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Acid hydrolysis of an ether bond assisted by the neighbouring amide group : effects induced by salts and by structural changes part 6[1-5]

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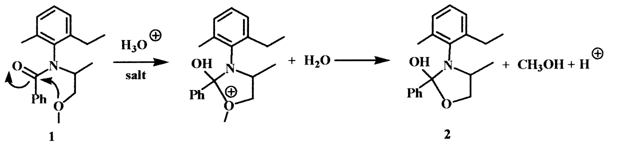
The acid hydrolysis of **1** assisted by the neighbouring amide group was kinetically investigated and salt effects were studied; the thermodynamic activation parameters calculated for the acid hydrolysis of other substrates (**3–6**) indicate that the methyl group in the side chain works on the enthalpic or on the entropic factor depending on the size of ring formed.

Keywords: acid cyclisation, ether hydrolysis, anchimeric assistence, salt effects, thermodynamic activation parameters

In our studies[1-5] on the acid ether cleavage of the substrate **1**[3] anchimerically assisted by an amide function we ascertained the mechanism of the hydrolytic process reported in Scheme 1 and deduced the kinetic Eqn (1) which describes the overall law rate of the following reaction scheme S + H$^+$ $\rightleftarrows$ SH$^+$ $\rightarrow$ [Cyclic intermediate]$^+$ + H_2O $\rightarrow$ **2** (S indicating the substrate **1**)

$$k_{obs} = [k_0\,[H^+]/(K_{SH^+} + [H^+])]\,F \qquad (1)$$

where k_0 is the slow step rate constant at the reference state, K_{SH^+}=[S][H$^+$]/[SH$^+$], $F = f_{SH^+}/f^\ddagger$ being the ratio of activity coefficients of SH$^+$ and the transition state.



Scheme 1 The salts are: LiCl, LiClO$_4$, NH4Cl, $(CH_3)_4NCl$

To obtain further knowledge about such an assisted reaction we extended our study to salt effects by performing kinetic measurements both at constant ionic strength and at constant acidity. The pseudo first order rate constants, measured at 71.2°C in the range 1–7.72 M HCl and at ionic strength I=8.7 M (LiCl), fit well the equation 1 which describes a hyperbola when F=constant (Fig. 1). From the fitting of Eqn (1), $k_0F = (7.5\pm0.7)10^{-3}s^{-1}$ and K_{SH^+}= 6.3±1.1 M/dm^3 (in the pH scale) were calculated. Kinetic measurements at constant ionic strength allowed us to evaluate the meaningful apparent K_{SH^+} of the protonated substrate which ionises outside of the pH range, recognising that the extrapolation of the acidity constant from H_0 scale to pH scale is of dubious worth.[7]

Kinetic data obtained at I=6.5 M (LiClO$_4$) fit well to the Eqn (1) showing that also in this case the $f_{SH^+}/f^\ddagger$ ratio can be considered constant, analogous to that observed for LiCl (Fig. 1): the values of $k_0F=(2.3\pm0.8)10^{-3}$ and K_{SH^+}= 0.85±0.1M/dm^3 were calculated.

On the basis of the pK_{SH^+} = -2.2±0.2 measured at 70°C and I=8.7 M (LiCl) by using acidity function H_0, at [HCl]<3.5 M (H_0> –1.2)[6] the substrate will be essentially unprotonated and the Eqn (1) becomes

$$k_{obs} = (k_0[H^+]/K_{SH^+})\,F \qquad (2)$$

that represents a straight line, as observed also at I=6.5 M (LiCl) (Fig. 1). Thus, this behaviour is largely due to [H$^+$] and K_{SH^+} values, the latter changing with both the ionic strength and the nature of the salt.

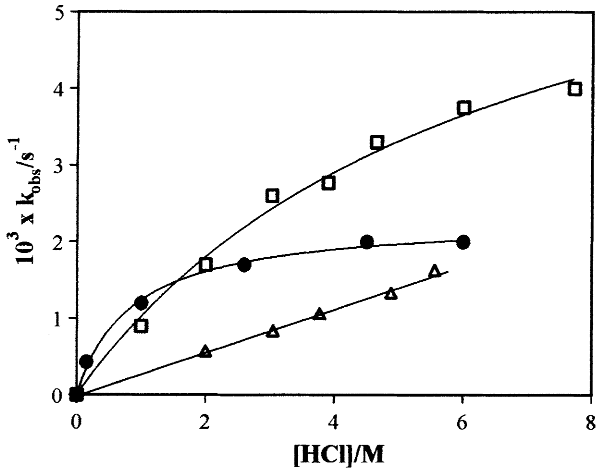


Fig. 1 Dependence of the rate constant *vs.* [HCl] for the hydrolysis of **1** at 71.2°C at I=8.7M (LiCl) (□), at I=6.5M (LiCl) (Δ) and (LiClO$_4$) (●).

To evaluate the salt effects connected to the change in ionic strength at constant acidity, kinetic measurements were performed at 3.03 M HCl in the presence of increasing amounts of lithium and ammonium salts. By plotting the lnk_{obs} against the ionic strength, a linear relationship with different slopes was found according to

$$\ln k_{obs} = \ln k + bI \qquad (3)$$

where k represents the rate constant measured at 3.03 M HCl in the absence of the salt and b is an empirical value.[8,9a] Thus, the influence on the k_{obs} exerted by the ions in solution, substantiated by the good fit to the Eqn (3), is primarily due to the change in activity coefficients of both the reactant species and the transition state (*i.e.* the 'primary salt effect') which is generally significant only at high values of ionic strength where the Debye–Huckel equation is not valid.[9b]

The thermodynamic activation parameters, obtained at 3.03 M HCl and I=8.7 M (LiCl), compared with those previously[3] found in the absence of salt, show that the LiCl causes a decrease in free activation energy ($\Delta\Delta F^\ddagger$ = 8 kJ/mol) due to a remarkable enthalpic advantage ($\Delta\Delta H^\ddagger$ = 21.6 kJ/mol) which exceeds the unfavourable change in entropy ($\Delta T\Delta S^\ddagger$ =13.6 kJ/mol). We believe that the decrease in $\Delta F^\ddagger$ caused by the presence of LiCl can be ascribed both to the increased ability to protonate the substrate, *i.e.* K_{SH^+} decrease, (secondary salt

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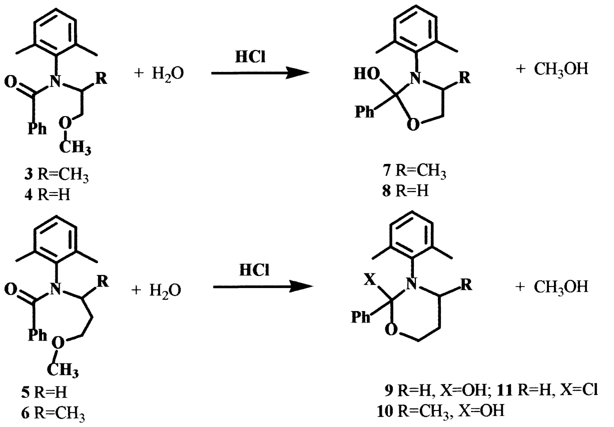
Table 5 Thermodynamic activation parameters for the hydrolysis of **3–6** at 7.42 M HCl[a]

	3	**4**	**5**	**6**	**1**[c]
k_{rel}[b]	103.7	5.4	1	12.8	126.4
$\Delta G^{\neq}$ kJ/mol	107 ± 1	116.3 ± 2	120.2 ± 5	113.6 ± 2	106 ± 3
$\Delta H^{\neq}$ kJ/mol	95.8 ± 1	110 ± 1	106 ± 4	107.4 ± 2	95 ± 2
$\Delta S^{\neq}$ J/mol/K	–34.8 ± 3	–19.4 ± 4	–44.6 ± 10	–19.2 ± 5	–35 ± 6
$T\Delta S^{\neq}$ kJ/mol	–11.2 ± 1	–6.3 ± 1	–14.2 ± 3	–6.2 ± 2	–11 ± 2

[a]Standard errors are calculated according to ref. 10; [b]calculated at 79.8°C, in 7.42MHCl; [c]values from ref. 3.



Scheme 3

effect) and to the increase in the $f_{SH^+}/f^{\ddagger}$ ratio (primary salt effect).[9c]

We have also subjected to kinetic investigation new substrates (**3**–**6**) in order to examine the effect of both the methyl group in the side chain and the chain length on the hydrolytic process.

The hydrolysis, performed in 7.42 M HCl at various temperatures, affords the respective five- or six-membered cyclic compounds **7**–**10** (Scheme 3).

A direct comparison of the relative rate constants (k_{rel}) measured at 79.8°C in 7.42 M HCl, shows that the reaction rate increases in the order **5**<**4**<**6**<**3**<**1** (Table 5). The thermodynamic activation parameters indicate that the presence of CH_3 in the side chain causes an appreciable rate increase. Probably, CH_3 forces the terminal reactant groups together in a restricted geometry ('proximity effect'[12]) favouring the intramolecular attack. Nevertheless, while the rate enhancement for **3** with respect to **4**, is caused by an enthalpic gain ($\Delta\Delta H^{\neq}$ =14.2/kJ/mol) which exceeds the unfavourable entropy change ($\Delta T\Delta S^{\neq}$ = 4.9 kJ/mol/K), for substrate **6** the decrease of the free activation energy in comparison with **5** is practically due to an entropic gain ($\Delta T\Delta S^{\neq}$ = 8 kJ/mol/K), the unfavourable enthalpy change being smaller ($\Delta\Delta H^{\neq}$=1.4 kJ/mol). Thus, the introduction of CH_3 in the side chain works on the enthalpic or on the entropic factor depending on the size of ring formed. The elongation of the chain by one CH_2 in the absence of the methyl group (compare **4** with **5**), causes an unfavourable entropy change accompanied by a smaller enthalpic advantage, while in the presence of CH_3 (compare **3** and **6**) the rate decrease is prevalently due to an enthalpic factor.

The experimental data reveal that for all the substrates investigated the rate constants decrease when $\Delta H^{\neq}$ increases except for the substrate **5** that, in comparison to **4**, gives a more favourable enthalpy change although it shows the lowest relative rate.

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References cited in this synopsis

1 A. Arcelli, G. Porzi and S. Sandri, *Tetrahedron* 1995, **51**, 9729
2 A. Arcelli, M. Papa, G. Porzi and S. Sandri, *Tetrahedron* 1997, **53**, 10513
3 A. Arcelli, G. Porzi, S. Rinaldi and S. Sandri, *J.Chem.Soc. Perkin 2* 2001, 296
4 A. Arcelli, R. Cecchi, G. Porzi, S. Rinaldi and S. Sandri, *Tetrahedron* 2001, **57**, 4039
5 A. Arcelli, R. Cecchi, G. Porzi, S. Rinaldi and S. Sandri, *Tetrahedron* 2001, **57**, 6843
6 C.H. Rochester, *Acidity Functions,* Academic Press; London; 1970, pp.21.
7 R.F. Cookson, *Chem. Rev.* 1974, **74**, 5 and references therein.
8 J.W. Moore and R.G.Pearson, *Kinetics and Mechanism*, J.Wiley and Sons; New York;1981, p. 272.
9 (a) C.H. Bamford and C.F.H.Tipper, *Comprehensive Chemical Kinetics*, Elsevier; New York; 1969, Vol.2, 337; (b) C.H. Bamford and C.F.H. Tipper, *Comprehensive Chemical Kinetics*, Elsevier; New York; 1969, Vol.2, 333; (c) C.H. Bamford and C.F.H.Tipper, *Comprehensive Chemical Kinetics*; Elsevier; New York; 1969, Vol.2, 357.
10 L.L. Schlager and F.A. Long, *Adv. Phys. Org. Chem.* 1963. **1**, 1.
12 F.C. Lightstone and T.C. Bruice, *J.Am.Chem.Soc.* 1996, **118**, 2595