Kinetics of the Formation of the Intermediate Complex in the Aromatic Nucleophilic Substitution of Methyl 4-Methoxy-3,5-dinitrobenzoate with Piperidine in Dimethyl Sulfoxide

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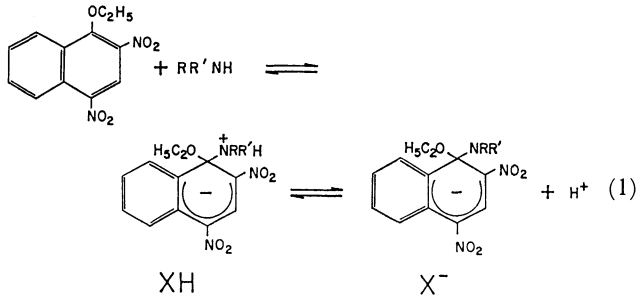
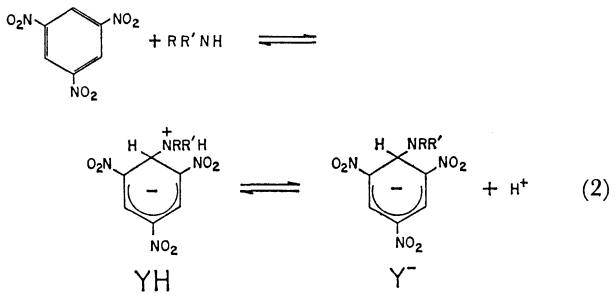
The intermediate complex in the aromatic nucleophilic substitution of methyl 4-methoxy-3,5-dinitrobenzoate with piperidine in dimethyl sulfoxide was confirmed by visible absorption spectroscopy. Kinetics of the formation of the intermediate were studied by a stopped-flow spectrophotometer, and rate and equilibrium constants were determined. The observable intermediate (Z^-) was the conjugate base of the initial zwitterionic complex (ZH). Proton transfer between ZH and Z^- was rate limiting and the intermediate formation was base catalyzed.

Bunnett and coworkers have confirmed the existence of the intermediate complex in the aromatic nucleophilic substitution of 1-ethoxy-2,4-dinitronaphthalene with primary and cyclic secondary amines in dimethyl sulfoxide (DMSO) and presented the mechanism for the formation and decomposition of the intermediate.[1,2] As regard to the formation of the intermediate, proton transfer between XH and X^- is rapid and therefore the formation of the intermediate is not base catalyzed.



XH X^-

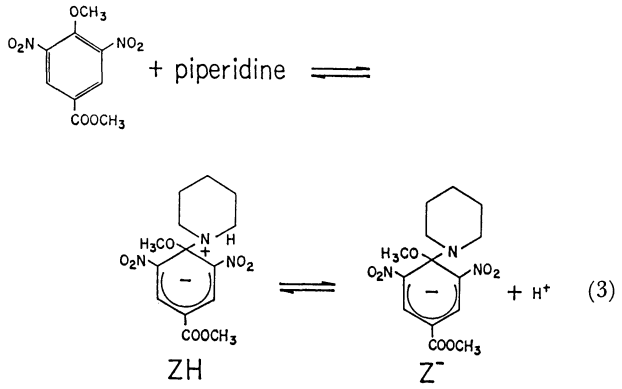
Contrary, kinetic studies on the formation of the anionic σ-complexes[3-5] of trinitrobenzene with primary and secondary amines have shown that proton transfer between YH and Y^- is rate limitting under certain conditions.[5-9]



YH Y^-

Crampton and Gibson have demonstrated from kinetics of the formation of the σ-complex from trinitrobenzene and piperidine in DMSO that proton transfer is rate limiting over the entire range of piperidine concentrations used.[9]

We have observed the visible absorption spectrum of the intermediate complex of methyl 4-methoxy-3,5-dinitrobenzoate (MDNB) with piperidine in DMSO and studied on kinetics of the formation of the intermediate.



ZH Z^-

Experimental

Materials. MDNB was prepared by esterification of 4-chloro-3,5-dinitrobenzoic acid followed by nucleophilic substitution of chlorine by sodium methoxide. The compd was recrystallized from methanol. NMR (DMSO-d_6); δ=8.63 (aromatic protons), 3.99 (OCH_3), 3.92 ($COOCH_3$). Methyl 3,5-dinitro-4-piperidinobenzoate was prepared by substitution of the methyl ester of 4-chloro-3,5-dinitrobenzoic acid with piperidine. The compd was recrystallized from methanol. NMR (DMSO-d_6); δ=8.39 (ring protons), 3.87 ($COOCH_3$), 3.00 (CH_2NCH_2), 1.56 ($CH_2CH_2CH_2$). Piperidine was refluxed over sodium and distilled. Piperidine hydrochloride was prepared from piperidine and concentrated hydrochloric acid in methanol and recrystallized from methanol. S. G. DMSO, tetrapropylammonium iodide, and 1,4-diazabicyclo-[2.2.2]octane (DABCO) were used as supplied.

Measurements. Piperidine (2.8×10^{-4} mol) was injected into a NMR tube containing a DMSO-d_6 solution (0.4 cm^3) of MDNB (2.0×10^{-4} mol) and NMR spectra were recorded on a Hitachi R-22 Spectrometer. Visible absorption spectra were recorded using a Hitachi RSP-2 Rapid Scan Spectrophotometer and a Hitachi 340 Spectrophotometer. Kinetic measurements were carried out using a thermostatted stopped-flow spectrophotometer (Union Giken RA-401).

Results

NMR Spectroscopy. After addition of piperidine to a solution of MDNB, the resonance peaks at δ= 8.63, 3.99, and 3.92 gradually disappeared and completely vanished 1 h after addition at 34 °C. At the expense of the peaks of MDNB, new resonance peaks appeared at δ=8.25, 3.77, 3.06, and 1.58. The new

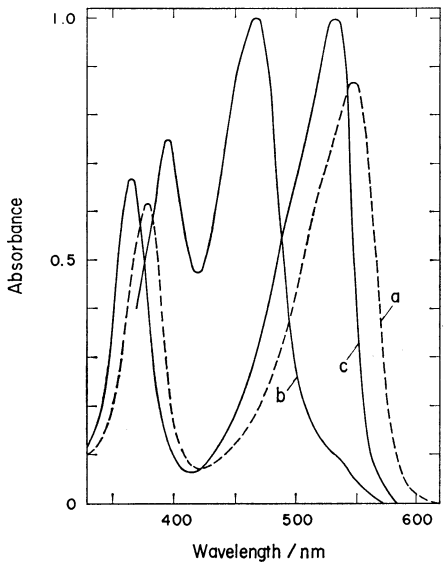
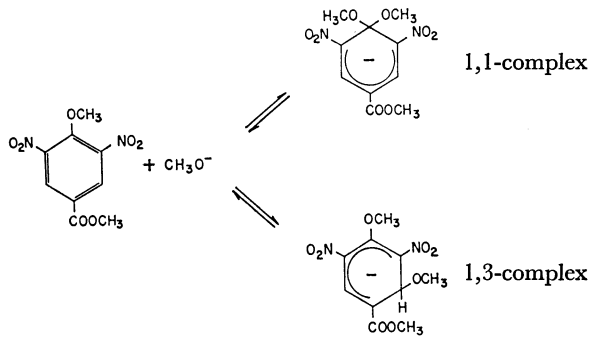


Fig. 1. The visible absorption spectrum observed immediately after mixing of MDNB (4.9×10^{-5} M, 1 M=1 mol dm^{-3}) with piperidine (0.32 M) in DMSO, a; the spectra observed with the DMSO solution containing MDNB (4.9×10^{-5} M), potassium methoxide (8.0×10^{-3} M), and methanol (0.8% by volume); b and c, *ca.* 1/3 s and 5 min after mixing respectively.

peaks are attributed to methyl 3,5-dinitro-4-piperidinobenzoate; δ=8.25 (aromatic protons), 3.77 ($COOCH_3$), 3.06 (CH_2NCH_2), 1.58 ($CH_2CH_2CH_2$). No evidence for formation of an anionic σ-complex was obtained from NMR spectroscopy.

Visible Absorption Spectroscopy. The spectrum observed immediately after mixing of MDNB with piperidine in DMSO is a in Fig. 1. The absorption bands at 378 and 545 nm slowly decreased in intensity and disappeared several hours after mixing at room temperature.

For comparison, we tried to observe the visible absorption spectra of MDNB with potassium methoxide in DMSO. The spectra observed *ca.* 1/3 s and 5 min after mixing are b and c in Fig. 1, respectively. The absorption bands at 395 and 465 nm appeared at the initial stage are attributed to the 1,3-complex.[10,11] The spectrum c with absorption maxima at 367 and 532 nm is due to the 1,1-complex.[10-12]



The similarity of the spectrum a to c leads to the conclusion that the spectrum c is due to the intermediate complex ZH or/and Z^-. The formation of the intermediate is too fast to be measured by conventional means but can be measured by a stopped-flow spectrophotometer.

Table 1. Equilibrium absorbance of MDNB with piperidine and piperidine hydrochloride in DMSO[a]

[Piperidine] / M	A_{545}[b] 20 °C	25 °C	30 °C
0.040	0.041	0.030	
0.051		0.048	0.026
0.061	0.084	0.068	
0.071	0.115		0.053
0.081	0.138	0.116	0.066
0.12	0.26	0.24	0.136
0.16		0.33	0.21
0.24	0.53		0.35
0.32[c]		1.16	

a) $[MDNB]_0$ 6.0×10^{-5} M; [piperidine hydrochloride] 5.0×10^{-3} M; [tetrapropylammonium iodide] 5.0×10^{-3} M. b) Absorbance at 545 nm. c) In the absence of piperidine hydrochloride and tetrapropylammonium iodide. Conversion of MDNB to Z^- is virtually complete. ε_{545} 19300 M^{-1} cm^{-1}.

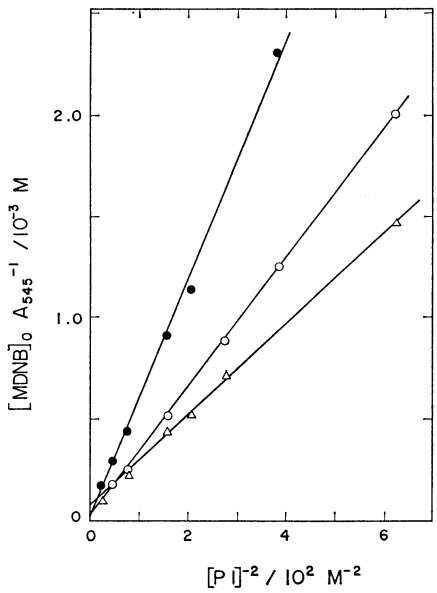


Fig. 2. Plots of $[MDNB]_0$ A_{545}^{-1} *vs.* $[Pi]^{-2}$.

Equilibria. Let us rewrite Eq. 3 as Eq. 4.

$$MDNB \underset{k_{-1}}{\overset{k_1[Pi]}{\rightleftharpoons}} ZH \underset{k_{PiH^+}[PiH^+]}{\overset{k_{Pi}[Pi]}{\rightleftharpoons}} Z^- \quad (4)$$

An equilibrium constant K for the over all conversion of MDNB into Z^- is defined by Eq. 5.

$$K = \frac{[Z^-][PiH^+]}{[MDNB][Pi]^2} \quad (5)$$

And then

$$K = \frac{k_1 k_{Pi}}{k_{-1} k_{PiH^+}}. \quad (6)$$

Assuming that k_{Pi} is much larger than k_{PiH^+},[13] Eq. 5 is rearranged as follows:

$$\frac{[MDNB]_0}{A} = \frac{[PiH^+]}{K\varepsilon[Pi]^2} + \frac{1}{\varepsilon}, \quad (7)$$

Table 2. Rate date in the presence of piperidine in large excess of MDNB at 25 °C[a)]

[Piperidine] M	[DABCO] M	k_{f1} s^{-1}	$k_{f1}/[Piperidine]^2$ $s^{-1}M^{-2}$
0.016		0.0068	27
0.020		0.0113	28
0.030		0.024	27
0.040		0.048	30
0.061		0.105	28
0.081		0.20	30
0.12		0.38	26
0.16		0.63	25
0.20		0.95	24
0.24		1.12	19.4
0.081	0.038	0.20	
0.081	0.076	0.22	
0.081	0.16	0.27	
0.081	0.23	0.28	
0.030[b)]		0.024	
0.12[b)]		0.36	
0.24[b)]		1.02	
0.12[c)]		0.38	

a) $[MDNB]_0$ 6.0×10^{-5} M. b) In the presence of salt; [tetrapropylammonium iodide] 1.00×10^{-2} M. c) In the presence of water; $[H_2O]$ 0.22 M.

where $[MDNB]_0$, A and ε are the stoicheiometric MDNB concentration, equilibrium absorbance, and the molar extinction coefficient, respectively.

In the presence of piperidine and piperidine hydrochloride in large excess of MDNB, equilibrium absorbance at 545 nm measured with a stopped-flow spectrophotometer is presented in Table 1. Measurements were carried out at μ 0.01 M using tetrapropylammonium iodide. Plots of $[MDNB]_0 A_{545}^{-1}$ *vs.* $[Pi]^{-2}$ in Fig. 2 give straight lines. K 0.117, 0.083, and 0.045 M^{-1} at 20, 25, and 30 °C respectively were obtained.

Kinetic Analysis. Kinetic runs were carried out in the presence of piperidine in large excess of MDNB and in the absence of piperidine hydrochloride. Under these conditions, we may write as follows:

$$MDNB \underset{k_{r2}}{\overset{k_{f1}}{\rightleftharpoons}} Z^- + AH^+, \tag{8}$$

where AH^+ is the species formed from deprotonatin of ZH by piperidine and is equall in concentration to Z^-, and k_{f1} and k_{r2} are the pseudo-first-order rate constant for the forward reaction and the second-order reverse rate constant, respectively. The solution for Eq. 8 is presented by Eq. 9.[14)]

$$\ln\left(\frac{[MDNB]_0[Z^-]_e+[Z^-]([MDNB]_0-[Z^-]_e)}{[MDNB]_0([Z^-]_e-[Z^-])}\right)= \left(\frac{2[MDNB]_0-[Z^-]_e}{[Z^-]_e}\right)k_{f1}t, \tag{9}$$

where $[Z^-]$ and $[Z^-]_e$ are concentrations of Z^- during the reaction and at equilibrium respectively.

Making use of the steady-state approximation with respect to ZH, k_{f1} is given by Eq. 10. The second-order rate constant k_{f2} for the forward reaction is given by Eq. 11.

$$k_{f1} = \frac{k_1[Pi]k_{Pi}[Pi]}{k_{-1}+k_{Pi}[Pi]} \tag{10}$$

$$k_{f2} = k_{f1}/[Pi]. \tag{11}$$

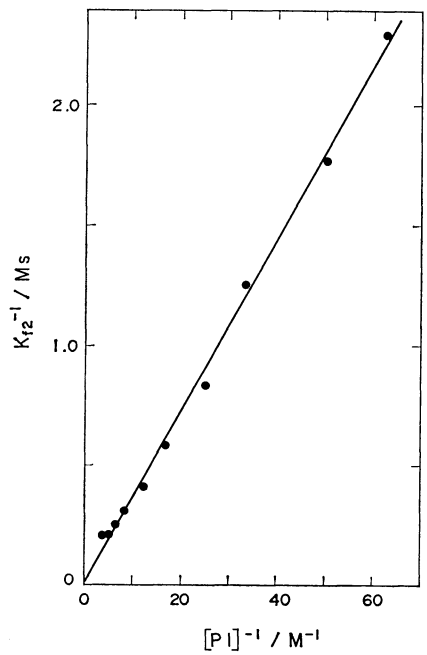


Fig. 3. A plot of k_{f2}^{-1} *vs.* $[Pi]^{-1}$.

Rate date are presented in Table 2. When concentrations of piperidine are smaller than 0.12 M values of $k_{f1}/[Pi]^2$ are substantially constant. This fact implies that k_{-1} is much larger than $k_{Pi}[Pi]$ and deprotonation of ZH is rate limiting in the forward direction.

Equation 10 is rearranged as Eq. 12.

$$\frac{1}{k_{f2}} = \frac{1}{k_1} + \frac{k_{-1}}{k_1k_{Pi}[Pi]} \tag{12}$$

A plot of k_{f2}^{-1} *vs.* $[Pi]^{-1}$ in Fig. 3 gives straight line. k_1k_{Pi}/k_{-1} 28 $s^{-1}M^{-2}$ and k_1 100 $s^{-1}M^{-1}$ were obtained from the inversion of the slope and of the intercept, respectively. And then k_{Pi}/k_{-1} 0.28 M^{-1}. From K 0.083 M^{-1}, k_{PiH^+} 340 $s^{-1}M^{-1}$.

Kinetic runs were made with piperidine and DABCO in large excess of MDNB. Under these conditions, k_{f1} is given by Eq. 13.

$$k_{f1} = \frac{k_1[Pi](k_{Pi}[Pi]+k_{DABCO}[DABCO])}{k_{-1}+k_{Pi}[Pi]+k_{DABCO}[DABCO]}, \tag{13}$$

where k_{DABCO} is the rate constant for deprotonation of ZH by DABCO. As shown in Table 2, k_{f1} increases with DABCO concentration. The intermediate formation is catalyzed by DABCO. At a given concentration of DABCO, k_{DABCO}/k_{-1} can be calculated from Eq. 13 using k_{Pi}/k_{-1} 0.28 M^{-1} and k_1 100 $s^{-1}M^{-1}$. The mean value of k_{DABCO}/k_{-1} obtained was 0.067 M^{-1}.

Kinetics were studied in the presence of both piperidine and piperidine hydrochloride in large excess of MDNB. Under these pseudo-first-order conditions, both forward and reverse reactions are pseudo-first-order and so observed rate constant k_{obsd} is the sum

Table 3. Rate date in the presence of piperidine and piperidine hydrochloride in large excess of MDNB at 25 °C[a)]

[Piperidine] / M	[Piperidine hydrochloride] / 10^{-3} M	[Tetrapropylammonium iodide] / 10^{-3} M	k_{obsd} / s^{-1}	k_{calcd} / s^{-1}
0.040	5.0	5.0	1.75	1.72
0.051	5.0	5.0	1.73	1.75
0.071	5.0	5.0	1.78	1.82
0.081	5.0	5.0	1.88	1.84
0.12	5.0	5.0	2.1	2.0
0.16	5.0	5.0	2.6	2.3
0.24	5.0	5.0	3.2	3.1
0.081	6.5	3.5	2.5	2.3
0.081	8.5	1.5	3.0	3.0
0.081	10.0		3.3	3.5
0.081[b)]	6.5	3.5	2.6	
0.081[b)]	8.5	1.5	3.1	

a) $[MDNB]_0$ 6.0×10^{-5} M. b) $[H_2O]$ 0.22 M.

Table 4. Summary of rate and equilibrium constants[a)]

	20 °C	25 °C	30 °C
k_1k_{Pi}/k_{-1} / $s^{-1}M^{-2}$		28±2	
k_{Pi}/k_{-1} / M^{-1}		0.28±0.16	
k_1 / $s^{-1}M^{-1}$		100±50	
k_{PiH^+} / $s^{-1}M^{-1}$		340±70	
k_{DABCO}/k_{-1} / M^{-1}		0.067±0.073	
K / M^{-1}	0.117±0.012	0.083±0.008	0.045±0.005
ΔG^0 / kcal mol^{-1}		1.47±0.10	
ΔH^0 / kcal mol^{-1}		−16.7±0.3	
ΔS^0 / kcal del^{-1} mol^{-1}		−0.061±0.013	

a) 1 cal=4.184 J.

of the forward and reverse component.

$$MDNB \underset{k_{r1}}{\overset{k_{f1}}{\rightleftharpoons}} Z^{-1} \quad (14)$$

$$k_{obsd} = k_{f1} + k_{r1} \quad (15)$$

Making use of the steady-state approximation with respect to ZH, k_{obsd} is given by Eq. 16.

$$k_{obsd} = \frac{k_1[Pi]k_{Pi}[Pi] + k_{-1}k_{PiH^+}[PiH^+]}{k_{-1} + k_{Pi}[Pi]} \quad (16)$$

Rate date are presented in Table 3. k_{calcd} was calculated from Eq. 16 using k_1 100 s^{-1} M^{-1}, k_{PiH^+} 340 s^{-1} M^{-1} and k_{Pi}/k_{-1} 0.28 M^{-1}.

In some cases, kinetic date were obtained in the presence of tetrapropylammonium iodide or water and are presented in Tables 2 and 3.

Rate and equilibrium constants are summarized in Table 4.

Discussion

Intermediate Complex. The similarity of the spectrum a in Fig. 1 to c of the Meisemheimer complex of similar structure affords an evidence for the formation of the intermediate complex.

NMR spectroscopy failed to detect an evidence for intermediate formation. Owing to its insufficient stability (K 0.045 M^{-1} at 30 °C), the intermediate is too small in concentration to be detected by NMR.

Plots of $[MDNB]_0$ A_{545}^{-1} *vs.* $[Pi]^{-2}$ give straight lines. This indicate that the intermediate exists predominantly as its conjugate base rather than the zwitterionic form.

Rate Limiting Proton Transfer. The most striking feature in the formation of the intermediate is that the deprotonation of ZH is rate limiting in the forward direction. The intermediate formation is base catalyzed.

Our results are k_1 100 s^{-1} M^{-1} and k_{Pi}/k_{-1} 0.28 M^{-1}. As the intercept of a plot of k_{f2}^{-1} *vs.* $[Pi]^{-1}$ is small, the value of k_1 obtained from the inversion of the intercept may have high uncertainity. Using our results, under [Pi] 0.06, 0.12, and 0.24 M, $k_{Pi}[Pi]$ are $0.017k_{-1}$, $0.034k_{-1}$, and $0.068k_{-1}$, respectively. These mean that under high piperidine concentrations a process from ZH to Z^- is not negligible. Thus, the depature from constant values of $k_{f1}/[Pi]^2$ under high piperidine concentrations in Table 2 will be appropriately explained by use of our results. As shown in Table 3, k_{calcd} values are in accordance with observed rate constants.

Bunnett *et al.* demonstrated that proton transfer is rapid and so not rate limiting in the formation of the intermediate complex from 1-ethoxy-2,4-dinitronaphthalene and piperidine in DMSO.[2)] The intermediate ZH of MDNB has two nitro groups which will prevent for piperidine to attack on ZH. The steric circumstance of the intermediate of 1-ethoxy-2,4-dinitronaphthalene is different from that of ZH. The difference of the steric circumstance will cause the difference of a rate limiting process.

Effect of Salt and Water. Rates are unaffected by the presence of tetrapropylammonium iodide (0.01 M). Furthermore, rates remain almost constant in the presence of water (0.22 M).

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13) It is known that the amine complex exists predominantly as its conjugate base rather than the zwitterionic form.[1,2,9]
14) See, for example, K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York (1965), p. 21.