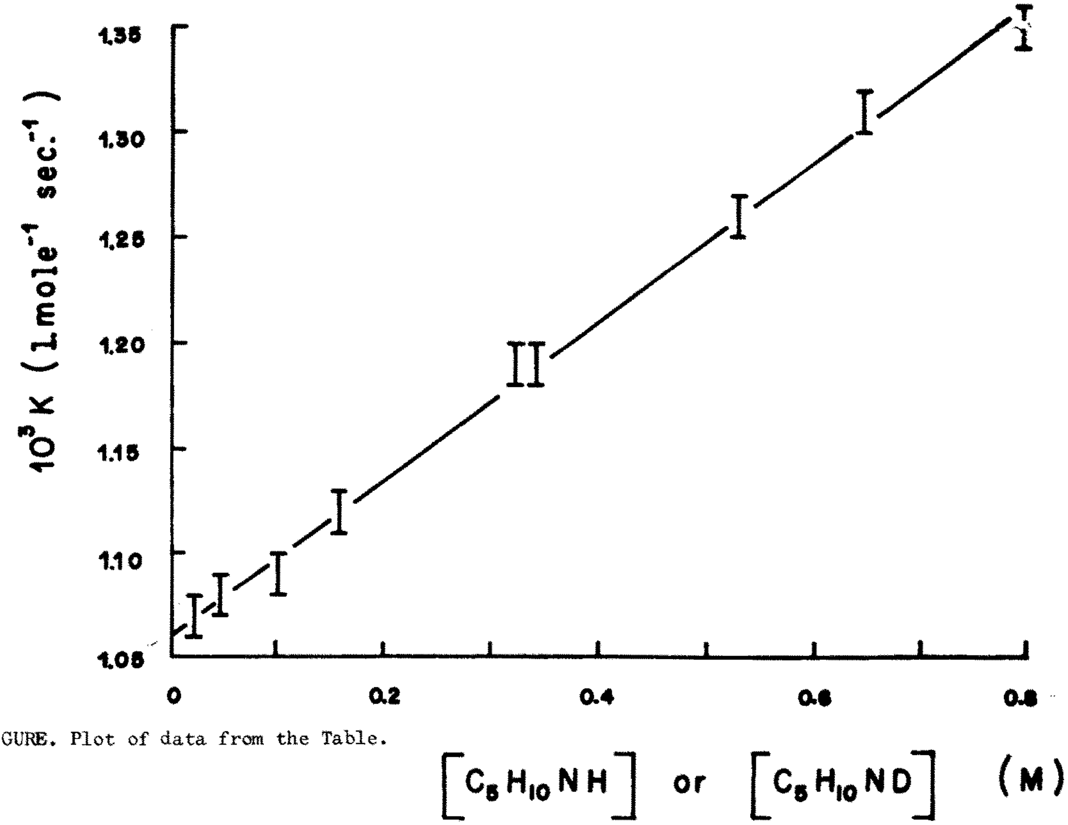


FIGURE. Plot of data from the Table.

These results clearly show that previous data reported by Brieux and his coworkers[4] for the reaction of 4-chloro-3-nitrobenzotrifluoride with piperidine or [1-^{2}H] piperidine in benzene at 35°C are in error. Therefore, current theories for both nucleophilic aromatic substitution[1] and deuterium kinetic isotope effects[8] do not need any revision at present, even when the above summarised results[4] for the reaction of piperidine with 1-chloro-2-nitrobenzene are considered. The trend of the rates observed in the last case[9] may in fact have quite a different origin from the suggested[9] change of the rate-limiting step, such as, for example, a change of the free energy of the reagents with changing composition of the medium (from 0.16 M piperidine in benzene to neat piperidine!). This should be carefully evaluated before definite conclusions about the mechanism can be drawn.[*]

In any case, available data[10] indicate that *ortho*-nitro substituted substrates are the worst possible choice of a substrate where one can hope to find base catalysis in reactions of the type shown in eq.(1). In fact, the *ortho*-nitro group is known[10] to be able to exert a powerful anchimeric assistence of the removal of an ammonium proton from type (I) intermediates.

ACKNOWLEDGMENT

This work has been financially supported by C.N.R., Roma.

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[*] For example, the observation that the rate of the reaction of piperidine with 1-chloro-2-nitrobenzene is slower in the polar solvent methanol than in the less polar benzene was taken[9] as a piece of evidence that the observed increase of the second-order rate coefficient with increasing piperidine concentration (and thereby with increasing polarity of the medium) cannot be attributed to a general medium effect. While the conclusion[9] can be true, the comparison of methanol with the solvent mixture benzene-piperidine is most unfortunate. In fact, only methanol can effectively hydrogen bond with the piperidine electron lone pair.