[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Kinetic Evidence for a Schiff Base Intermediate in the Knoevenagel Condensation[1]

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The reaction of piperonal with nitromethane, when catalyzed by *n*-butylammonium acetate, shows kinetics consistent with a mechanism in which piperonylidenebutylamine is formed and subsequently condenses with nitromethane to yield the final product, 3,4-methylenedioxy-β-nitrostyrene. The rates of these two steps have been measured and when combined yield the over-all rate. The effectiveness of primary amines, and probably ammonia, as catalysts for this reaction in the presence of an acid is therefore due to their ability to convert the aldehyde to the more reactive Schiff base.

The recent proposal of an aldimine intermediate in the ammonium acetate catalyzed nitrostyrene condensation was based on the kinetics of the over-all reaction of vanillin with nitromethane.[2] A more detailed analysis of a similar reaction is now presented. The rate of formation of 3,4-methylenedioxy-β-nitrostyrene (PNM) from piperonal, catalyzed by *n*-butylamine, has been measured and compared with the rates of the proposed steps (1) and (2) of this condensation.

$$\mathrm{RCHO + BuNH_2 \longrightarrow RCH{=}NBu + H_2O} \qquad (1)$$

$$\mathrm{RCH{=}NBu + CH_3NO_2 \longrightarrow RCH{=}CHNO_2 + BuNH_2} \qquad (2)$$

All the reactions were run in methanol at 25°.

The reaction of butylamine with piperonal to form the Schiff base[3] is second order and goes at least 99% to completion at 0.02 *M* concentrations. The rate constant, 1.97 l./mole-min., remains constant in very basic solution (0.023 *M* NaOMe), showing that the reaction does not require acid catalysis, although it may become important at higher acidities. *n*-Butylamine, unlike the much weaker base, semicarbazide,[4] is therefore capable of attacking the unprotonated carbonyl group. Since the most successful observations of nitrostyrene formation were made in more acidic media, as described below, it was necessary to obtain a value for the rate of Schiff base formation in the presence of one equivalent of acetic acid. It was sufficient for this study to use an excess of butylammonium acetate and to consider the reaction first order in piperonal. Typical results are shown in Fig. 1 and Table I.

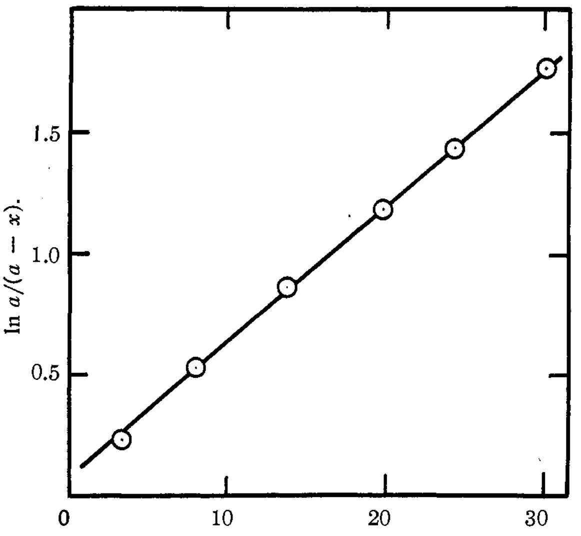

Fig. 1.—Schiff base formation: 0.02041 *M* piperonal; 0.1768 *M* BuNH$_3$OAc.

TABLE I

RATE OF SCHIFF BASE FORMATION

Piperonal, concn., moles/l.	BuNH$_3$OAc concn., mole/l.	k_1, min.$^{-1}$
0.02041	0.1768	0.0566
.02145	.1768	.0544
.01425	.1768	.0562
.02222	.1922	.0601

The condensation of nitromethane with an aldehyde or a Schiff base is reversible[2,5] and subject to acid and base catalysis. Useful kinetics were therefore observed only when acetic acid and an excess of nitromethane were present. Figure 2, in which $w = 1/(b - a) \ln a(b - x)/b(a - x)$, shows that the reaction of Schiff base with nitromethane follows an approximately second-order course (specific rate k_2) at a given butylammonium acetate concentration; linearity was observed through only 25% of the reaction.

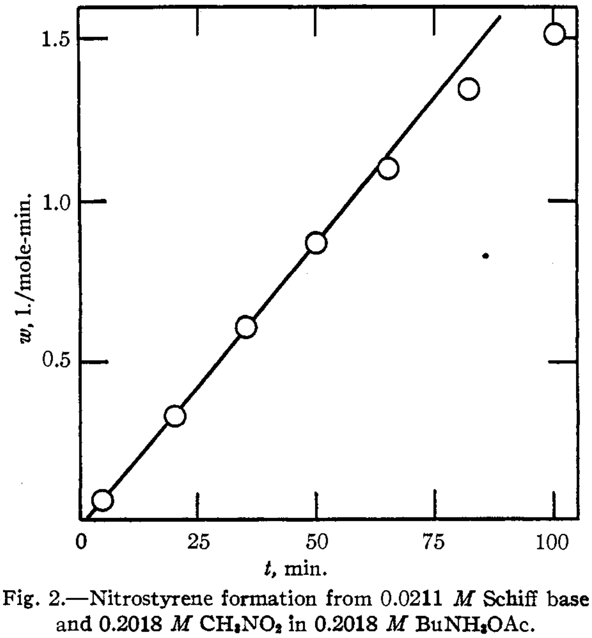

Fig. 2.—Nitrostyrene formation from 0.0211 *M* Schiff base and 0.2018 *M* CH$_3$NO$_2$ in 0.2018 *M* BuNH$_3$OAc.

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(1) From the dissertation of David W. Peck, University of Virginia, 1952.

(2) T. I. Crowell and F. A. Ramirez, THIS JOURNAL, **73**, 2268 (1951).

(3) For a similar example, see G. Vavon and P. Montheard, *Bull. soc. chim.*, **7**, 551 (1940).

(4) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932).

(5) D. E. Worrall, *ibid.*, **60**, 2841 (1938); R. Stewart, *ibid.*, **74**, 4531 (1952).

When piperonal reacts with nitromethane under the same conditions, there are several indications that (1) is the first step. Figure 3 shows the induction period in nitrostyrene production, followed by second-order kinetics. The rate constant, k_2', defined as the slope of the linear portion of the curve, is nearly equal to k_2, indicating that the Schiff base participates in, or is rapidly converted to the participants of the slow step of the aldehyde–nitromethane reaction. When the butylammonium acetate concentration is so low that (1) is partly rate determining, $k_2' < k_2$ (Table II). The induction period, arbitrarily defined as the point of intersection of the extrapolated line with the time axis (see Fig. 3) lengthens as decreasing catalyst concentration slows step (1).

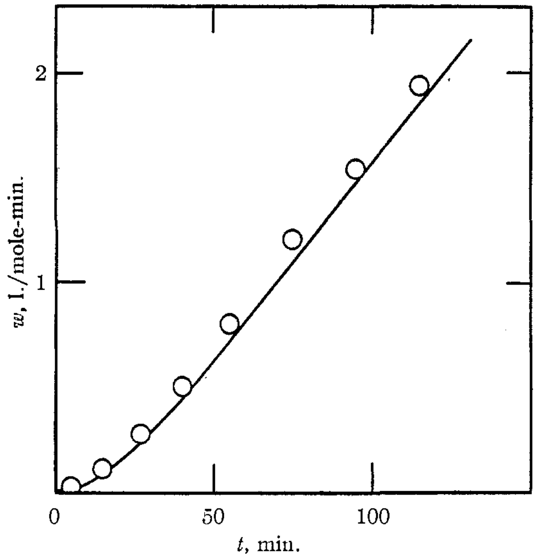


Fig. 3.—Nitrostyrene formation: experimental points and theoretical curve.

TABLE II

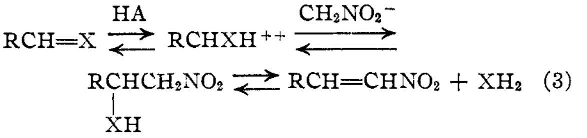
RATES OF NITROSTYRENE FORMATION

$BuNH_3OAc$ concn., *M*	k_2, l./mole-min.	k'_2, l./mole-min.	Induction period, min.
0.5	0.0206	0.0221	3
.2	.0180	.0194	14
.1	.0156	.0166	30
.05	.0134	.0136	79
.0288	.0121	.0093	143
.2016[a]	.0194	Very small	...

[a] Et_3NHOAc.

Knowing the rates of (1) and (2), it is possible to calculate the resultant rate of nitrostyrene formation. This was done, and the fair agreement of the observed points with the calculated line in Fig. 3 is strong evidence that these steps are actually part of the mechanism. Further evidence that the carbonyl compound cannot react rapidly with nitromethane is the fact that the Schiff base, but not piperonal, condenses readily with nitromethane when triethylamine acetate is the catalyst. The tertiary amine acetate evidently provides sufficient acid and base to promote reaction of the Schiff base, at the same rate as in butylammonium acetate, but of course cannot convert the aldehyde to the Schiff base.

The high reactivity of the >C=N—R group relative to the >C=O group is possibly due to the greater susceptibility of the former, more basic compound to general acid catalysis. If the reaction indicated by (2) actually takes place stepwise as shown in (3), it can be easily seen that the first step, protonation by HA ($BuNH_3^+$ or HOAc) will proceed more rapidly or completely when X = NBu than when X = O.



$$\mathrm{RCH{=}X \underset{}{\overset{HA}{\rightleftarrows}} RCHXH^{++} \overset{CH_2NO_2^-}{\rightleftarrows}}$$
$$\mathrm{\underset{\displaystyle XH}{RCH}CH_2NO_2 \rightleftarrows RCH{=}CHNO_2 + XH_2} \quad (3)$$

The reactive nitromethane species is formulated here as the anion, which would predominate over the aci form (pK_A 3.3 in H_2O[6]) in our slightly basic solution.

The above conclusions cannot be extended to amine catalysis in the absence of acetic acid. Since secondary and tertiary amines are known to catalyze the aldehyde–nitromethane reaction[7] and similar condensations,[8] the nitromethide ion can certainly react with the aldehyde or with derivatives other than the simple Schiff base. The reversibility of step (2) when free amine catalysts were used unfortunately complicated the kinetics so soon after the start of the reaction that no quantitative results were obtained.

Experimental

Materials.—Commercial nitromethane, *n*-butylamine and triethylamine were fractionated. Piperonal was recrystallized three times from ethanol–water. Reagent methanol was the solvent for kinetic runs and dilutions. The Schiff base, piperonylidene *n*-butylamine, was prepared by the general method of Campbell[9]; b.p. 160° (10 mm.), m.p. 23°, % N (titrated as butylamine) 6.74 (calcd. 6.83), gravimetric assay as piperonal-2,4-dinitrophenylhydrazone, 101.7% (this characteristically high result[10] was also obtained on a sample of pure piperonal). PNM was prepared according to Lange and Hambourger.[11]

Kinetics of Schiff Base Formation.—Standard butylamine solution was pipetted into a weighed amount of piperonal in solution in a 100-ml. volumetric flask. After diluting to the mark at 25.00 ± 0.02°, the reaction was followed by two methods: A. By titration of the butylamine remaining in a 10-ml. sample against standard methanolic HCl, using brom cresol green as indicator. A small correction was made for the effect of Schiff base on the end-point. B. By dilution of a 1-ml. sample with methanolic HCl and spectrophotometric analysis. In acid solution, the Schiff base is easily determined in the presence of piperonal by the ultraviolet absorption peak of its conjugate acid (λ 348 mμ, ϵ 1.73 × 10^4). The rate constant for the rather rapid reaction of piperonal with butylamine was 1.97 ± 0.08 l./mole-min. (method A); 1.75 ± 0.15 (method B). In the presence of butylammonium acetate, method B was used. The spectra, in acid and neutral solutions, of the reaction mixture showed it to contain the Schiff base.

Kinetics of Nitrostyrene Formation.—Standard solutions of butylamine and acetic acid were pipetted into a 25-ml.

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[6] D. Turnbull and S. H. Maron, THIS JOURNAL, **65**, 212 (1943).

[7] D. E. Worrall, *ibid.*, **56**, 1556 (1934).

[8] A. R. Day, "Electronic Mechanisms of Organic Reactions," American Book Company, New York, N. Y., 1950, p. 123.

[9] K. N. Campbell, *et al.*, THIS JOURNAL, **70**, 3868 (1948).

[10] H. A. Iddles and C. E. Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934).

[11] N. A. Lange and W. E. Hambourger, THIS JOURNAL, **53**, 3865 (1931).

volumetric flask containing weighed quantities of piperonal, or Schiff base, and nitromethane. Diluted 1-ml. samples were analyzed with the spectrophotometer. The extinction coefficient of PNM at 364 mμ, the main absorption peak, was 1.65×10^4 over the concentration range used. It was necessary to avoid acid solutions in which the very similar spectrum of the Schiff base salt would interfere. One run (0.5 *M* $BuNH_3OAc$), followed by gravimetric analysis for piperonal + Schiff base, gave $k_2 = 0.0200$ l./mole-min., which checks within 10% the value of 0.0221 obtained using the spectrophotometer. Table III shows the data obtained using approximately 0.2 *M* $BuNH_3OAc$, yielding the value of k_2' given in Table II.

TABLE III

RATE OF NITROSTYRENE FORMATION

Piperonal concn., *M*	CH_3NO_2 concn., *M*	$BuNH_3OAc$ concn., *M*	Induction period, min.	k'_2, l./mole-min.
0.02044	0.2018	0.2018	14	0.0194
.01987	.2018	.2018	13	.0194
.02273	.2411	.2025	14	.0200
.02017	.2187	.1922	14	.0197
.02611	.0205	.1768	14	.0194
.01996	.0195	.1768	12	.0190
.02089	.0200	.1768	15	.0190
.04375	.2018	.2018	(19)	.0187
		Average	14	.0193

The *curve* in Fig. 3 is based on the following experiments: (a) Schiff base formation from 0.02017 *M* piperonal in 0.1922 *M* butylammonium acetate: $k_1 = 0.0601$ min.$^{-1}$. (b) PNM formation from 0.02218 *M* Schiff base and 0.2187 *M* nitromethane in 0.1922 *M* $BuNH_3OAc$ and 0.0215 *M* acetic acid: $k_2 = 0.0191$ l./mole-min. The *points* represent 0.02017 *M* piperonal, 0.2187 *M* nitromethane and 0.1922 *M* $BuNH_3OAc$.

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Derivatives of Sulfenic Acids. VIII. Studies of Some α-Nitro Sulfides and Sulfones

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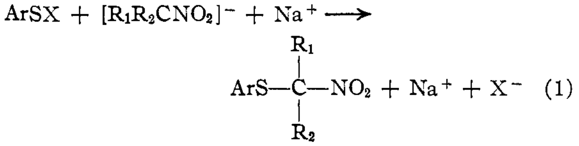
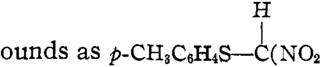
2-Chloroethyl 1-nitroethyl sulfone and 3-nitrophenyl 1-nitroethyl sulfone were obtained by oxidizing the products from the appropriate sulfenyl chlorides and the sodium salt of nitroethane. The reductions of 1-nitroethyl *p*-tolyl sulfide and of the corresponding sulfone, as well as the reaction of the latter with sodium *p*-toluenesulfinate, are also described.

In a previous paper[1] the synthesis of a series of α-nitro sulfides, by reaction of sulfenyl halides and sodium salts of nitroalkanes (equation 1, Ar = aryl; X = Cl, Br or SCN; and R_1, R_2 = alkyl or H) was reported, and evidence for the designated structures of the products was cited.



$$ArSX + [R_1R_2CNO_2]^- + Na^+ \longrightarrow ArS\!-\!\overset{R_1}{\underset{R_2}{C}}\!-\!NO_2 + Na^+ + X^- \quad (1)$$

The present paper describes further work with this novel class of sulfides and with some related α-nitro sulfones.

Besides the work of Melnikov,[2] in which certain α-nitro sulfides were mentioned as unstable intermediates, the only other reference to such substances which we have encountered is to the preparation (as intermediates, in unstated yields) of compounds as  $p\text{-}CH_3C_6H_4S\!-\!\overset{H}{C}(NO_2)\overset{O}{C}R$ (I), R = CH_3 or C_6H_5, by reaction of the corresponding β-keto sulfides with sodium ethoxide and ethyl nitrite, followed by acidification.[3]

Investigations of the related α-nitro sulfones have also been limited. By treatment of I (R = CH_3) with hydrogen peroxide, Arndt and Rose[3] obtained a low yield of nitromethyl *p*-tolyl sulfone; and this sulfone was also obtained by Shriner and Greenlee,[4] *via* sodium *p*-toluenesulfinate and bromonitromethane. By reaction of sodium benzenesulfinate and chloronitromethane, Tröger and Nolte[5] obtained a low yield of nitromethyl phenyl sulfone, but were unable to repeat their original preparation. The synthesis of *p*-bromophenyl nitromethyl sulfone is also mentioned in their paper. Recently, Backer[6] reported products as di- and tri-(methylsulfonyl)-nitromethane. 1-Nitroethyl *p*-tolyl sulfone and 2-nitrophenyl 1-nitropropyl sulfone were reported in our earlier paper.[1]

The syntheses of two new α-nitro sulfones, by oxidation of the corresponding crude sulfides, were effected in the present study. The intermediate α-nitro sulfides involved were 2-chloroethyl 1-nitroethyl sulfide and 1-nitroethyl 3-nitrophenyl sulfide. The pure α-nitro sulfides were not isolated, since the products were oils which failed to crystallize, and which decomposed on distillation at reduced pressures. Yields of the pure sulfones were: 2-chloroethyl 1-nitroethyl sulfone, II (61%) and 1-nitroethyl 3-nitrophenyl sulfone, 57%. The corresponding crude sulfides were obtained in 85 and 91% yields, respectively. 2-Chloroethyl 1-nitroethyl sulfide and the corresponding sulfone represent the first examples of their respective groups in which the sulfur moiety stems from an aliphatic sulfenyl chloride ($ClCH_2CH_2SCl$). The latter sulfone (II) neutralized two moles of alkali, suggesting that dehydrochlorination, as well as salt formation, was involved.

The ultraviolet absorption spectra of sulfone II and of nitroethane were determined and found to be

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[1] N. Kharasch and J. L. Cameron, THIS JOURNAL, **73**, 3864 (1951).

[2] N. Melnikov, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 1546 (1937); *C. A.*, **31**, 8504 (1937); *cf.* also ref. 1.

[3] F. Arndt and J. D. Rose, *J. Chem. Soc.*, **147**, 1 (1935).

[4] R. L. Shriner and S. O. Greenlee, *J. Org. Chem.*, **4**, 242 (1939).

[5] J. Tröger and E. Nolte, *J. prakt. Chem.*, **101**, 136 (1920).

[6] H. J. Backer, *Rec. trav. chim.*, **68**, 827, 844 (1949); **69**, 610 (1950).