Leaving Ability and Basicity of Leaving Groups Attached by First-row Elements

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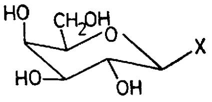
Summary The S_N1 hydrolyses of β-D-galactopyranosyl derivatives with nitrogen, oxygen, and fluorine aglycones have been measured, and at constant pK_a have been shown to adopt the order of rates F > O >> N.



(I)

It is generally accepted that, in the absence of steric effects, rates of heterolysis of carbon–heteroatom bonds vary monotonically and inversely with the basicity of the leaving group, provided that the heteroatom is kept constant. The effect of change in heteroatom, at constant basicity, is not clear; protonated amines leave faster than alkoxides from a phthalimidium ion,[1] but for generation of formaldehyde from its tetrahedral adducts alkoxides seem to be expelled faster than amines.[2]

We now report that in a conformationally defined system giving rise to a cation, nitrogen leaving groups of the same pK_a as HF leave slower than oxygen leaving groups of similar basicity, which in turn leave slower than fluoride ion. In the β-D-galactopyranosyl system (I) the pyranose ring adopts the $^4C_1$ conformation and constrains the leaving groups to an equatorial position. Therefore the relative dispositions of leaving group and of the ring oxygen atom providing electronic 'push' are kept constant.

We have shown[3] that in 1M KCl, the rates of S_N1 hydrolysis of β-D-galactopyranosyl pyridinium salts extrapolated to 25 °C are given by $\log_{10}(k/\mathrm{s}^{-1}) = 4{\cdot}35 - 1{\cdot}26\,\mathrm{p}K_a$. Interpolation at $\mathrm{p}K_a = 3{\cdot}2$ (the pK_a of HF[4]) gives $k = 5 \times 10^{-9}\,\mathrm{s}^{-1}$.

The pH-independent, S_N1 hydrolysis of 2,4-dinitrophenylgalactoside has been observed[5] ($k = 5 \times 10^{-6}\,\mathrm{s}^{-1}$ at 25 °C in 0·8M KCl), but is probably significantly sterically assisted.[6] We therefore measured the same process with its 3,4-isomer (k/s^{-1}, measured between 100 and 60 °C extrapolates to 8×10^{-9} at 25 °C in 1M $NaClO_4$: $\Delta H^{\ddagger} = 26{\cdot}8 \pm 0{\cdot}3$ kcal mol^{-1}; $\Delta S^{\ddagger} = -4 \pm 1$ cal $\mathrm{mol}^{-1}\,\mathrm{K}^{-1}$).[†] Other labile aryl galactosides with both *ortho* positions free are not available, but the S_N1 hydrolysis-rate of the galactoside of a phenol of pK_a 3·2 can be deduced from $\log k = \mathrm{A} - \beta_{\mathrm{lg}}\mathrm{p}K_a$ and two independent but concordant estimates of β_{lg}. That for the pH-independent hydrolysis of aryloxytetrahydrofurans is 1·07,[7] and that calculated from the rates of spontaneous hydrolysis of 2,4- and 2,5-dinitrophenyl galactosides in 1M $NaClO_4$[‡] ($2{\cdot}15 \times 10^{-6}$ and $9{\cdot}5 \times 10^{-8}\,\mathrm{s}^{-1}$, respectively) is 1·08. An unhindered

[†] 4·184 Joules = 1 calorie.

[‡] The change in 'inert' electrolyte was required for the hydrolysis of the fluoride, which was followed using a (Cl^--sensitive) lanthanum fluoride electrode. The kinetic consequences (2—3-fold decrease in the rate of hydrolysis of 2,4-dinitrophenyl galactoside) are precedented: J. L. Hogg and W. P. Jencks, *J. Amer. Chem. Soc.*, 1976, **98**, 5643.

phenolate of the same basicity as fluoride ion is then estimated to leave at 2×10^{-6} s^{-1}.[8]

At 25 °C in 1M $NaClO_4$ galactosyl fluoride (I; X = F) hydrolyses by specific acid-catalysed, specific base-catalysed, and pH independent pathways, the last at a rate of 6×10^{-5} s^{-1} ($\Delta H^{\ddagger} = 21{\cdot}3 \pm 1$ kcal mol^{-1}; $\Delta S^{\ddagger} = -5 \pm 3$ cal mol^{-1} K^{-1}).†

Since, in the particular reaction studied, there is the same change in disposition of charges as in the reference ionisation, it is unlikely that the change in leaving group charge bears upon the observed order of leaving abilities F>O>>N. This is confirmed by a study of galactosyl azide (I; X = $-\overset{-}{N}-\overset{+}{N}\equiv N$), which is inert to S_N1 reactions, caramelising before it undergoes hydrolysis at neutrality. However, an upper limit of 10^{-5} s^{-1} at 90 °C for the S_N1 reaction can be inferred; this is around the S_N1 rate[3] of a galactosyl pyridinium ion derived from a pyridine of pK_a 4·6.[9]

Hydrogen fluoride, phenols, and protonated pyridines are 'normal' acids by the Eigen[10] classification, so leaving ability cannot follow a different kinetic acidity scale.

The observed order of leaving abilities follows the degree of stabilisation or destabilisation of equatorial substituents by the anomeric effect if the electrostatic model[11] of the operation of this effect is adopted. However, experimentally it is observed that the anomeric effect for azide is comparable to that for acetate,[12] yet galactosyl azide is still inert to S_N1 reactions. Moreover, on the 'no-bond resonance' model of the operation of the anomeric effect,[13] it arises from preferential stabilisation of the axial epimer.

We therefore tentatively conclude that the observed order of leaving abilities, N<<O<F, represents the 'intrinsic leaving group abilities' of these elements from carbon in water.

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