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Evidence for proton transfer from carbon to chloride ion in solution

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Abstract—Unambiguous evidence for proton transfer from carbon to chloride ion in solution has been obtained for the first time, in the formation of hydroxamic acids from aldehydes and nitrosobenzenes in acetonitrile.

Proton transfers are fundamental processes of central importance in many fields of chemistry and biochemistry.[1–12] A very broad range of phenomena has been studied, including proton transfers in DNA and related systems,[2–4] proton coupled electron transfer processes,[5–7] multiple proton transfers[8] and proton transfers involving phosphorus, sulfur and other atoms.[9,10] Proton transfers which involve carbon,[11,12] are of considerable interest. Thus, for example proton transfer from carbon to Brønsted bases constitutes an important step in many complex biochemical processes.[13] However, the possible involvement of halide ions in proton transfers from carbon has been considered only occasionally. Recently, two reports[14,15] appeared dealing with the question of the possible involvement of chloride ion in proton transfer from carbon. Meng and Thibblin[14] proposed that the leaving chloride in certain elimination reactions at tertiary carbon abstracts the proton from the β-C–H bond within the carbocation–chloride contact ion pair in acetonitrile-water solvent. In the paper by Moss, Sauers and co-workers,[16] which appeared two years later, essentially the same question was addressed though within a different context, that is, the investigation of the fragmentation of 2-norbornyloxychlorocarbenes in MeCN. We have reported[15] the observation of unusual interconnected salt effects and kinetic isotope effects in the acid catalysed reactions of aldehydes with *C*-nitroso compounds in mixed solvents in the presence of halide ions, which could suggest the involvement of chloride ion in the proton transfer from carbon. There are also other reports[17,18] where the promoting influence of the added chloride on the elimination was considered. However, the evidence reported so far does not seem to be conclusive.[19] Now, we have obtained unambiguous evidence for proton transfer from carbon to chloride ion in the formation of hydroxamic acids from aldehydes and nitrosobenzenes in 99.9% acetonitrile solution. The overall reaction[†] is the same as in water[20–22] or in some mixed solvents[15] but the process is complex in all cases involving several steps prior to final formation of the hydroxamic acid. Taking into regard the mechanism of the reaction proposed earlier[20–23] for the reaction in water and in mixed solvents, and the results obtained in 99.9% acetonitrile, the key features of the mechanism in acetonitrile can be described by Scheme 1.

The reaction is acid catalysed. The products of the reaction are undetectable after several hours in the absence of a catalyst.[‡] As expected, the addition of acid to a solution of aldehyde in 99.9% acetonitrile leads to an increase in the rates of both acid-catalysed hydration of the aldehyde and acid-catalysed dehydration of the aldehyde hydrate. Thus, broadening of the ^{1}H NMR absorption signal of the proton attached to the carbonyl group on addition of HCl to a solution of formaldehyde in 99.9% acetonitrile was observed (Fig. 2B). A completely analogous broadening was obtained by adding

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[†] The overall reaction is: RCHO + Ph–NO → RC(O)N(Ph)OH, the reaction goes to completion under the conditions employed and the corresponding *N*-phenylformylhydroxamic or *N*-phenylacetohydroxamic acids in the case of acetaldehyde are the products, as confirmed by methods reported elsewhere.[20–22,24,25]

[‡] One could doubt that traces of acidic impurities may cause the very slow process.

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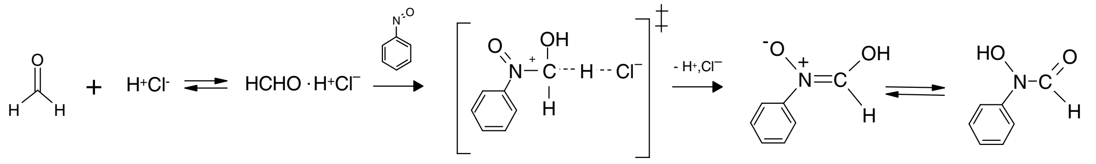

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Scheme 1.

of $HClO_4$ to the aldehyde solution in 99.9% acetonitrile. The addition of excess $HClO_4$ did not alter the established aldehyde/aldehyde hydrate equilibrium noticeably, as shown by the UV evidence (see also below).

The proton transfer to the aldehyde oxygen atom is probably the cause of the catalysis. Dipolar addition species probably do not exist as discrete intermediates in the general acid catalysed reactions of formaldehyde with water and alcohols. These reactions proceed by a concerted class e mechanism.[26] An attractive possibility here would be a concerted mechanism involving a nitroso compound as the addition species and the formation of a nitrosocarbinolic cation as the resulting intermediate in the reaction. An assessment of the precise timing of the proton transfer or the corresponding transition states or intermediates in the process, is a very subtle task. However, these limitations do not bring into question the main conclusions arising from this investigation.

The observed ρ Hammett parameter is negative suggesting a nucleophilic[20–23] role for the nitroso compound and in the presence of $HClO_4$ as the catalyst, the observed primary deuterium kinetic isotope effect (PKIE) between formaldehyde and d_2-formaldehyde in the reaction suggests that proton transfer from the CH_2 carbon of the nitrosocarbinolic intermediate to a molecule of water should be the rate controlling step. The evidence in support of the mechanism and the proton transfer from carbon to chloride ion in the reaction comprises of the following:

(1) A levelling-off was observed in the dependence of the rate constants observed for the formation of the *N*-phenylformohydroxamic acids in the reaction of formaldehyde with substituted nitrosobenzenes on the aldehyde concentration, at small and constant concentrations of HCl or $HClO_4$ as the catalysts, in 99.9% acetonitrile (Fig. 1). This observation is consistent with the involvement of a complex[§] between the aldehyde and the solvated hydronium ion in the presence of $HClO_4$ catalyst, or the analogous complex involving the ion pair H^+Cl^- when hydrochloric acid is used (see below).

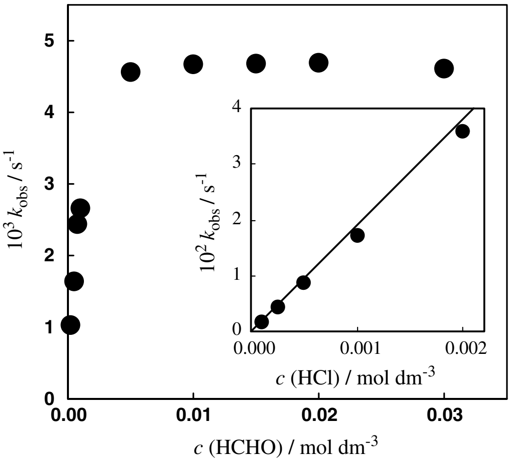

Figure 1. The dependence of the observed rate constants for the formation of *N*-phenylformylhydroxamic acid in 99.9% MeCN on the aldehyde concentration, in excess. [HCl] = 0.00025 M, [nitrosobenzene] = 0.00002 M, throughout. The pseudo-first order rate constants were determined spectrophotometrically, using the method reported.[19–21] Inset: the corresponding dependence of the observed rate constants on the concentration of HCl. [HCHO] = 0.0057 M, throughout, at 25 °C.

(2) When aldehyde concentration was kept constant and in a sufficiently large excess over the HCl concentration (or vice versa) a strong linear dependence of the observed rate constants on the HCl concentration in the reaction was obtained (see Fig. 1, inset). The slopes of the linear dependencies are essentially the same for the same concentrations of reactant in a large and constant excess. Further increase of the concentration of the minor reaction component leads to departure from linearity in the dependence observed. This observation corroborates the involvement proposed above of a complex between the aldehyde and the catalyst. The observed concentration dependence shows that the H^+Cl^- ion pair must be involved in the complex.[§,¶]

(3) The spectroscopic evidence obtained seems to be in support of the presence of chloride ions in the kinetically observed association complex in the pro-

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[§] An estimate from the kinetic measurements of the concentration quotient for the formation of the complex with HCl, tentatively assuming the process: $HCHO + H^+Cl^- \rightleftarrows HCHO{\cdot}H^+Cl^-$ gave a value of ca. $10^4\ M^{-1}$. At present, more information on the nature of this complex, solvation of the species that constitutes the association, etc. are not easily accessible. Recall that $HClO_4$ is fully dissociated in MeCN, while the association constant for HCl is of the order of $10^8\ M^{-1}$ in the same medium.[27] Similar levelling-off in the dependence of the observed rate constants for the reaction on the aldehyde concentration in excess was obtained for the reaction of nitrosobenzene with acetaldehyde but at substantially greater concentrations of the aldehyde.

[¶] Obviously, nonlinear dependence should be obtained if the complex involved the solvated hydronium ion only (arising from the dissociation of HCl).

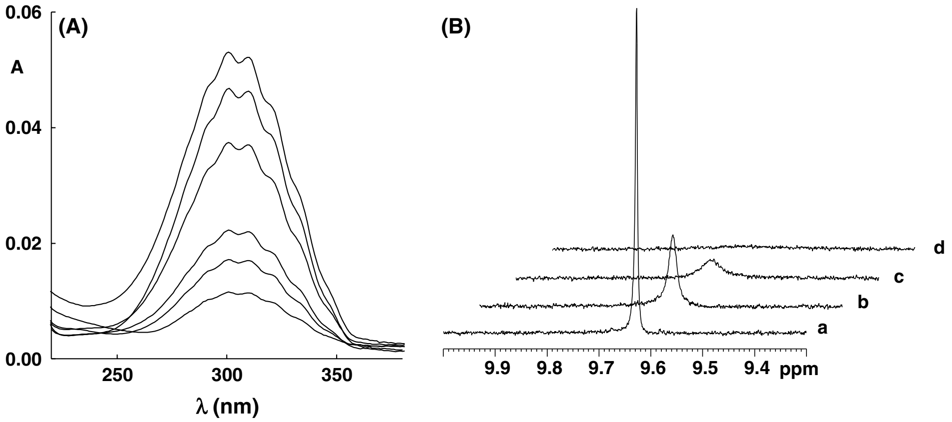


Figure 2. (A) Change in the UV spectra of 0.01 M formaldehyde in 99.9% acetonitrile solution on addition of (downward): 0.001 M HCl, 0.005 M HCl, 0.01 M HCl, 0.02 M HCl, 0.03 M HCl and 0.05 M HCl. The spectra of HCl were subtracted since HCl absorbs slightly in the range, at 25.0 °C. (B) Change in the ^{1}H NMR signal of carbonyl protons of 0.01 M HCHO in 99.9% acetonitrile-d_3 on addition of (a) 0.001 M HCl, (b) 0.005 M HCl, (c) 0.01 M HCl and (d) 0.02 M HCl, at 25 °C.

cess. The aldehyde carbonyl absorption band in the UV spectrum of formaldehyde in 99.9% acetonitrile disappears in part[‖] on the addition of HCl to the solution (Fig. 2A).

The change is reversible. The spectrum of the aldehyde was instantaneously and quantitatively regenerated on addition of an equivalent of a base (e.g., triethylamine), but no change in the carbonyl peak in the spectrum was observed on the addition of the same amount of $HClO_4$ to the aldehyde solution in 99.9% acetonitrile. This observation suggests that the absorbance of the carbonyl group is not strongly influenced by the solvated hydronium ion in the complex which is indicated by the kinetic experiments. In contrast, the influence of HCl is obvious from the UV spectra (Fig. 2A) and could be a consequence of dipole–dipole interactions of the carbonyl group and the H^+Cl^- ion pair in the association.

(4) The observed primary deuterium kinetic isotope effect k_H/k_D between formaldehyde and d_2-formaldehyde is 4.7 when $HClO_4$ is used in the reaction (Table 1). This PKIE is consistent with a rate-controlling proton transfer from carbon[27,28] of the CH_2 moiety in the nitrosocarbinolic intermediate **2** to a molecule of water.[**] This PKIE can be compared with the values of ca. 7 obtained for the reaction

Table 1. Kinetic isotope effects in the reaction of formaldehyde and nitrosobenzene in 99.9% acetonitrile[a]

Catalyst	$10^3\ k_H/s^{-1}$	$10^3\ k_D/s^{-1}$	PKIE
$HClO_4$	1.57 (0.05)	0.34 (0.01)	4.68 (0.23)
HCl	2.25 (0.06)	2.26 (0.07)	1.00 (0.04)

[a] [HCHO] = [DCDO] = 0.0022 M, throughout. [$HClO_4$] = 0.0003 M, [HCl] = 0.0003 M. At 298 K.

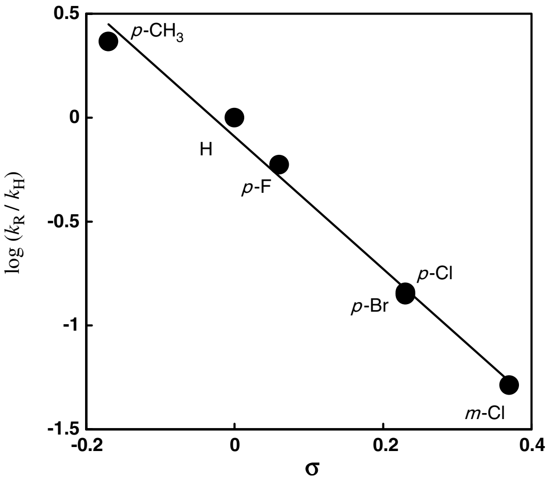
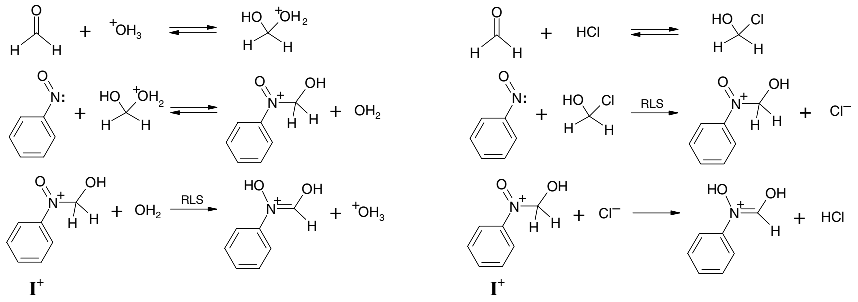


Figure 3. The plot of $\log k_R/k_H$ versus Hammett σ parameters for the reaction of the substituted nitrosobenzenes with formaldehyde in 99.9% acetonitrile containing hydrochloric acid catalyst. [HCHO] = 0.005 mol dm^{-3}, [HCl] = 0.0015 mol dm^{-3} and [***R***-C_6H_4–NO] = 0.0001 mol dm^{-3}, at 25.0 ± 0.1 °C. $\rho = -3.18$ ($r = 0.995$).

[‖] The appearance of the carbonyl absorption band in the UV spectrum is very slow after the addition of small amounts of formaldehyde hydrate (ca. 14 M solution) to 99.9% acetonitrile, but the new aldehyde/hydrate equilibrium is established within a minute or less (within seconds in the case of $HClO_4$) and is stable for hours on addition of 10^{-4} to 10^{-3} M HCl. With regard to the proposed complex, comparison with the kinetic observations shows that the disappearance of the absorbance of the carbonyl peak on the further addition of HCl is not complete even at several times excess of the acid. In our opinion, this is not surprising since there is no covalent, but only dipole–dipole, interactions between the carbonyl group and the H^+Cl^- ion pair in the complex, which changes the carbonyl group absorption coefficient only marginally. At present, we do not have information about the molar absorption coefficients of the aldehyde and the complex in the medium. Finally, there is no obvious reason for the absence of aggregates containing more than one HCl per one carbonyl group at higher acid concentrations. The further addition (in excess of 0.001 M) of $HClO_4$ did not influence the carbonyl absorbance noticeably though the kinetic results suggested the occurrence of association in the process.

[**] The reaction solution contained ca. 0.022 M of water. The HPLC grade MeCN used contains 0.017 M of water.



Scheme 2.

in water[20] and in some mixed solvents.[15] The corresponding PKIE observed when HCl was used is 1.0. The observed absence of a PKIE could be the consequence either of a change in the rate controlling step in the reaction or a change in the transition state for the proton transfer[††] (or possibly both of these). In order for a change to occur in the rate-controlling step, to cancel the observed PKIE of 4.7, the proton transfer step must become correspondingly faster, or one of the preceding reaction steps must become correspondingly slower than the proton transfer step. The reaction systems in the two experiments differed only with regard to the presence of the catalytic acid. The existence of the proposed complex of HCl and aldehyde in the process is also consistent with the result, since the chloride ion is already present in the encounter complex at the time when the nitroso compound enters the process and the C–N bond is formed. Therefore, it seems reasonable to conclude that chloride ion is involved in the proton transfer from the CH_2 moiety in the process.[††]

(5) The observed ρ Hammett parameter in the reaction is -3.18 (Fig. 3) when HCl was used as the catalyst. The corresponding value observed under the same reaction conditions in the presence of $HClO_4$ as the catalyst was -1.69. The change of the ρ parameter is consistent with a change in the rate-controlling step which becomes a proton transfer from the CH_2 in the presence of $HClO_4$, as indicated by the observed PKIE in this case.

A referee has suggested a different reaction pathway (Scheme 2) to the nitrosocarbinolic cation intermediate I^+. The key feature of the mechanism suggested is the formation of chloromethanol in the case of HCl catalysis. However, we believe that the observed changes in the UV and NMR spectra are not unambiguously in support of the formation of chloromethanol in the system. Thus, (i) the disappearance of the absorbance of the aldehyde carbonyl band at 300 nm in Figure 2A does not correspond[‡‡] to the association constant of the kinetically observed complex (see Fig. 1); (ii) the broadening of the ^1H NMR absorption line of the proton attached to the carbonyl group was observed on addition of HCl as well as on addition of $HClO_4$; (iii) a levelling-off was observed in the dependence of the rate constants observed for the formation of the *N*-phenylformylhydroxamic acids in the reaction of formaldehyde with substituted nitrosobenzenes on the aldehyde concentration, at small and constant concentrations of HCl as well as $HClO_4$, in 99.9% acetonitrile. Therefore, the formation of the nitrosocarbinolic cationic intermediate, by a concerted mechanism involving the nitroso compound, the aldehyde and the catalyst is perhaps a more attractive possibility at present, as already noted above.

In conclusion, the evidence obtained suggests that a proton transfer takes place from the carbon of the CH_2 moiety to the chloride in the formation of hydroxamic acids from aldehydes and nitrosobenzene. This observation could be of use for understanding the role of chloride in certain elimination reactions in nonaqueous solvents and the potential role of the ion in processes in related biological environments. It is noteworthy that the rate constant of formation of hydroxamic acid in the reaction in 99.9% acetonitrile is 10^3 times greater than the corresponding rate constant in water. This observation could be of value for the preparation/synthesis of hydroxamic acids since the biochemical/biomedicinal significance of this class of compounds is well known.[32,33]

Acknowledgements

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[††] The PKIE could also be substantially reduced if there were a highly 'asymmetric' transition state for the proton transfer.[28,29] We have also performed the appropriate control ^1H NMR experiments using solutions containing formaldehyde, d_2-formaldehyde and HCl in various proportions in CD_3CN. No H/D exchange was detected over a period of several hours.

[‡‡] Chloromethanol has never been detected in a solution but was studied in argon matrices[30] and in the gas phase[31] as the product of certain photochemical processes and the lifetime of the compound is measured in seconds. Chloroform and dichloromethane have a negligible absorbance at 300 nm; therefore the same should be the case with chloromethanol. From the kinetic measurements, the association constant of the complex is $\sim 10^4\ M^{-1}$, and at 0.01 M of both HCl (dry HCl was used) and aldehyde, there would be more than 90% of chloromethanol formed. This is inconsistent with the experiment (Fig. 2A) where the absorbance at 300 nm is more than a half that of the initial one.

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