Salt effects and kinetic isotope effects interconnected. Evidence for the involvement of chloride ion in the C–H bond breaking in aqueous solution?

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An unusual change of the primary kinetic isotope effect in the formation of hydroxamic acid from nitrosobenzene and formaldehyde in mixed solvents on addition of very small quantities of salts and at higher salt concentration in water was observed and interpreted in terms of ion pairing and hydrogen bonding phenomena in the reaction.

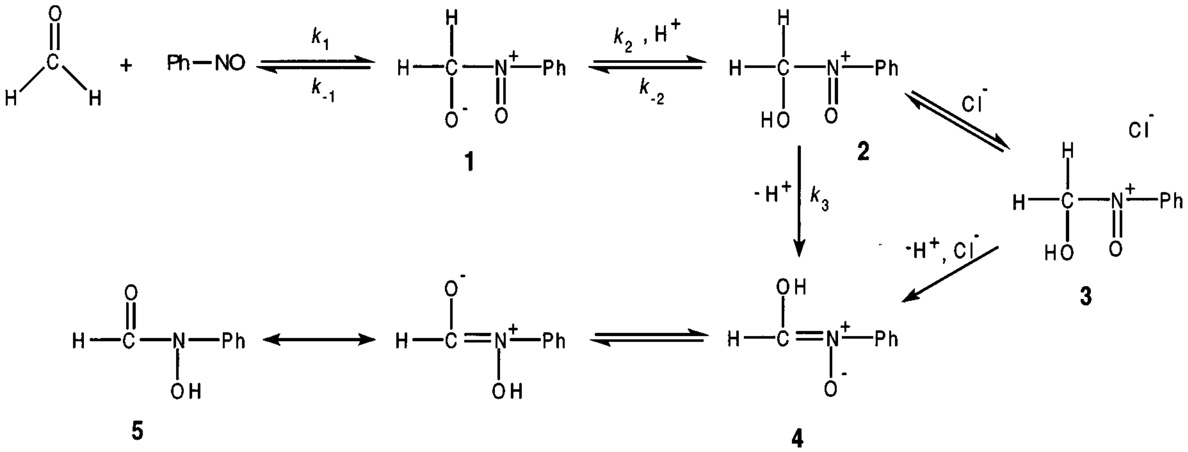
Salt effects are of great importance for organic chemistry and biochemistry.[1–5] We have reported here the observation of the unusually interconnected salt effects and the kinetic isotope effects in the reactions of the aldehydes with nitrosobenzenes[6] (Scheme 1). The reactions lead to the formation of the *N*-phenylhydroxamic acids. It is worthwhile noting the chemical/biochemical, pharmaceutical and industrial significance of hydroxamic acids and they have important applications as, among others, important siderophores and enzyme inhibitors.[7,8]

In the above mentioned formation of *N*-phenylformohydroxamic acid from nitrosobenzene and formaldehyde in an aqueous acidic medium the primary kinetic isotope effect (PKIE), k_H/k_D of *ca.* 8 between formaldehyde and formaldehyde-d$_2$ was observed.[6] In order to account for this PKIE, rate-controlling proton transfer from the carbon of the cation intermediate **2** was proposed.[6]

Recently, we have observed that this PKIE remained essentially unchanged when the reaction was performed in an acetonitrile–water medium (92.6% of acetonitrile). Quite surprisingly, a dramatic change of the PKIE (from k_H/k_D 7.6 to 3.8) was observed on the addition of only small amounts of salt (*e.g.* 0.001 M benzyltrimethylammonium chloride) into the reaction mixture. Similar results were obtained in an acetone–water (92.6% of acetone) reaction mixture in the presence of very low concentrations of LiCl. More surprisingly, a similar change of the kinetic isotope effect was observed when 1 M of benzyltrimethylammonium chloride was added to the water reaction medium, while the corresponding kinetic isotope effect remained *ca.* 8 in the presence of up to 4 M of inorganic chlorides or perchlorates. The results are summarized in Table 1. As we have observed, the addition of salts into the reaction mixture, both in mixed solvents and in water causes only the change of the observed rate constants. We have established that *N*-phenylformohydroxamic acid (*N*-phenylacetohydroxamic acid in the case of acetaldehyde reactant) was the only product of the reaction, regardless of the medium used. Also, spectroscopic evidence on the disappearance of the reactants and the formation of products during the reaction was the same in all the experiments.

The proposed mechanism of the reaction (**1**→**2**→**4**→**5** in Scheme 1), based on the kinetic evidence with regard to the order of the reaction, the acid catalysis, the dependence of the observed rate constants on the Hammett σ parameters, solvent isotope effects and substrate kinetic isotope effects was discussed elsewhere.[6] With regard to the mechanism and the evidence presented here, it seems reasonable to suppose that the unusual effects observed are the consequence of the formation of the cation intermediate–chloride ion pair **3** in the reaction. Fig. 1 shows that the dependence of the observed rate constants on the salt concentration is linear, consistent with the proposed formation of the ion pair **3**, deviations above concentration of 0.01 M salt being ascribed to increasing ion pairing in the added salt. Another feature that suggests the role of the ion pairing in the process is the observation of the strong difference between the effect of the small, symmetrical chloride ion which possesses great charge density, and bulky perchlorate with the dispersed charge. Thus, for example, 0.1 M of perchlorate in acetonitrile–water does not change the PKIE relative to the value observed in the water solution while 0.001 M of chloride causes a dramatic decrease of the PKIE observed. At the same time, the observed rate acceleration, calculated per mole of the anion, shows that Cl^- is *ca.* 1300 times more effective than ClO_4^- ion (see Table 1).

The most intriguing point among the reported results is the question of the reduced PKIE in the presence of low concentrations of inert salts. The change is the same for two different



Scheme 1

Table 1 Salt effects and kinetic isotope effects in the reactions of nitrosobenzene with formaldehyde and acetaldehyde

Solvent	Salt	Relative rate[a]	PKIE[b]
water	$NaClO_4$ 2.0 M	3.6	7.78 (0.32)[c]
CH_3CN–water[d]	none	0.32	
CH_3CN–water[e]	none	3.1	7.58 (0.46)
CH_3CN–water[e]	$PhCH_2(CH_3)_3N^+Cl^-$ 0.001 M	41.0[f]	3.76 (0.12)
CH_3CN–water[e]	$PhCH_2(CH_3)_3N^+Cl^-$ 0.005 M	189.8	3.89 (0.06)
Acetone–water[e]	none	0.58	6.34 (0.17)
Acetone–water[e]	LiCl 0.0044 M	30.0	
Acetone–water[e]	LiCl 0.0088 M	44.0	2.19 (0.08)
water	$PhCH_2(CH_3)_3N^+Cl^-$ 1.03 M	4.6	4.26 (0.05)
water	$PhCH_2(CH_3)_3N^+Cl^-$ 2.78 M	14.0	4.03 (0.14)
water	$LiClO_4$ 3.75 M	11.7	8.57 (0.71)
water	$Mg(ClO_4)_2$ 2.0 M	7.7	
water	NaCl 4.0 M	77.4	7.01 (0.31)
water	LiCl 4.0 M	132.3	7.05 (0.36)
water	$CaCl_2$ 2.0 M	125.3	
water	$MgCl_2$ 1.92 M	230.0	
water	NaCl 4.0 M	53.6[g]	

[a] Relative to the rate constant in water without the salt added. At 25 °C. Pseudo-first order rate constants were obtained spectrophotometrically (using HP8452 UV/VIS spectrophotometer) as described elsewhere.[6] Usually, concentrations of the total formaldehyde (0.575 M) and H^+ ($HClO_4$ 0.1 M) were 2.2×10^4 and 5×10^3 times that of nitrosobenzene. [b] Primary kinetic isotope effect between formaldehyde and formaldehyde-d_2. [c] From ref. 6. [d] 70% of acetonitrile. [e] 92.6% acetonitrile or acetone in water. [f] Relative rate constant enhancement calculated per mole of the salt added. [g] Value for acetaldehyde. $[CH_3CHO_{tot.}] = 1$ M, [HCl] = 1 M.

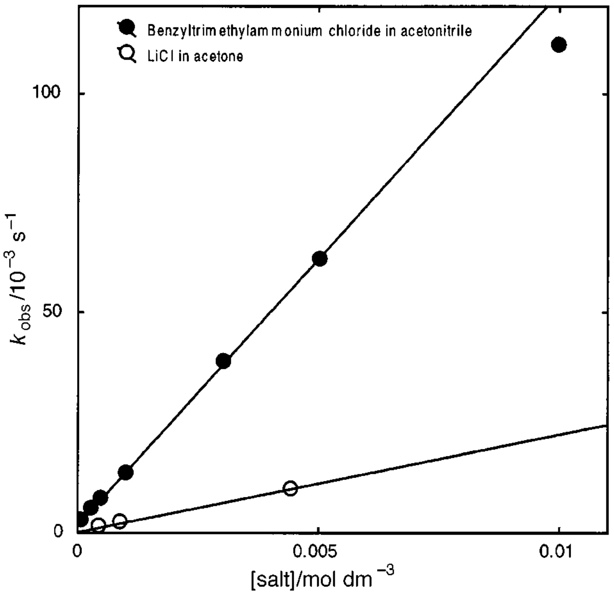


Fig. 1 The dependence of the k_{obs} for the reaction of formaldehyde with nitrosobenzene in acetonitrile–water (92.6% acetonitrile) solution in the presence of benzyltrimethylammonium chloride and in acetone–water (92.6% acetone) in the presence of LiCl. Rate constants determined as described in Table 1

concentrations of salt, which does not suggest a partial change in rate-determining step. The possibility could be considered that a hydrogen bond between the leaving proton from the cation intermediate and the chloride ion could be formed within the ion pair **3** in the transition state for the proton transfer from carbon. This hydrogen bonding could change some features of the transition state thus leading to the change of the PKIE observed. Another possibility is that the pK_a of the carbon acid in **3** could perhaps be changed significantly due to the formation of ion pair **3**, relative to the intermediate **2**. Since the magnitude of the PKIE depends on the ΔpK_a between the proton donor (carbon of **2** or **3**) and the proton acceptor (water molecule) included in the proton transfer, the change of the PKIE would be the consequence of the change of pK_a of proton donor on the formation of ion pair **3**.

The case of benzyltrimethylammonium chloride in water solution does not seem less enigmatic. However, the above considerations could perhaps apply to the case, since the ion pairing of benzyltrimethylammonium cation and chloride in water should be particularly suppressed due to a greater solvent polarity of water relative to the mixed solvents. Since the concentration of the quaternary salt in the related experiments was much greater than in the experiments in mixed solvents, the existence of a small fraction of 'free' chloride ions would not be excluded. Hence, the formation of the ion pair **3** under the conditions employed does not seem to be improbable. Obviously, this interpretation of the observed effects, although expressed in a somewhat different fashion is fully consistent with the viewpoint[9] about the role of the "basic" salts in the C–H bond heterolysis.

We believe that the results presented here, especially the interesting role of the particular anion, could be useful in the field of the phenomena connected with salt effects. For example in some important syntheses beneficial effects caused by very small concentrations of particular salts were observed[10] and the origin of these effects is still poorly understood. It is known on the other hand that anions play essential roles[11] in biological processes and participate in the great majority of all enzymatic reactions.

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