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AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS IN THE NAPHTHALENE SERIES. A KINETIC STUDY OF THE REACTION BETWEEN 2,3-DINITRONAPHTHALENE AND PIPERIDINE IN BENZENE

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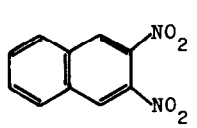
Abstract - The title reaction shows a curvilinear dependence (downward curvature) of the overall third order rate constant (second order in piperidine) on amine concentration. This and other experimental results have been rationalized with a stepwise mechanism of the anomalous addition-elimination (AEa) type involving a change in rate-determining step within the kinetically significant addition process.

2,3-Dinitronaphthalene (1) reacts with piperidine in benzene to afford quantitatively[1] 1-piperidino-3-nitronaphthalene (2). This reaction represents a rare example of easy aromatic cine-substitution[2] in which the nitro group is both the activating and the leaving group.[3] Our continuing interest in the field of aromatic nucleophilic substitutions with rearrangement[4] has prompted us to investigate in detail the mechanism of this reaction,[5] and results are herein reported together with a discussion of their implications.



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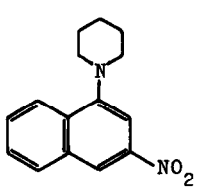

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Results and discussion

The title reaction is a clear first order process with respect to substrate (more than tenfold variations in substrate concentration cause rate variations well within tha experimental error) but its rate shows a complex dependence on piperidine concentration ([Pip]), the general behaviour being similar at the three temperatures investigated.[6] Plots of the second order rate constant (k_{II}, $M^{-1}s^{-1}$) vs. [Pip] (not shown) are curvilinear (upward curvature) and extrapolation to zero [Pip] gives intercepts which are zero or nearly zero: thus no term of the overall second order (first order in piperidine) plays a significant role in the rate-law. Plots of the third order rate constant (k_{III}, $M^{-2}s^{-1}$) vs. [Pip] present a downward curvature, while extrapolation to zero [Pip] gives sizable intercepts (Fig. 1). An analytical expression of the third order rate

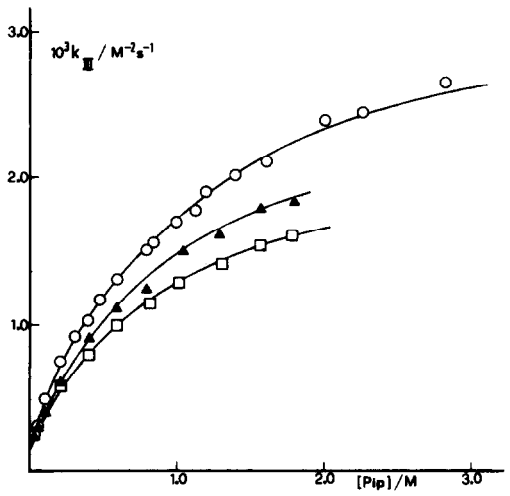


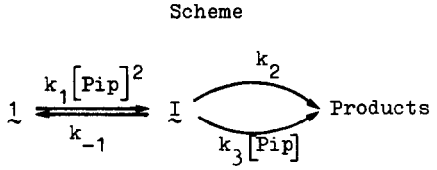
Figure 1 - Dependence of the overall 3rd order rate constant (k_{III}, $M^{-2}s^{-1}$) on [Pip] for the reaction between 1 and piperidine in benzene at 22°C (○), 50°C (▲), and 60°C (□). Solid lines are the theoretical lines obtained from the kinetic parameters in the Table.

constant consistent with such behaviour (eq. 1) can be obtained from the Scheme

$$k_{III} = \frac{k_1(k_2 + k_3[Pip])}{k_{-1} + k_2 + k_3[Pip]} \qquad (1)$$

under the steady-state approximation for intermediate I, the mechanistic

Scheme



meaning of the experimental results thus lying on a change in rate-determining step (brought about by a variation in [Pip]) within a stepwise mechanism. A standard treatment[7] of eq. 1 allows the calculation of k_1 and of the k_3/k_{-1}, k_2/k_{-1}, and k_3/k_2 ratios (values are reported in the Table); the curves drawn making use of calculated parameters (Fig. 1, solid lines) nicely

Table

Kinetic parameters (see Scheme) for the reaction between 1 and piperidine in benzene at different temperatures.

	22°C	50°C	60°C
$10^3 k_1$ ($M^{-2}s^{-1}$)	3.64	2.90	2.37
k_3/k_{-1} (M^{-1})	0.87	0.97	1.14
$10^2 k_2/k_{-1}$	6.04	6.82	7.54
k_3/k_2 (M^{-1})	14.4	14.2	15.1

reproduce the experimental behaviour in the whole range of [Pip] examined. The k_3/k_2 ratio (ca. 15) is intermediate between values typical for base catalysis (≥50) and values which are instead taken as evidence of "medium" effects (≤5), and therefore its significance, according to Bunnett's criterion,[8] is not straightforward. Some help at this regard comes, however, from inspection of data of Fig. 2, where the rate variations which are brought about by the addition of variable amounts of tertiary amines at constant [Pip] are shown: while 1,4-diaza[2,2,2]bicyclooctane (DABCO) causes, on the overall third order rate constant, variations which are comparable to those caused by piperidine itself,[9] other amines are

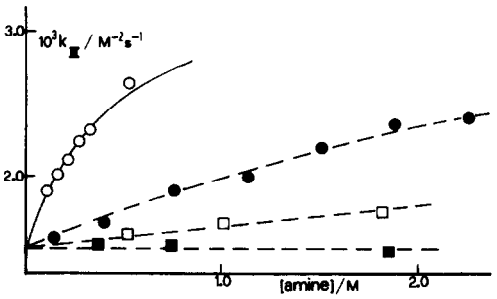
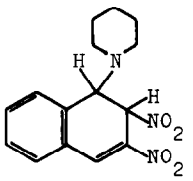


Figure 2 - Dependence of the overall 3rd order (2nd order in piperidine) rate constant (k_{III}, $M^{-2}s^{-1}$) on the concentration of added tertiary amines at constant 0.8M piperidine and 22°C: ○, DABCO; ●, pyridine; □, 2-picoline; ■, N-methylpiperidine. The solid line is theoretical, while dashed lines are simply notional

much less effective and factors like steric hindrance and/or basicity can even prevent any measurable effect from showing up. This specificity seems to suggest that, although medium effects surely play a role in reactions carried out in aprotic solvents when high concentrations of reagents are reached,[10] the bulk of the effect exerted by piperidine in our system should be regarded as true catalysis, with the mechanistic significance outlined in the Scheme. It must be noted that the levelling off of a catalytic effect could find explanations different from a change in rate-determining step, such as, for example, association of the catalyst with starting materials (activity coefficient effect).[11] Anyway, although solubility sets a limit to the concentration of DABCO in benzene (ca. 0.6M at 22°C), a mathematical analysis of the rate data obtained in the presence of DABCO and reported in Fig. 2 allows to estimate a levelling off of the effect exerted by DABCO at a k_{III} value ($3.55 \cdot 10^{-3}$ $M^{-2}s^{-1}$) matching, within experimental error, the limiting value calculated for piperidine itself (k_1, see Table); this result gives, in our opinion, strong support to the interpretation of the curvature above based on a change in rate-determining step,[11] with formation of intermediate $\underset{\sim}{I}$ (k_1, Scheme) being rate-determining at high concentrations of catalyst.

Ionic mechanisms commonly invoked in order to account (when radical pathways can be ruled out[12]) for an aromatic nucleophilic cine-substitution reaction[2] are initiated by the attack of the nucleophile either on a ring atom, with the formation of an addition intermediate within an overall addition-elimination mechanism, or on a hydrogen bonded to a ring atom, most often leading to an aryne intermediate within the classical elimination-addition (EA) mechanism. The latter mechanism would call, in our case, for the piperidine promoted HNO_2 elimination from $\underset{\sim}{1}$ to yield 1,2-dehydro-3-nitronaphthalene, followed by a regiospecific addition of the amine to the aryne. Actually, the type of substrate (the nitro group is not a good leaving group for aryne formation[3]) and the nature of the nucleophile[13] should not favour the occurrence of such mechanism. Furthermore, a number of experimental results also support its unlikelihood: a) the high order in the amine; b) the absence of substrate isotope effect (k_H/k_D is unity within experimental error when $\underset{\sim}{1}$ is replaced by 1,4-dideuterio-2,3-dinitronaphthalene at 0.2M piperidine and 50°C) coupled with the lack of deuteriation of the α positions of the substituted ring both in unreacted $\underset{\sim}{1}$ and in $\underset{\sim}{2}$ when reaction is carried out with N-deuteriopiperidine and quenched before completion; c) the sizable piperidine isotope effect (k_H/k_D = 2.6 when piperidine is replaced by 83% N-deuteriated 0.2M piperidine at 50°C).

Hence we favour initial nucleophilic attack on a ring carbon atom and, among conceivable pathways, we regard as most likely the addition of a piperidine molecule to the C-1/C-2 bond of $\underset{\sim}{1}$ to yield $\underset{\sim}{3}$, followed by elimination of HNO_2. Furthermore, the high product isotope effect (p.i.e.[14]) associated with the proton transfer to C-2 (8±2 at both 0.1M and 2.0M piperidine at 22°C: see experimental) seems to represent a kinetic rather than an equilibrium effect and therefore suggests that such proton transfer



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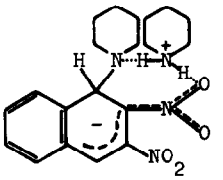
should either be itself involved in the rate-determining step[14a] or follow it,[14b] but not precede it, thus excluding the elimination process from being rate-determining. Actually the sizable piperidine isotope effect referred to above suggests in turn that the rate-determining step, at least at $[Pip] \leq 0.2M$, could well be such proton transfer to C-2.[15]

The faster elimination from intermediate 3 of a HNO_2 molecule rather than of a piperidine molecule could appear to be in contrast with what is known[16] for the addition of amines to β-nitrostyrenes, where the reversibly formed addition product does not lose a HNO_2 molecule. Different factors could anyway favour, in our system, HNO_2 elimination: a) steric interaction with adjacent nitro and piperidino groups could prevent the nitro group bonded to C-2 from fully stabilizing a negative charge on C-2, thus decreasing the acidity of the H-2 atom with respect to the corresponding H atom in α to the nitro group in the β-nitrostyrene/amine adducts; b) the nitro group bonded to C-3 could increase the lability of H-1 in 3 by means of a conjugative interaction through the two π bonds of the cyclohexadiene ring.

The rationalization of two catalytic amine molecules within the addition process is not straightforward. To our knowledge the only clear cut example of an overall fourth order activated nucleophilic addition reported in the literature is represented by the addition of aniline to ketenes in benzene,[17] where the term of the third order in base is justified with a concerted process (involving two aniline molecules acting bifunctionally) favoured by a strong base (triethylamine). We are dealing, anyway, with a quite different system where the two catalytic amine molecules catalyze consecutive steps (k_1 and k_3). This means that the nature of the intermediate formed in the process described by k_1 (I, see Scheme) should be such as to justify the occurrence of further catalysis (k_3) in order to accomplish the final proton transfer leading to the addition product 3. As concerns the role exerted within k_1 by the second piperidine molecule, it is likely that it assists the nucleophilic attack of the first molecule on C-1, either through a specific interaction with a nitro group, or through the formation of a dimer with the attacking molecule itself,[18,20] or through both such effects. A possible structure for the intermediate I is 4,



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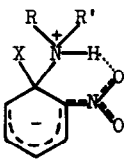

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or an alternative one in which the second amine molecule is H-bonded to the nitro group at C-3. H-Bonding to an o-nitro group within a structure like 5 is commonly regarded as strongly contributing to the stability of the zwitterionic intermediate in nucleophilic substitutions between primary or secondary amines and 2-nitro- or 2,4-dinitro-

activated benzene[21a] and naphthalene[21b] derivatives following the normal addition-elimination (S_NAr) pathway. The requirement in our system of an extra amine molecule should find its explanation in the presence of the nitro group at C-3 and could result from the reciprocal hindering effect of the two vicinal nitro groups which twists one or both of them out of the plane of the aromatic ring system;[22] the neat effect of the nitro group at C-3 could then be that of determining, for the zwitterionic intermediate (and the transition state leading to it), a geometry disfavouring H-bonding as in 5. The activation parameters calculated for k_1 are $\Delta H^{\neq}$ ca. $-11 kJ \cdot mol^{-1}$ and $\Delta S^{\neq}$ ca. $-329 J \cdot {}^{o}K^{-1} \cdot mol^{-1}$. Beyond the unavoidable experimental errors, the activation enthalpy value is clearly indicative of a stepwise process for k_1, with the slow step preceded by at least one fast, enthalpically unfavourable, preequilibrium;[23] anyway, whether the first step involves two amine molecules (dimerization) or substrate and one amine molecule (nucleophilic attack or specific interaction with a nitro group) is hard to tell on enthalpic grounds as both processes can exhibit a negative equilibrium enthalpy in an aprotic solvent.[24,25] As far as catalysis within k_3 is concerned, it must be underlined that the catalytic effectiveness of unhindered tertiary amines (Fig. 2) has been taken by some authors as evidence for the involvement of primary or secondary amines as general base rather than bifunctional catalysts in aprotic solvents.[26] However, the lack of quantitative information on the relative basicities of the amines above in benzene, coupled with the fact that the type of catalysis could be affected by the basicity of the amine,[27] leaves some doubts on this point.

Experimental

Melting points are uncorrected. UV, IR, and ^{1}H-NMR spectra were recorded respectively on a Gilford 2400-S spectrophotometer, a Perkin Elmer 257 Infrared spectrophotometer, and a Varian XL-100-12 spectrometer (tetramethylsilane as internal standard). Irradiation was provided by a 300W Ultra Vitalux Osram Sunlamp placed about 20cm from the reaction flask. T.l.c. analyses were performed on 0.2mm layers of Kieselgel GF_{254} DC-Fertigplatten (Merck).

Materials - Benzene (Erba) was purified from thiophen by the mercury acetate method,[28] refluxed over sodium, and distilled before use. Liquid amines were refluxed over KOH and distilled from sodium before use. DABCO was crystallized from benzene and sublimed before use. N-Deuteriopiperidine[29] and di-tert-butyl nitroxide[30] were prepared according to the literature. The amine resulted to be ca. 83% deuteriated (IR analysis[29]). 2,3-Dinitronaphthalene (1) (Ega Chemie) was crystallized from ethyl alcohol to the constant m.p. of 176-177°C (lit.[31] 172-174°C). 1,4-Dideuterio-2,3-dinitronaphthalene was prepared by H/D exchange from 1 and CH_3ONa in CH_3OD at reflux. The recovered dinitrocompound was ca. 85% deuteriated (^{1}H-NMR analysis). 1-Piperidino-3-nitronaphthalene (2) was prepared by adding a tenfold excess of piperidine to a solution of 1 in benzene. The solution was left to stand overnight (no unreacted substrate could be detected by t.l.c. analysis), washed with water to remove the excess amine, dried (Na_2SO_4), and evaporated, and the residue was crystallized from ethyl alcohol, giving 90% of product, m.p. 116-117°C (lit.[1] 116-117°C), λ_{max} (C_6H_6) 288nm (ε 14000), 388nm (ε 3000), τ ($CDCl_3$) 1.54 (1H, d, J 2.15Hz), 1.77 (1H, m), 2.02 (1H, m), 2.23 (1H, d, J 2.15Hz), 2.38 (2H, m), 6.89 (4H, m), 8.17 (6H, m). The τ 1.54 doublet corresponds to H-4 and the τ 2.23 doublet to H-2.[32]

Determination of p.i.e.[14] and search for deuterium incorporation in the reaction with N-deuteriopiperidine - The procedure described above for the preparation of 2 was followed, using both 0.1M and 2.0M 83% N-deuteriated piperidine at 22°C. The percentage of deuterium at C-2 in the product was determined by ^{1}H-NMR analysis through the decrease of the intensity of the τ 2.23 doublet, while no deuteriation

at C-4 could be detected (no decrease of the intensity of the τ 1.54 doublet observed). The p.i.e. value was calculated as $([C_5H_{10}NH]/[C_5H_{10}NH]) \cdot ([2\text{-}H]/[2\text{-}D])$.[14] Tests were duplicated at both 0.1M and 2.0M piperidine. In one occasion the reaction was quenched before completion by the addition of D_2SO_4 and the recovered unreacted substrate showed no deuterium incorporation. It must be pointed out that no H/D exchange at C-2 of 2 occurred when treating 2 with deuteriated piperidine in analogous conditions.

Kinetics - Kinetic runs were initiated by the addition of a negligible volume of a stock solution of 1 in benzene to 2ml of base solution contained in a thermostated spectrophotometric cell, and the reaction was followed by recording (Gilford 2400-S spectrophotometer) the absorbance (A) increase at 400nm. At all but very low [Pip] pseudo first order conditions were employed, using a more than tenfold excess of piperidine, and pseudo 1st order rate constants were obtained from semilogarithmic $(A_\infty - A_t)$ vs. t plots (which always showed good linearity up to at least three half times). At [Pip] $\leq$ 0.1M the initial rates method was employed, with A_t vs. t plots showing good linearity up to at least 3% reaction. The two methods gave, at 0.1M piperidine, the same constant within experimental error (±4%). The final spectrum of the reaction mixture always matched within ±3% that of a mock solution corresponding to 100% formation of 2 and no other product could be detected by t.l.c. analysis. Each value reported in the Figures is the mean of at least two independent runs, agreement always being within experimental error.

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