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BASE CATALYSIS IN NUCLEOPHILIC AROMATIC SUBSTITUTION

Sidney D. Ross and Raymond C. Petersen
Sprague Electric Company
North Adams, Massachusetts 01247

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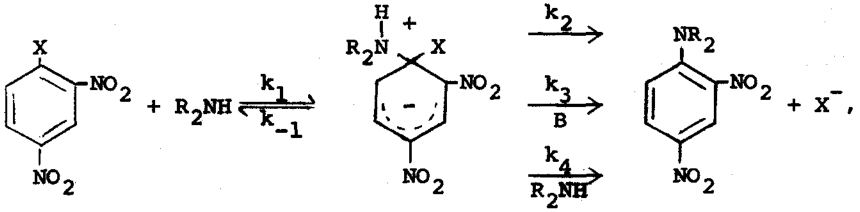
Base catalysis in nucleophilic aromatic substitution is generally described in terms of the following mechanism (1, 2, 3),



I II III

where R_2NH is the nucleophile (e.g. piperidine in the reaction with 2,4-dinitrophenyl phenyl ether) and B is the basic catalyst (e.g. hydroxide ion in the above reaction). Applying the steady state approximation with respect to II one obtains the rate equation,

$$\underline{1.} \qquad \frac{d[\mathrm{III}]}{dt} = \frac{k_1[\mathrm{I}][R_2NH]\left(k_2 + k_3[B] + k_4[R_2NH]\right)}{k_{-1} + k_2 + k_3[B] + k_4[R_2NH]} \cdot$$

For experimental purposes it is customary to define a second-order rate constant, k_2^* , usually determined in the limit of zero time, as follows,

$$\underline{2.} \qquad k_2^* = \frac{d[\mathrm{III}]}{dt\ [\mathrm{I}][R_2NH]} = \frac{k_1\left(k_2 + k_3[B] + k_4[R_2NH]\right)}{k_{-1} + k_2 + k_3[B] + k_4[R_2NH]} \cdot$$

Equation 2. is then discussed in terms of two limiting conditions. The first is

$$\underline{3.} \qquad k_2 + k_3[B] + k_4[R_2NH] \gg k_{-1},$$

in which case equation 2. reduces to

$$\underline{4.} \qquad k_2^* = k_1,$$

and this defines the limiting rate in the presence of a large concentration of the basic catalyst, B.

The second limiting condition is

5. $$k_{-1} \gg k_2 + k_3[B] + k_4[R_2NH],$$

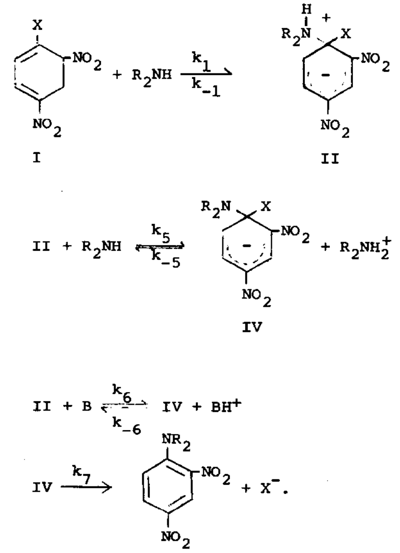
in which case equation 2. becomes

6. $$k_2^* = \frac{k_1}{k_{-1}}\left(k_2 + k_3[B] + k_4[R_2NH]\right) .$$

By determining k_2^* at constant $[I]_o$ and $[R_2NH]_o$ and varying $[B]_o$ and plotting k_2^* vs $[B]_o$, one obtains a curve which is linear at low $[B]_o$, with slope equal to $\frac{k_1k_3}{k_{-1}}$ and intercept equal to $\frac{k_1}{k_{-1}}\left(k_2 + k_4[R_2NH]_o\right)$ and which at high $[B]_o$ flattens out to k_1. It is also possible to make measurements at low and constant $[B]_o$, constant $[I]_o$ and varying $[R_2NH]_o$. If catalysis by the nucleophile, R_2NH, is significant a plot of k_2^* vs. $[R_2NH]_o$ will have an initial linear portion with slope equal to $\frac{k_1k_4}{k_{-1}}$ and intercept equal to $\frac{k_1}{k_{-1}}\left(k_2 + k_3[B]_o\right)$.

Both of these limiting conditions have been observed experimentally, and plots of both k_2^* vs. $[B]_o$ and k_2^* vs. $[R_2NH]_o$ have been shown to have characteristics consistent with this proposed mechanism. These observations (1, 2, 3) have been accepted as the strongest evidence for the intermediate complex mechanism in nucleophilic aromatic substitution.

It is our present purpose to propose an alternate mechanism for base catalysis in nucleophilic aromatic substitution. This mechanism may be formulated as follows:



A less general form of this mechanism was first proposed by Murto (4) to describe the reactions of 1-X-2,4,6-trinitrobenzenes with hydroxide ion. The presently proposed mechansim differs from that of Jencks and Bunnett in that the proton transfer step is reversible and precedes the product forming step. This is, in our opinion, more consistent with a priori chemical expectations than to have the proton transfer concerted with the product forming step and hence irreversible.

By applying the steady state approximation to both II and IV, one can derive rate equation 7.

$$\underline{7.}\quad \frac{d[III]}{dt} = k_7[IV] = \frac{k_7\left(k_1[I][R_2NH]\right)\left(k_5[R_2NH] + k_6[B]\right)}{k_7\left(k_{-1} + k_5[R_2NH] + k_6[B]\right) + k_{-1}\left(k_{-5}[R_2NH_2^+] + k_{-6}[BH^+]\right)}$$

For the special case where

$$\underline{8.}\quad k_7\left(k_{-1} + k_5[R_2NH] + k_6[B]\right) >> k_{-1}\left(k_{-5}[R_2NH_2^+] + k_{-6}[BH^+]\right)$$

equation 7. reduces to equation 9.

$$\underline{9.}\quad \frac{d[III]}{dt} = \kappa_7[IV] = \frac{k_1[I][R_2NH]\left(k_5[R_2NH] + k_6[B]\right)}{k_{-1} + k_5[R_2NH] + k_6[B]}$$

Once again it is possible to define an experimental second-order rate constant, k_2^*.

$$\underline{10.}\quad k_2^* = \frac{d[III]}{dt[I][R_2NH]} = \frac{k_1\left(k_5[R_2NH] + k_6[B]\right)}{k_{-1} + k_5[R_2NH] + k_6[B]}$$

Experimentally k_2^* is normally determined in the limit of zero time, at which time the special case defined by 8. might be expected to hold, since $[R_2NH_2^+] \approx 0$ and $[BH^+] \approx 0$. Morever, $k_5 > k_{-5}$ and $k_6 > k_{-6}$, since in the usual case B and R_2NH are probably stronger bases than IV.

Equations 9. and 10. permit two limiting cases, both of which have been observed experimentally. With

$$\underline{11.}\quad k_{-1} >> k_5[R_2NH] + k_6[B],$$

equation 9. reduces to 12.

$$\underline{12.}\quad \frac{d[III]}{dt} = \frac{k_1}{k_{-1}}[I][R_2NH]\left(k_5[R_2NH] + k_6[B]\right)$$

and

$$13.\quad k_2^* = \frac{k_1}{k_{-1}}\left(k_5[R_2NH] + k_6[B]\right)$$

with

14. $$k_5[R_2NH] + k_6[B] \gg k_{-1},$$

equation 9. reduces to 15.

15. $$\frac{d[III]}{dt} = k_1[I][R_2NH],$$

and

16. $$k_2^* = k_1.$$

It is apparent that when condition 8. is satisfied, the presently proposed mechanism affords a fit for the experimental observations that is completely equivalent to that given by previous hypotheses. It is to be noted that for this special case the measured rate constants are independent of the magnitude of k_7. It is also to be noted that it is possible to conceive of the possibility of cases where condition 8. does not obtain and where only the more general rate expression, equation 7., is applicable.

It is further apparent that the presently proposed mechanism is consistent with the experimentally observed isotope effects with a deuterated nucleophile (e.g. R_2ND). For the limiting case defined by 14., a zero isotope effect would be observed. For the limiting case defined by 11., a maximum isotope effect would be found. All intermediate situations would result in isotope effects intermediate in magnitude between these two extremes.

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