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Reaction of 2-Nitroso-2-Methyl Propane with Formaldehyde, Glyoxylate and Glyoxylic Acid.

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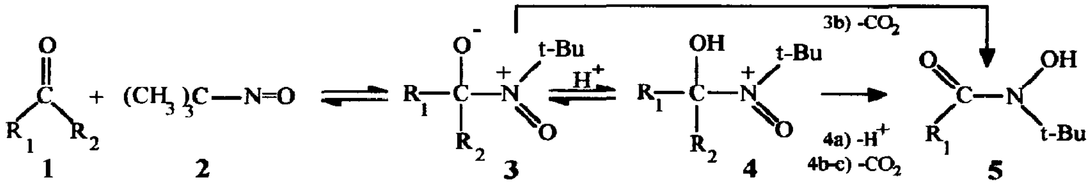
Abstract: 2-nitroso-2-methyl propane reacts with formaldehyde, glyoxylate, glyoxylic, pyruvic and phenylglyoxylic acid giving the corresponding N-t-butyl hydroxamic acids. These reactions involve formation of the dipolar addition intermediates and 2-nitroso-2-methyl propane acts as a nucleophile in the reaction step in which these intermediates are formed.

There is a large number of the addition reactions of the C-nitroso compounds where nitroso group acts as electrophile, but only few nucleophilic reactions of this group are known to date.[1] These have been reported only recently, and among other things, include reactions of nitrosobenzenes with glyoxylate[1a], pyruvic acid and acetaldehyde[1c], substrates whose exceptional biochemical significance is well known[2]. Products of the reactions are hydroxamic acids, a class of compounds of great biochemical, pharmaceutical and industrial importance[3-5]. The nucleophilic properties of C-nitroso group of nitrosoaromatics are connected with the existence of the lone electron pair on the nitrogen. One of the experimental manifestations of its presence is the largest ^{15}N chemical shift anisotropy measured to date[6]. Another evidence comes from the solution multinuclear NMR studies[7] and theoretical calculations[8]. However, chemical properties of the nitroso group are highly dependent on the rest of the molecule of the nitroso compound, and the role of the atom on which nitroso group is attached is very pronounced[9]. Finally, nucleophilic action of the nitroso group was demonstrated only for nitrosoaromatics. To knowledge, there is no corresponding evidence for an aliphatic C-nitroso group.

We now reported that 2-nitroso-2-methyl propane reacts with formaldehyde, glyoxylate, glyoxylic, pyruvic and phenylglyoxylic acid giving the corresponding N-t-butyl hydroxamic acids. The evidence obtained clearly suggests that these reactions involve formation of the dipolar intermediates (**3**) and that 2-nitroso-2-methyl propane acts as a nucleophile in the reaction step in which these intermediates are formed (Scheme 1).

Scheme 1.



1a) $R_1 = R_2 = H$, 1b) $R_1 = H$, $R_2 = COO^-$, 1c) $R_1 = H$, $R_2 = COOH$, 1d) $R_1 = CH_3$, $R_2 = COOH$,
1e) $R_1 = Ph$, $R_2 = COOH$

This evidence includes: *i*) stoichiometry and products of the reactions, *ii*) acid catalysis / pH rate profile and general acid catalysis, *iii*) solvent deuterium isotope effects, *iv*) substrate isotope effect, *v*) order of reactivity of carbonyl substrates investigated, *vi*) comparison with similar reactions of nitroso-aromatic compounds. In particular:

a) Formaldehyde.

i) At constant hydronium ion concentration the observed kinetics are second order overall and first order with respect to both carbonyl and nitroso compounds. N-t-butyl formohydroxamic acid is the only product, as shown by spectroscopic evidence and product isolation[11]. This is consistent with C-N bond formation and nucleophilic attack of the nitroso group on carbon of formaldehyde.

ii) The observed reaction rate constants depend linearly (without the intercept) on the hydronium ion concentration. Catalysis with general acids was also observed. The inverse solvent deuterium isotope effect k_{D_2O} / k_{H_2O} of 2.02 (0.01) was observed. These observations are consistent with the occurrence of the proton transfer to a dipolar addition intermediate (3a) formed in the preceding reaction step[1b-d].

iii) The observed primary kinetic deuterium isotope effect k_H / k_D of 4.52 (0.01) between HCHO and DCDO in the reaction, is consistent with the rate-controlling proton transfer from carbon[12] of the nitrosocarbinolic intermediate (4a). This intermediate resulted from the proton transfer to the dipolar intermediate (3a) of the first reaction step, and subsequently undergoes the proton transfer, leading to the product, hydroxamic acid (5a).

iv) The whole reaction (points *i-iii*) appears to be closely similar to that of formaldehyde with nitrosobenzenes, for which nucleophilic attack of nitroso group on the carbonyl carbon was proposed[1b, d]. In addition, we observed that the reaction of 2-nitroso-2-methyl propane with acetaldehyde is at least two order of magnitude slower than the reaction with formaldehyde, obviously in consistence what we would expect if nucleophilic attack of nitroso group on carbonyl carbon occurred.

b). Glyoxylate and glyoxylic acid.

i). N-t-butylformohydroxamic acid is the only reaction product under conditions employed[11], in the

Table 1.

nitrosobenzene			2-nitroso-2-methyl propane		
[HCl], mol dm^{-3}	pH	k_{H_2O}/k_{D_2O}	[HClO$_4$], mol dm^{-3}	pH	k_{H_2O}/k_{D_2O}
2.24		1.53 (0.04)	2.19		1.40 (0.09)
1.07		1.42 (0.01)	1.00		1.43 (0.10)
	1.25	2.62 (0.05)		1.25	1.66 (0.11)
	1.68	2.24 (0.10)		1.66	1.31 (0.08)
	2.69	1.54 (0.03)		2.68	1.33 (0.08)
	3.99	1.27 (0.04)		3.97	1.30 (0.07)
	6.15	1.20 (0.02)		6.43	1.17 (0.03)

Table 1. Changes of the solvent deuterium isotope effect in the reactions of 2-nitroso-2-methyl propane and nitrosobenzene with glyoxylate on changing of pH or hydronium ion concentration at 25°C. Ionic strenght: 0.20 mol dm^{-3} and 0.14 mol dm^{-3} in the reactions with nitrosobenzene and 2-nitroso-2-methyl propane, respectively. Isotope effects were obtained using at least four paired experiments. Rate constants were determined following procedures described earlier[1c].

whole range of 0-7 pH, where there is nonlinear pH rate profile and continous change in solvent deuterium isotope effect in the reaction (Fig. 1, and Table 1). At particular hydronium ion concentration, observed kinetics are second order overall and first order with respect to both carbonyl and nitroso compound.

ii). Magnitudes of the observed reaction rate constants and solvent deuterium isotope effects (Fig. 1, and Table 1) at particular proton concentration reveal the involvement of the dipolar intermediates in the reaction. This is corroborated by the observation of the catalysis by general acids. Reaction with glyoxylic acid includes acid catalysed and uncatalysed reaction path. Nitrosocarbinolic intermediate (4c) arising from the proton transfer to the dipolar intermediate (3c) probably decarboxylates via cyclic transition state where transfer of carboxylic proton would be in some sense simultaneous with heavy atom reorganization, as indicated by the observed small size solvent deuterium isotope effect in the acid catalysed reaction[14].

iii). The observations mentioned (*i-iii*) reveal close similarity between reaction of 2-nitroso-2-methyl propane and that of nitrosobenzenes with glyoxylate and glyoxylic acid. For the latter reactions, nucleophilic attack of nitroso group on the carbonyl group was proposed[1a-c] .

Fig 1.

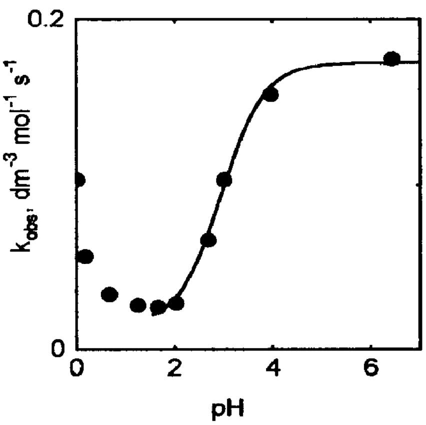


Fig 1. The dependence of the rate constants for the reaction of glyoxylate with 2-nitroso-2-methyl propane on the pH, at 25°C. Ionic strenght 0.14. Rate constants were determined spectrophotometrically, using methods described in ref. 1c. The solid curve are theoretical lines in accord to the equation :
k_{obs} = [Gl] K_a [(k_1 + k_2 H^+) / (K_a + H^+)], where Gl is total glyoxylate, K_a is the dissociation constant of hydrated glyoxylic acid, k_1 and k_2 are rate constants for the reactions via the intermediates 3b and 4b respectively. The values obtained for k_1, k_2 and pK_a are: k_1 17.3 (0.4) x 10^{-2} dm^3 mol^{-1} s^{-1}, k_2 14.0 (6.0) dm^6 mol^{-2} s^{-1} and pK_a 2.97. In the range 0.1- 2.2 mol dm^{-3} H_3O^+, the observed rate dependence follows (after the correction regarding the salt effects) the equation
k_{obs} = k [Gl] [H^+], with value of k of 1.7 x 10^{-2} dm^6 mol^{-2} s^{-1}.

c). Pyruvic and phenylglyoxylic acid.

i). The products in these reactions are N-t-butyl acetohydroxamic[15] and N-t-butyl benzohydroxamic[16] acids, respectively. The observed kinetics are, at constant proton concentration, first order with respect to the nitroso and carbonyl compound, and second order overall. The reactions involve acid catalysed and uncatalysed reaction path, as evidenced by the linear dependence of the observed reaction rate constant on the hydronium ion concentration, having an intercept analogously to the case of the reaction of pyruvic acid with nitrosobenzene[1c] . These observations, as well as the solvent deuterium isotope effects k_{H_2O} / k_{D_2O} (1.20 (0.01) at 1.1 M H^+ and 1.14 (0.01) at 0.4 M H^+ in the case of the reaction of 2-nitroso-2-methyl propane with pyruvic acid), reveal close similarity with the reaction of pyruvic[1c] and phenylglyoxylic acid with nitrosobenzene for which nucleophilic attack of nitroso nitrogen was proposed[1c]. The established order of reactivity for the investigated carbonyl compounds where relative rates are glyoxylic acid[17] > glyoxylate > pyruvic acid > phenylglyoxylic acid also suggests occurrence of the nucleophilic attack on the carbonyl carbon.

All the reactions studied are accelerated by the added neutral salts, where k_{obs} increase linearly or exponentially, depending on the both reaction and salt chosen. The reactions proceeded also in acetic acid, not unexpectably taking into regard the observation (cf. above) of general acid catalysis in the reactions. We also find that reactions in acetic acid presents an useful synthetic way to the N-t-butyl hydroxamic acids.

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11. Products of the reactions of 2-nitroso-2-methyl propane with formaldehyde and with glyoxylate are identical, as showed by its spectroscopic and physical properties: m.p. 62-64°C; uncorrected (lit.[13] 61-63°C), H^1 NMR (in acetone) δ 1.41 (s, 9H N-t-butyl; lit.[13] ($CDCl_3$) δ 1.43), δ 8.20 (s, 1H, O=CH; lit.[13] ($CDCl_3$) δ 8.11), IR (KBr) 3600-2300 (br), 1651 (s), 1371 (s), 1220 (s), 1079 (vs) cm^{-1}; lit.[13] IR (CCl_4) 3394-2633 (br), 1661 (vs), 1372 (s), 1351 (s), 1083 (m), 1034 (m) cm^{-1}. Monohydroxamato iron (III) complex: λ_{max} 502 nm (0.1 M $HClO_4$, 8x10^{-3} Fe^{+3}).
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14. See also disscusion in ref. 1c, and references cited therein.
15. ^{1}H NMR (acetone): δ 1.38 (s, 9H, N-t-Bu) and δ 2.01 (s, 3H, CH_3), lit.[13] ($CDCl_3$) δ 1.47 and δ 2.20; IR (KBr) 3190 (br), 1620 (m), 1415 (m), 1365 (s), 1110 (s) cm^{-1}, lit.[13] ($CHCl_3$) 3274 (br), 1654 (vs), 1457 (m), 1379 (s), 1365 (s), 1098 (m) cm^{-1}; Monohydroxamato iron (III) complex: λ_{max} 518 nm (0.1 M $HClO_4$, 8x10^{-3} Fe^{+3}).
16. ^{1}H NMR (acetone): δ 1.49 (s, 9H, N-t-Bu) and 7.30-7.60 (m, 5H, ArH), lit.[13] ($CDCl_3$) δ 1.31 and δ 7.25-7.60; IR (KBr) 3160 (br), 1575 (s), 1445 (s), 1365 (s), 1096 (s) cm^{-1}, lit.[13] ($CHCl_3$) 3239 (br), 1584 (s), 1464 (m), 1365 (vs), 1076 (w) cm^{-1}; Monohydroxamato iron (III) complex: λ_{max} 504 nm (0.1 M $HClO_4$, 8x10^{-3} Fe^{+3}).
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