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A STUDY OF THE INTERMEDIATES IN THE MANNICH REACTION OF NITROALKANES

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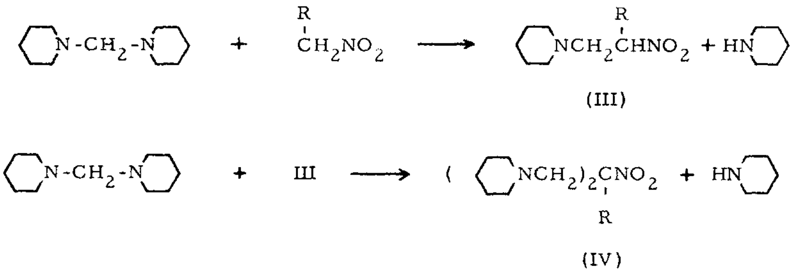
It has been established (1, 2) that the Mannich reaction of nitroalkanes proceeds through the initial reaction of amine and formaldehyde. This reaction gives two products I and II, both of which should be expected to react as intermediates with an active hydrogen compound to form the Mannich base.

$$R_2NH + HCHO \longrightarrow \underset{(I)}{R_2NCH_2OH} \xrightleftharpoons{R_2NH} \underset{(II)}{R_2NCH_2NR_2} + H_2O$$

In a previous publication (3) we reported the kinetics of the reaction of 2-nitropropane with methylene bisamines in media of varying dielectric constant. The reactivity of N-hydroxymethylamines, however, had been difficult to examine because of their instability and the concomitant difficulties in obtaining a pure sample (4). The present study involves kinetics of the reaction of methylene bispiperidine with nitromethane, nitroethane, and 2-nitropropane using the previously described method (3). This communication provides evidence that the N-hydroxymethylamine is a more reactive intermediate than the methylene bisamine.

The Mannich base of nitroethane and piperidine has been reported along with the disubstitution product, 2-nitro-2-methyl-1, 3-bis-(N-piperidyl) propane(5). Mannich bases, III, of nitromethane have not been reported, however, since all attempts to prepare them under the usual Mannich conditions had led exclusively to the disubstitution products IV, (1, 5, 6).



Because of the possibility of forming the disubstitution products, IV pseudo first order kinetics were determined using tenfold excesses of the nitroalkanes and anhydrous dioxane and N, N-dimethylformamide (DMF) as solvents. Moreover, the reported inability to obtain the monoalkylation products, III, of nitromethane prompted us to measure the rates of the second alkylation step. Table I shows the activation parameters for reactions run at 65.2°, 73.2°, and 78.6°C and represents kinetic runs over a dielectric constant range of 2 - 28.

TABLE I

Activation Parameters

Nitroalkane	Solvent	ΔH^*	ΔF^*	ΔS^*
Nitromethane	Dioxan	23.2	28.0	-13.9
Nitromethane	DMF	17.0	27.3	-29.0
Nitroethane	Dioxane	16.4	27.0	-30.7
Nitroethane	DMF	19.1	26.2	-20.5
2-Nitropropane	Dioxane	8.8	27.3	-53.5
2-Nitropropane	DMF	16.7	26.3	-28.0

Analysis of reaction products in our kinetic runs showed that only III (R = H or CH_3) were formed in all cases employing methylene bispiperidine in anhydrous dioxane, DMF, or mixtures of these solvents. Kinetic runs employing III as reactants (R = H or CH_3) along with methylene bispiperidine yielded no measurable reaction even after ten days at 78.6°, whereas pseudo first order rate constants for the formation of III in the above solvents are in the range 0.23 to 2.4 hrs.$^{-1}$ for R = H, and 0.87 to 4.8 hrs.$^{-1}$ for R = CH_3.

The ΔH* values in TABLE I show a general decrease in enthalpy of activation with increasing substitution in the nitroalkane. Simultaneously there is a general increase in -ΔS* as expected. More striking results are the rather large magnitude of the ΔS* values, and the drop with increased dielectric constant, except in the case of nitromethane. This suggests not only crowding, but also a building up of charge in the transition state. If, under the conditions of the experiments, an immonium ion (7) were the reactive species produced from either I or II, then a dispersal of charge would occur in the transition state resulting in a relatively small entropy of activation. Such an immonium ion is therefore rendered unlikely in the media examined except, perhaps, for nitromethane in DMF solution.

Attempts to prepare the dialkylation product, IV, of nitromethane by the method of Blomquist and Shelley (5) were unsuccessful when methylene bispiperidine was substituted for piperidine and formaldehyde. Instead, a 51 percent yield of III (R = H) was obtained (b_5 86°, n_D^{22}1.4909, anal: Calcd. for $C_7H_{14}NO$: C 53.1; H 8.92; N, 17.7. Found: C, 53.7; H, 9.11; N, 17.1). Attempts to make IV (R = H) employing methylene bispiperidine in the presence of a trace of water (0.055 mole per mole methylene bispiperidine) were successful, however, indicating either that the second alkylation step, at least, proceeds through the N-hydroxymethylamine, I or that specific solvation by water converts the methylene bisamine or III into a more reactive species.

That specific solvation is not necessarily a controlling factor in the second alkylation step is evidenced by the reaction of N-ethoxymethylpiperidine (8) with nitromethane. Thus, under strictly anhydrous conditions, with dioxane as solvent, this reaction yields IV as the main product (79% yield). This same result was obtained even when the ratio aminoether/nitromethane was as low as 1/4, and shows that disubstitution can occur in the absence of water.

Evidence that the N-hydroxymethylamine might be the intermediate in the first alkylation step has also been obtained: Thus when kinetic runs were carried out using methylene bispiperidine and 2-nitropropane in the presence of small amounts of water (up to 0.25 mole water per mole methylene bispiperidine), initial rates were greater than those obtained under anhydrous conditions (9). Moreover, the reaction approached zeroth order. These data are best explained through the proposition that N-hydroxymethylpiperidine reacts at a much faster rate than methylene bispiperidine with which it is in equilibrium, and, since the water is recycled, its concentration remains essentially constant throughout the reaction, hence the concentration of N-hydroxymethylamine remains nearly constant during the early stages of the reaction.

It should be recognized that in the kinetic runs employing small amounts of water, specific solvation by water cannot be entirely ruled out as an explanation of the enhanced rates observed. It is further noted that several mechanisms probably operate, and that their relative importance varies with conditions. This problem is currently under investigation in our laboratory.

It was reported recently (10) that the intermediate in the Mannich reaction of 2, 4-dimethylphenol with morpholine and formaldehyde is methylene bismorpholine. We have found, however, (11) that equilibrium in the amine-formaldehyde reaction is established very rapidly. This makes it difficult to accept the above authors' interpretation of their kinetic data.

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