acetate was added over a period of 5 min. The reaction mixture, which turned black immediately upon adding sodium trichloroacetate, was heated under reflux for 30 min. The solvent was removed by evaporation under reduced pressure to leave a brown solid residue. The solid was extracted several times with ether. The ether extract was washed with dilute aqueous sodium bicarbonate, then with water, and was dried over anhydrous magnesium sulfate. After decolorizing with charcoal, the ether was evaporated, and a white solid was isolated. This solid was recrystallized from benzene to 8.3 g. (7.6% yield) of white crystals of **3**, micro m.p. 137–138°, lit.[8] m.p. 131–132°.

Anal. Calcd. for $C_5H_3Cl_3O_3$: C, 27.62; H, 1.39; Cl, 48.92. Found: C, 27.53; H, 1.16; Cl, 48.72.

Basic hydrolysis of the product, followed by acidification, yielded maleic acid and chloroform.

Reaction of Sodium Trichloroacetate with Succinic Anhydride.—To a solution of 30.0 g. (0.30 mole) of succinic anhydride in 150 ml. of 1,2-dimethoxyethane, heated under reflux, was added 60.1 g. (0.32 mole) of solid sodium trichloroacetate. The addition was carried out under a nitrogen atmosphere over a 45-min. period, the solid being added through a large rubber tube connecting the reaction flask to the addition flask. As carbon dioxide was evolved, the reaction mixture changed gradually from a pink to a brown-black color. After 1.5 hr., the rate of evolution of carbon dioxide had slowed considerably. The reaction mixture was then poured into 200 ml. of water. The aqueous solution was extracted with ether, and the dried ether solution was evaporated to yield a solid, which on crystallization from ligroin provided 3.5 g. of white crystals, micro m.p. 79.0–79.9°. The aqueous solution was acidified with dilute hydrochloric acid and again extracted with ether. Evaporation of the ether left a solid, which on crystallization from ligroin provided 11.5 g. of white crystals of **4**, micro m.p. 78.0–79.5°. The infrared spectra of the two batches of material were identical in every respect. The combined yield was 15.0 g. (23%).

Anal. Calcd. for $C_5H_5Cl_3O_3$: C, 27.36; H, 2.30; Cl, 48.47. Found: C, 27.34; H, 2.40; Cl, 48.38.

Reaction of Sodium Trichloroacetate with *cis*-4-Cyclohexene-1,2-dicarboxylic Anhydride.—To a solution of 15.2 g. (0.12 mole) of the anhydride in 75 ml. of 1,2-dimethoxyethane, heated under reflux with stirring in a nitrogen atmosphere, was added 22.3 g. (0.12 mole) of solid sodium trichloroacetate in small portions over a period of 0.5 hr. Carbon dioxide was evolved and a fine white precipitate separated. The reaction was allowed to continue until the evolution of CO_2 ceased, about 0.5 hr. after the addition of sodium trichloroacetate was complete. The reaction mixture was added to 200 ml. of water and extracted with ethyl ether. The ether solution was washed with water, dried, and evaporated to yield an oily brown residue which slowly crystallized. The product was recrystallized from benzene–petroleum ether to yield 8.4 g. (31.2%)of tan crystals of **5**, micro m.p. 121.5–122°, lit.[10] m.p. 126–126.5°.

Anal. Calcd. for $C_9H_7Cl_3O_3$: C, 40.11; H, 2.60; Cl, 39.47. Found: C, 40.29; H, 2.83; Cl, 39.19.

Basic hydrolysis of the product, followed by acidification, yielded *cis*-4-cyclohexene-1,2-dicarboxylic acid.

Acknowledgment.—Support by the West Virginia University Senate Research Committee is gratefully acknowledged. The authors would like to thank Miss Audry Owen, who was supported by the National Science Foundation in an undergraduate participation program, for determining the pK_a values and Mr. Ray Wilkins for the ultraviolet measurements.

Kinetics of the Reaction of Nitroalkanes with Methylenebispiperidine. A Study of the Mannich Reaction[1a]

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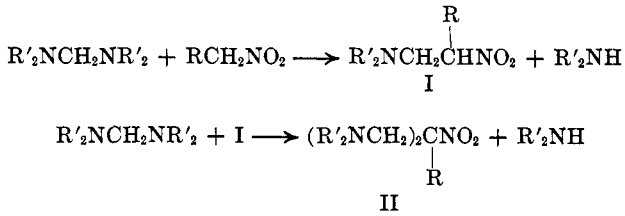
Pseudo-first-order kinetics are reported for the Mannich reaction of methylenebispiperidine with nitromethane, nitroethane, and 2-nitropropane in the solvents dioxane and dimethylformamide. Evidence presented supports the *aci* tautomer as the reactive form of the nitroalkane. A cyclic transition state is suggested for all three nitroalkanes in media of low dielectric constant, and for nitroethane and 2-nitropropane in media of moderately high (~25) dielectric constant. Under the latter conditions nitromethane probably reacts through a linear polar transition state. A rather large entropy of activation is found for the reaction of 2-nitropropane. While nitromethane and nitroethane fail to undergo a second alkylation with methylenebispiperidine in anhydrous media, the second alkylation occurs when water is present or when ethoxymethylpiperidine is used as reactant. These observations, along with rate studies employing 2-nitropropane and methylenebispiperidine in the presence of small amounts of water, point strongly to the N-hydroxymethylpiperidine as the intermediate in these Mannich reactions.

In a previous publication[2] we reported kinetics of he reaction of 2-nitropropane with methylenebisiperidine and methylenebismorpholine in media of arying dielectric constant. We now wish to report n extension of that work to other nitroalkanes, *viz.*, itromethane and nitroethane, as part of the over-all roblem of the effects of structure on reactivity and nechanism in the Mannich reaction.

The present kinetic study involves pseudo-first-rder reactions of piperidine with nitromethane, nitrothane, and 2-nitropropane, the effect of medium dielectric constant in the range 5–28, and the effect of small amounts of water on reaction rate.

Mannich bases, I (R = CH_3), of nitroethane have been reported along with the disubstitution products[3]



$$R'_2NCH_2NR'_2 + RCH_2NO_2 \longrightarrow R'_2NCH_2\overset{R}{C}HNO_2 + R'_2NH$$

I

$$R'_2NCH_2NR'_2 + I \longrightarrow (R'_2NCH_2)_2\underset{R}{C}NO_2 + R'_2NH$$

II

II (R = CH_3). Mannich bases, I (R = H), of nitromethane had not been reported, however, since all

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[1] (a) Presented at the 148th National Meeting of the American Chemial Society, Chicago, Ill., Sept. 1964. A preliminary communication of part f this work appeared in *Tetrahedron Letters*, 2889 (1964). (b) To whom ommunications concerning this paper should be addressed. (c) Student articipant sponsored by National Science Foundation Undergraduate cience Education Grant No. GE-1210.

[2] J. E. Fernandez and J. S. Fowler, *J. Org. Chem.*, **29**, 402 (1964). Inludes several references to work on the mechanism of the Mannich reaction.

[3] (a) A. T. Blomquist and T. H. Shelley, Jr., *J. Am. Chem. Soc.*, **70**, 147 (1948); (b) W. D. Emmons, *et al.*, *ibid.*, **75**, 1993 (1953).

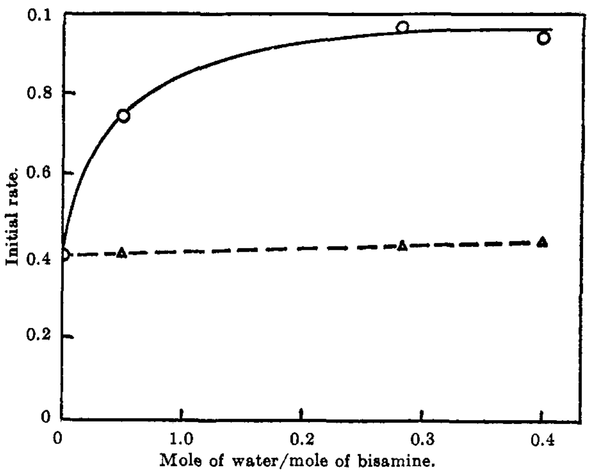
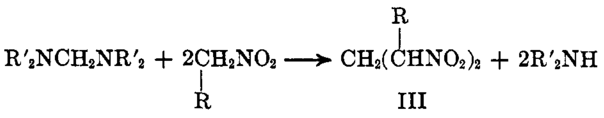


Figure 1.—Effect of water on initial rate in the reaction of 2-nitropropane with methylenebispiperidine.

attempts to prepare them had led exclusively to the disubstitution products, II (R = H).[3–5]

Rates were followed as previously described[2] using near-infrared spectroscopy by following the N–H absorption at 1.53 μ as a function of time. To avoid formation of the bis(aminomethyl)nitroalkanes (II), tenfold excesses of the nitroalkanes were employed. Another possible side reaction is formation of the methylenebisnitroalkane[6] (III); however, no evidence



$$R'_2NCH_2NR'_2 + 2\underset{R}{CH}NO_2 \longrightarrow CH_2(\overset{R}{C}HNO_2)_2 + 2R'_2NH$$

III

of these compounds was found in the reaction mixtures. Because of the reported[3–5] difficulties in obtaining the monoalkylated Mannich bases, I (R = H), of nitromethane, attempts were made to measure the rates of the second alkylation step. Further, in pursuit of an answer to the long-standing question of the relative reactivities of methylenebisamines and N-hydroxymethylamines, we studied reaction rates of the reaction of 2-nitropropane with methylenebispiperidine in the presence of water.

Experimental

Materials.—Chemicals used, their source, and methods of purification are stated. Distillations were carried out through a Vigreux column with the exception of the *p*-dioxane which was refluxed over sodium for 3 days, then distilled through a 25-plate sieve-tray column. 2-Nitropropane was redistilled, b.p. 119–120°; nitroethane, redistilled, b.p. 114–115°; nitromethane, redistilled, b.p. 101–102°; methylenebispiperidine was prepared from the corresponding secondary amine and formaldehyde, b.p. 88° (4.6 mm.). The near-infrared spectrum of this compound showed no secondary amino N–H absorbance at 1.53 μ.[7] Dioxane was redistilled, b.p. 101°; N,N-dimethylformamide, Eastman Spectro Grade, was used as received.

Apparatus.—Runs were made in constant-temperature oil baths maintained at 78.60 ± 0.03, 65.20 ± 0.03, and 73.20 ± 0.03°.

Procedure.—Kinetic runs under anhydrous conditions were carried out and analyzed as described previously.[2] The effect of dielectric constant on reaction rate was determined by running reactions in solvents of varying DMF–dioxane composition. To eliminate the possibility of dialkylation of nitromethane and nitroethane, all runs were carried out in tenfold excesses of nitroalkane to not more than 30% completion. Pseudo-first-order rate constants were determined by plotting the first-order function log (C_0/C) against time, where C_0 is the initial concentration of reactant methylenebisamine and C is the concentration at time t (Table I). Reactions employing N-(2-nitroethyl)piperidine and N-(2-nitro-1-propyl)piperidine as active hydrogen compounds with methylenebispiperidine were too slow to measure at 78.6° using either dioxane or DMF as solvents under the above conditions.

TABLE I

KINETICS OF THE REACTION OF NITROALKANES WITH METHYLENEBISPIPERIDINE[a]

Temp., °C.	k, hr.$^{-1}$	Solvent[b]	Dielectric constant[c]
		Nitromethane	
65.2	0.062, 0.046	Dioxane	
73.2	0.12, 0.13	Dioxane	
78.6	0.25, 0.21	Dioxane	9
65.2	0.24, 0.16, 0.22	67% DMF	
73.2	0.33, 0.33	67% DMF	
78.6	0.57, 0.63	67% DMF	22
78.6	0.26, 0.33	33% DMF	16
78.6	2.3, 2.5	100% DMF	28
78.6	0.93, 0.93	85% DMF	25
78.6	0.12, 0.15	50% TEA–dioxane	10
78.6	0.21, 0.18	50% TEA–DMF	17
		Nitroethane	
65.2	0.35, 0.27	Dioxane	
73.2	0.55, 0.56	Dioxane	
78.6	0.88, 0.86	Dioxane	7
65.2	0.90, 0.95	67% DMF	
73.2	2.0, 1.6	67% DMF	
78.6	3.1, 3.1	67% DMF	20
78.6	1.8, 1.5[d]	Dioxane	10
78.6	4.7, 5.0	100% DMF	26
78.6	2.0, 1.8	33% DMF	14
		2-Nitropropane	
65.2	0.27, 0.28	Dioxane	
73.2	0.38, 0.36	Dioxane	
78.6	0.45, 0.41	Dioxane	6
65.2	0.72, 0.97	67% DMF	
73.2	1.5, 1.5	67% DMF	
78.6	2.6, 2.2	67% DMF	17
78.6	1.5, 1.4	33% DMF	11
78.6	3.7, 4.0	100% DMF	26

[a] In all cases [nitroalkane] = 2.5 *M* and [methylenebispiperidine] = 0.25 *M*. [b] Concentrations are in mole per cent; DMF = N,N-dimethylformamide, TEA = triethylamine. [c] Dielectric constants used are obtained as follows: for DMF, obtained by linear extrapolation of the data of G. R. Leader and J. F. Gormley [*J. Am. Chem. Soc.*, **73**, 5731 (1951)]; for 2-nitropropane, obtained from "Lange's Handbook of Chemistry" (9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, p. 1224); for nitromethane, obtained by extrapolation of a plot of ϵ *vs.* tC (International Critical Tables, Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 82); for nitroethane and *p*-dioxane, obtained from "Handbook of Physics and Chemistry" (Chemical Rubber Publishing Co., 41st Ed., 1960, p. 2516). Dielectric constants for mixtures including solutes were calculated from the equation $\epsilon_{\text{solution}} = \Sigma_i\epsilon_i(\text{mole fraction})_i$. [d] In this run, $[EtNO_2]$ = 5.0 M.

Kinetic Runs Employing Water.—The effect of small quantities of water on the reaction of 2-nitropropane with methylenebispiperidine was studied by measuring reaction rates at 78.6° in dioxane solution using a 2-nitropropane concentration of 2.5 *M* and a methylenebispiperidine concentration of 0.25 *M* as described above. In these runs, however, small amounts of water were added. The effect of water on the Beer's law plot of piperidine in dioxane was determined, and the appropriate Beer's law plot was used for each run. Plots of log (C_0/C) *vs.* time were

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(4) L. Henry, *Ber.*, **38**, 2027 (1905); *Bull. acad. roy. Belg.*, [3] **26**, 200 (1897).

(5) M. Senkus, *J. Am. Chem. Soc.*, **68**, 10 (1946).

(6) G. B. Bachman and M. T. Atwood, *ibid.*, **78**, 484 (1956).

(7) W. Kaye, *Spectrochim. Acta*, **6**, 257 (1954).

not linear in these cases, and the departures from linearity were greater at the higher water concentrations. Plots of concentration *vs.* time were also different from the runs without water in that they were nearly linear. Moreover, uncertainty in the equilibrium constants for the methylenebisamine–N-hydroxymethylamine equilibria made kinetic analysis of these data impossible. A good estimate of the effect of water on the rate is shown by the initial rates obtained graphically from the concentration–time plots. These data are exhibited in Figure 1 (each point represents two to four determinations). Also plotted in Figure 1 are the rates (Figure 2), assuming that the only effect of the added water is due to increases in the dielectric constant.[8]

Preparation of N-(2-Nitroethyl)piperidine.—To 182.1 g. (3 moles) of nitromethane was added 54.6 g. (0.3 mole) of methylenebispiperidine in 70 ml. of *p*-dioxane. The solution was rapidly brought to 78.6° and maintained at this temperature for 45 hr., at which time the dioxane was removed on the aspirator and the tarry residue was distilled. The pale yellow fraction boiling at 86° (5 mm.) represented a 51% yield of N-(2-nitroethyl)piperidine, $n^{22}\text{D}$ 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.

Isolation of N-(2-Nitro-1-propyl)piperidine.—Distillation of a typical kinetic run mixture employing nitroethane yielded the monoalkylated compound as the main isolable product leaving behind considerable tarry residue. The product had b.p. 94–112° at 4 mm., $n^{25}\text{D}$ 1.4753. The literature gives b.p. 87° (1 mm.) and $n^{20}\text{D}$ 1.4469,[3a] and b.p. 67–68° (1–1.5 mm.) and $n^{20}\text{D}$ 1.4650.[3b]

Reaction of Nitromethane with Methylenebispiperidine.—To determine the effect of small amounts of water on the products of this reaction, experiments were performed employing conditions similar to those described by Blomquist and Shelley.[3a] Thus 10 g. (0.055 mole) of methylenebispiperidine, 1.64 g. (0.026 mole) of nitromethane, and 0.5 g. (0.028 mole) of water were stirred at room temperature for 4 hr. After standing overnight, 3.5 g. (51%) of 2-nitro-1,3-di(N-piperidyl)propane had formed, m.p. 91–92° after recrystallization from ethanol, lit.[3a] m.p. 93.5–94.0°.

A repetition of the above experiment using 0.05 g. of water instead of 0.5 g. resulted in an oil layer after standing overnight, which disappeared after standing at room temperature for 3 days. After 2 weeks, crystals began to form. Evaporation of this mixture under vacuum yielded 1.0 g. (15%) of the same disubstitution product, m.p. 91°.

A reaction employing 20 g. (0.23 mole) of piperidine, 19 g. (0.23 mole) of 37% formalin, and 14 g. (0.23 mole) of nitromethane under the same conditions gave a nearly quantitative yield of crystals, m.p. 90–91°, which is in agreement with Blomquist and Shelley.[3a]

Reaction of Nitromethane with N-Ethoxymethylpiperidine.—A reaction was run employing 4.27 g. (0.07 mole) of nitromethane and 10.0 g. (0.07 mole) of N-ethoxymethylpiperidine[9] under anhydrous conditions. A crude yield of 7.0 g. (79%) was obtained, m.p. 87–89°. A mixture with an authentic sample of 2-nitro-1,3-di(N-piperidyl)methane melted at 87–89°. The infrared spectrum of this product was identical with that of an authentic sample.

A similar run also under anhydrous conditions employing an excess of nitromethane (0.0419 mole of nitromethane and 0.0209 mole of N-ethoxymethylpiperidine) gave a quantitative yield of the 2-nitro-1,3-di(N-piperidyl)propane.

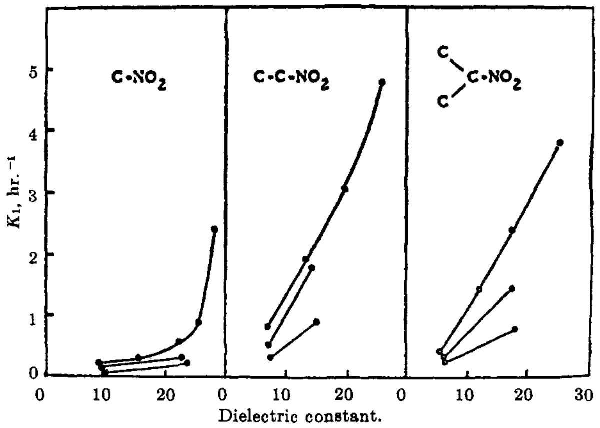

Figure 2.—Effect of dielectric constant on rate constant for the reaction of nitroalkanes with methylenebispiperidine. The curves represent isotherms: upper = 78.6°, middle = 73.3°, lower = 65.2°.

Interpretation

Generalizations from these data follow. (1) Reactivity toward methylenebispiperidine decreases in the order nitroethane > 2-nitropropane > nitromethane. (2) In all cases the reaction rate increases with dielectric constant. (3) The entropy of activation ($-\Delta S^*$) increases in the order nitromethane < nitroethane < 2-nitropropane in dioxane solution, and in the order nitroethane < 2-nitropropane < nitromethane in dimethylformamide solution. (4) Small amounts of water produce increases in the reaction rate which cannot be explained on the basis of dielectric-constant changes. (5) Reaction of nitromethane with methylenebispiperidine results in monoalkylation of the nitromethane in anhydrous media and dialkylation when small amounts of water are present. (6) Reaction of nitromethane with N-ethoxymethylpiperidine yields the dialkylated compound as the major product.

The ΔH^* values in Table II show that in dioxane solution the energy requirement in forming the transition state decreases with substitution in the nitroalkane. This is consistent with the cyclic hydrogen-bonded transition state proposed previously[2] since the *aci*-nitro equilibrium constants increase in this order.[10] In the more polar solvent system, however, this regularity is not observed. Whereas an increase in solvent polarity reduces ΔH^* for nitromethane, the other two compounds show an increase in ΔH^*. These variations were not predictable. The ΔS^* variations with structure, however, are more indicative of mechanistic changes accompanying solvent changes. An increase in dielectric constant should result in a decrease in the magnitude of ΔS^* if the same mechanism is operative. The increase in magnitude of ΔS^* for nitromethane on increasing solvent dielectric constant

Table II

Activation Parameters[a]

Nitroalkane	Solvent	ΔH^*	ΔS^*
Nitromethane	Dioxane	23	−14
	67% DMF–dioxane	17	−29
Nitroethane	Dioxane	16	−31
	67% DMF–dioxane	19	−21
2-Nitropropane	Dioxane	9	−54
	67% DMF–dioxane	17	−28

[a] $\Delta H^* = E^* - RT$, the values of E^* were determined from plots of log k *vs.* $1/T$ (Figure 3). The values of ΔS^* were determined from $\Delta S^*/2.303R = \log k_2 - \log ek_B/h - \log T + E^*/2.303RT$ where $k_2 = k$ (pseudo first order)/[nitroalkane] = second-order rate constant expressed in liters per mole second (Joseph F. Bunnett in "Investigation of Rates and Mechanisms of Reactions," part I, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 201). The values of ΔH^* are in kilocalories per mole, and values for ΔS^* are in calories per mole degree. Average deviations are ±2 kcal./mole for ΔH^* and ±4 kcal./mole for ΔS^*.

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[8] See footnote c of Table I for the estimation of dielectric constants.

[9] C. M. McLeod and G. M. Robinson, *J. Chem. Soc.*, 1470 (1921).

[10] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 560.

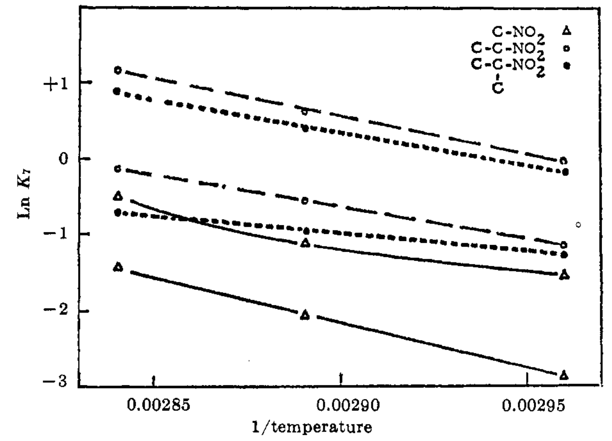
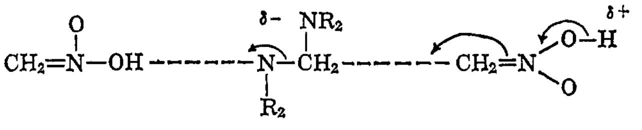


Figure 3.—Arrhenius plots of the reaction of nitroalkanes with methylenebispiperidine. The upper curve in each case represents the reaction in 67% DMF–33% dioxane solvent and the lower curve represents that in 100% dioxane solvent.

is suggestive of a change in mechanism to one involving charge separation in the transition state. This suggestion is strengthened by the plots of k_1 *vs.* dielectric constant (Figure 2). Nitroethane and 2-nitropropane exhibit the same general smooth increase in rate with dielectric constant, whereas nitromethane exhibits a sudden change in slope near ϵ 20. The curvature in the Arrhenius plot for nitromethane in DMF solution (Figure 3) also suggests a change in mechanism.

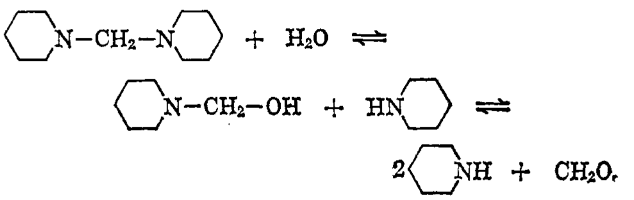
Two ionic mechanisms are possible. One involves reaction of the anion of nitromethane with the protonated methylenebisamine resulting in destruction of charge in the transition state. The other involves the combination of neutral molecules with a build-up charge in the transition state (IV). The latter mechanism is made more attractive than the former by the rather large negative ΔS^*. Moreover, this latter mechanism is in accord with the previously observed[2] reduction in second-order rate constant when 2-nitropropane was treated with excess methylenebispiperidine. That the anion of nitromethane does not react with methylenebispiperidine is suggested by the reduction in rate constant for reactions run in triethylamine–dioxane mixtures.



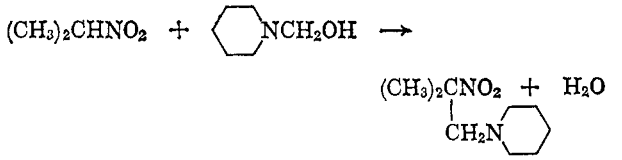
IV

The fact that several workers[3-5] have found only disubstitution products in the Mannich reactions of nitromethane and only small amounts of monosubstitution products with nitroethane seems to suggest that the second substitution occurs at a faster rate than the first. To test this theory we isolated the monosubstitution products, I (R = H,CH_3), which we found to be the main products in our kinetics runs. Rate constants for the reactions of these Mannich bases with methylenebispiperidine were too small to measure.

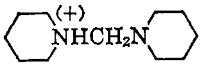
An interesting result was obtained in the experiments employing small quantities of water (see Experimental). While the monoalkylation product, I, of nitromethane had not been isolated previously, we obtained it as the major product in all runs employing methylenebispiperidine in the absence of water. When small quantities of water (0.05 mole/mole of methylenebisamine) were employed, however, the major product was the dialkylation product II. This observation suggests that at least the second alkylation step may proceed through the N-hydroxymethylpiperidine VI, which exists in equilibrium with methylenebispiperidine (V).



Evidence that the N-hydroxymethylpiperidine may be the intermediate in the first alkylation step has also been obtained. Thus, when kinetic runs were carried out using methylenebispiperidine and 2-nitropropane in the presence of small amounts of water (up to 0.25 mole of water/mole of methylenebispiperidine), initial rates were greater than those obtained under anhydrous conditions, as is shown in Figure 1 which also includes the rates (see Figure 2) assuming that the only effect of the water is to increase the dielectric constant of the medium. Moreover, the reaction exhibited complex kinetics, and the plot of concentration of product *vs.* time was nearly linear during the early part of the reaction. These data are best explained through the proposition that the N-hydroxymethylamine reacts at a much faster rate than the methylenebisamine 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-hydroxymethylpiperidine remains nearly constant during the early stages of the reaction.

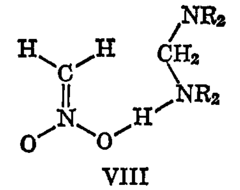


The reaction of methylenebispiperidine with water to form the ammonium ion which can then react by an ionic mechanism through elimination of the neutral piperidine molecule must be ruled out because the nitroalkane which is in large excess exceeds water in its acidity.[9] Any reaction proceeding through this mechanism should not be significantly affected by the presence of the small amounts of water employed.



It is recognized that, in the runs employing water, specific solvation effects cannot be ruled out entirely as an explanation of the enhanced rates. It is further noted that several mechanisms may operate and that their relative importance varies with conditions.

The unusually large negative entropies of activation are probably due in part to the unfavorable stereochemistry of the transition state; *i.e.*, for reaction to occur, the methylene carbon atom of the methylenebisamine must be situated at a point perpendicular to the plane of the $H_2C{=}N{<}$ group. The usually relaxed six-membered ring does not readily allow this configuration. The necessary configuration is rendered even less likely by the nearly linear O—H- - -N hydrogen bond. Therefore, the transition state probably requires a large strain from the normal hydrogen-bonded adduct VIII.



VIII

Ion-pair character in the hydrogen-bonded cyclic transition state may also contribute to the large entropies of activation. The importance of this effect, however, is difficult to assess.

The *meso* Reactivity of Porphyrins and Related Compounds. I. Nitration

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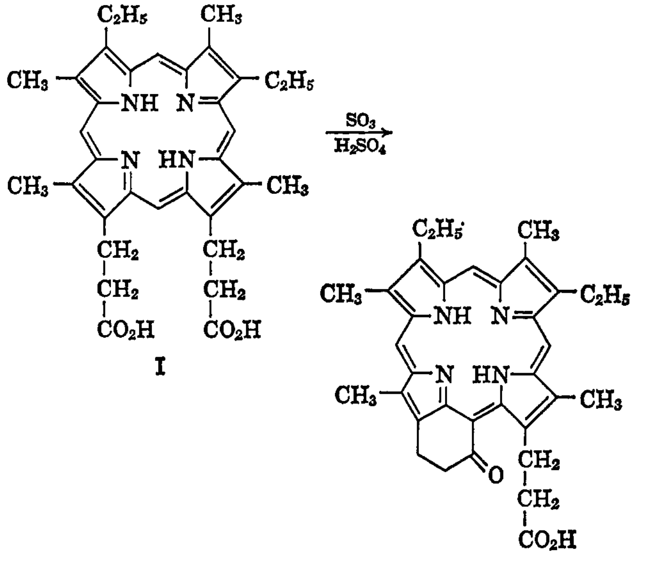
The nitration of octaalkylporphyrins under a variety of conditions has been studied. Octaethylporphyrin gave a mononitro derivative under mild conditions, and this is shown to be the *meso*-substituted compound. Longer reaction times led to the α,β- and α,γ-dinitrooctaethylporphyrins and to a tri-*meso*-substituted derivative. Mononitro compounds have also been obtained from octamethylporphyrin and mesoporphyrin. Nitration of octaethylchlorin with nitronium tetrafluoroborate gave the γ-nitro and γ,δ-dinitro derivatives: dehydrogenation of the former yielded the same nitrooctaethylporphyrin as had been obtained by direct substitution of the porphyrin.

The direct *meso* substitution of porphyrins has been a particularly obscure problem, although several examples of such reactions, *e.g.*, mesorhodin formation,[1] halogenation,[2] and nitration, have been advanced. The obscurity has lain essentially in proving the presence of a *meso* substituent in the product. Because we consider it likely that *meso* reactivity is important in the biological degradation, and possibly also in the biological action, of the natural porphyrins, chlorins, and corrins, an investigation of such reactivity is being carried out using n.m.r. spectroscopy to detect *meso* substitution. Nitration was chosen for the initial work firstly because there is much information available about this reaction in simpler systems,[3] and secondly because in the porphyrin case there appeared to be considerable doubt as to whether *meso* substitution was indeed involved.

Fischer and his colleagues carried out occasional investigations on the nitration of porphyrins over a period of about 16 years. Coproporphyrin,[4] isouroporphyrin II,[5] etioporphyrins I and II,[6] phylloporphyrin,[7] pyrroporphyrin,[8] deuteroporphyrin,[8] mesoporphyrin,[8] and rhodoporphyrin[8] were nitrated, generally with concentrated or fuming nitric acid as the reagent. The reactions were disconcertingly complex; for example, (i) mono-, di-, and trinitro compounds were obtained from etioporphyrin I under conditions[6] which differed in slight, but evidently highly important, detail; (ii) good analyses, especially of carbon, were often not observed, owing in part, apparently, to contamination by halogen[6,8]; (iii) oxidative cleavage was observed[4]; (iv) even if the reactions observed were solely monosubstitutions at a *meso* position, all the above examples, the type I porphyrins excepted, would be expected to give mixtures of positional isomers.



I

II

Although certain reservations were apparent,[9] Fischer seems to have favored the *meso* formulation[6,8] for the nitro compounds, even for certain compounds containing a free β-position.[8] The important arguments for *meso* substitution were as follows. (i) Analogous halogenated derivatives were known. Thus etioporphyrin

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(1) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. II-1, Akademische Verlagsgesellschaft, Leipzig, 1937, p. 544.

(2) See ref. 1, p. 235.

(3) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Butterworth and Co. (Publishers) Ltd., London, 1959.

(4) H. Fischer and J. Hilger, *Z. physiol. Chem.*, **149**, 65 (1925); H. Fischer and W. Fröwis, *ibid.*, **195**, 49 (1931).

(5) H. Fischer and E. Thurnher, *ibid.*, **204**, 68 (1932).

(6) H. Fischer and A. Treibs, *Ann.*, **466**, 188 (1928); H. Fischer and W. Neumann, *ibid.*, **494**, 225 (1932).

(7) H. Fischer, M. Speitmann, and H. Meth, *ibid.*, **508**, 154 (1934).

(8) H. Fischer and W. Klendauer, *ibid.*, **547**, 123 (1941).

(9) See ref. 1, p. 263.