Evidence for Charge Localisation by Strong Hydrogen Bonding in Fluoride–Phenol Complexes and its Effects on Reactivity/Selectivity

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Measurements of yields and rates of methylation of substituted phenols, and correlations for the prediction of [^{11}C]MeI labelling conditions, show evidence for charge localisation in fluoride–phenol strong hydrogen-bonded complexes and its effects on selectivity/reactivity.

The use of fluoride ions for hydrogen-bond assisted reactions has been shown to be of synthetic utility[1] and the observations of enhanced reactivity and/or selectivity have been explained by the localisation of charge within the three atom XHF$^-$ (X = O or N) H-bond. Although *ab initio* calculations[2] and spectroscopic studies of gas-phase fluoride adducts[3] have supported the concept of charge localisation by inhibition of resonance delocalisation a clear demonstration of its effects in solution, where ion–solvent and ion–pair interactions become important, have not been shown. One of us previously reported a spectroscopic study that showed evidence for medium-dependent inhibition of resonance delocalisation of charge by strong hydrogen bonding in fluoride–phenol complexes.[4] In our present studies on the rapid methylation of phenolic compounds, for labelling with [^{11}C]MeI, we have obtained results that show clear evidence for H-bond charge localisation in solution and its effects on reactivity/selectivity.

The labelling of tracers for positron emission tomography (PET) is often performed using [^{11}C]methyl iodide. The short halflife of carbon 11 ($t_{0.5}$ 20 min) makes it essential to find rapid labelling conditions, and the maximum radiochemical yield is controlled by the competitive and consecutive reactions that accompany the desired labelling. Optimum labelling conditions thus depend on reaction rates and initial concentra-

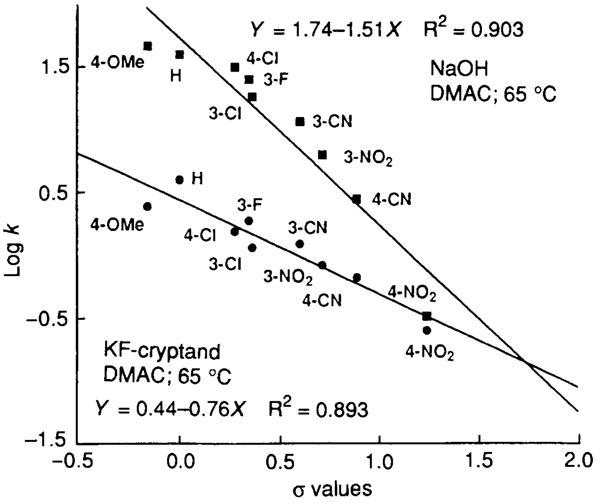

Fig. 1 Plot of log *k vs.* σ-values for methylation of substituted phenols in DMAC at 65 °C using NaOH, (■), or KF–cryptand 222, (●)

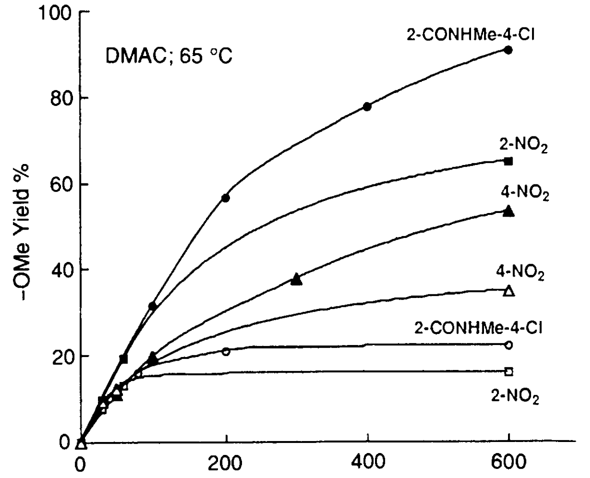

Fig. 2. Yield curves for methylation of some deactivated phenols using NaOH (□, ○, △), and KF–cryptand 222 (■, ●, ▲)

tions. As part of our study on the development of computer software to predict optimum reaction times for controlling a fully automated synthesis apparatus, we measured the rate of methylation of phenol and found that the most rapid labelling, following second-order kinetics for up to 80–90% of the reaction, was obtained using aqueous NaOH (10 mol dm^{-3}, 20 μmol): phenol (2.5 μmol): MeI (0.25 μmol) in 275 μl of *N*,*N*-dimethylacetamide (DMAC). Similarly a KF–cryptand 222 system was optimised as; KF (80 μmol): cryptand 222 (1.25 μmol): phenol (2.5 μmol): MeI (0.25 μmol) in 275 μl of DMAC. We then measured the initial rates of methylation for a series of substituted phenols ($X\text{-}C_6H_4OH$) in both systems (Table 1) and looked for correlations suitable for prediction.

Fig. 1 shows the Hammett-type linear free-energy plots, of log *k* against σ substituent constants, for some 3- and 4-substituted phenols in both base systems at 65 °C. Fairly good correlations were obtained (NaOH; $R^2 = 0.903$, $n = 9$ and KF–cryptand; $R^2 = 0.893$, $n = 9$) over a wide range of reactivity. The negative reaction constants (ρ values) obtained from the slopes, are indicative of the removal of electron density from the oxygen atom reaction centre in the transition state relative to the initial state. The fact that the slope for the KF–cryptand system ($\rho = -0.87$) is almost half that observed using NaOH as base ($\rho = -1.71$), clearly indicates the decreased electron demand of the substituents on the reaction centre, and thus the charge-localizing effect of the fluoride–phenol H-bond. The two correlation lines cross near the points for X = 4-NO_2, suggesting that the usefulness of the KF–cryptand system is limited to the rapid labelling of the most deactivated phenols.

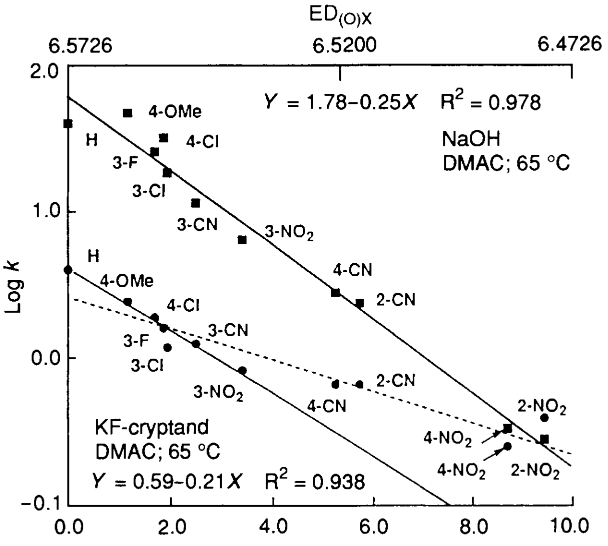

Fig. 3 Plots of log *k vs.* (*a*) electron density on phenolate oxygen calculated by the AM1 method and (*b*) relative charge-withdrawing effect of substituents, for methylation of substituted phenols in DMAC at 65 °C using NaOH, (■), or KF-cryptand 222, (●)

However, comparison of the initial rates of reaction does not give the complete picture. When yield–time curves for methylation are plotted, improved selectivity in the KF–cryptand system owing to charge localisation becomes evident. Fig. 2 shows the yield curves for some deactivated phenol compounds using both systems. Initial rates are similar but deprotonation with NaOH leads to poor final yields of 10–30%, whereas KF–cryptand gives much higher 50–90% yields. The reason for the low yields in the NaOH system is not fully understood, but MeI is apparently consumed while much of the large excess of phenol remains unconverted.† The improved yields in the KF–cryptand system result in higher predicted radiochemical yields for [^{11}C]MeI labelling of deactivated phenols, such as biologically important salicylamides, offsetting drawbacks due to cost and toxicity.

In an attempt to improve and increase the scope of our rate predictions we investigated some other correlations of rates. The electron density on the phenolate ion oxygen atom was calculated using the AM1 quantum mechanical model[5] (Table 1). Fig. 3 shows the log *k* (NaOH) values plotted against the electron densities, [$ED_{(O)X}$], calculated for the substituted phenolate ions. All the 3- and 4-substituted phenols, as well as some 2-substituted ones, correlated very well ($R^2 = 0.978$, $n = 11$) with the calculated [$ED_{(O)X}$] values. As it was not possible to calculate accurately the electron densities in the [OHF]$^-$ H-bond by the AM1 method we used the [$ED_{(O)X}$] electron densities to calculate relative charge-withdrawing effects for the substituents, ($RCWE_X$), and Fig. 3 also shows the log *k* (KF–cryptand) values plotted against these. Although the log *k* (KF–cryptand) values show a fairly good correlation with the $RCWE_X$ values (Fig. 3, dotted line, log *k* (KF–cryptand) = 0.42–0.11($RCWE_X$), $R^2 = 0.896$, $n = 11$), on closer analysis the values for the phenols substituted with strong electron-withdrawing −M (+R) groups (X = 4-NO_2, 2-NO_2, 4-CN and 2-CN) can be seen to be deviating from a correlation line

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† We have obtained evidence for some decomposition of DMAC to dimethylamine and acetate in the strongly alkaline conditions.

Table 1 Rates of methylation, substituent constants and calculated electron densities for substituted phenols

X-C_6H_4OH X	log *k* (NaOH)	log *k* (KF–cryptand)	σ_m, σ_p^-	X-$C_6H_4O^-$ $ED_{(O)X}$[a]	$RCWE_x$[b]	$CRCWE_x$[c]
H	1.602 ± 0.040	0.61 ± 0.11	0.00	6.5726	0.00	0.00
4-OMe	1.675 ± 0.011	0.386 ± 0.026	−0.16	6.5611	1.15	1.15
4-Cl	1.500 ± 0.036	0.200 ± 0.020	0.27	6.5541	1.85	1.85
3-F	1.410 ± 0.024	0.276 ± 0.056	0.34	6.5557	1.69	1.69
3-Cl	1.270 ± 0.029	0.068 ± 0.015	0.36	6.5533	1.93	1.93
3-CN	1.062 ± 0.001	0.100 ± 0.034	0.56	6.5479	2.47	2.47
3-NO_2	0.803 ± 0.068	−0.080 ± 0.011	0.71	6.5387	3.39	3.39
4-CN	0.441 ± 0.061	−0.180 ± 0.019	0.89	6.5202	5.24	3.67
2-CN	0.370 ± 0.076	−0.180 ± 0.031	—	6.5151	5.75	3.67
4-NO_2	−0.480 ± 0.060	−0.602 ± 0.033	1.24	6.4855	8.71	5.68
2-NO_2	−0.550 ± 0.032	−0.410 ± 0.010	—	6.4783	9.43	4.76

[a] Electron density on phenolate oxygen calculated by AM1 method.‡ [b] Relative charge-withdrawing effect; $RCWE_X = 100(ED_{(O)H}\text{-}ED_{(O)X})$. [c] Corrected relative charge-withdrawing effect for KF–cryptand system.

drawn for the other phenols [log *k* (KF–cryptand) = 0.59–0.21 ($RCWE_X$), $R^2 = 0.938$, $n = 7$]. For the reaction of 4-cyanophenol we used IR spectroscopy and the ν(C≡N) band[4] to confirm that the strong OHF^- hydrogen bonded complex was formed in the reaction solution mixture, without significant amounts of free phenolate anion. We believe that the comparatively high rates for the phenols with strong ^-M groups is evidence that inhibition of resonance delocalisation of charge by strong H-bonding does alter reactivity in solution. The higher R^2 values for the correlations of rates using the calculated electron-withdrawing effects, compared with those obtained with the σ values, and the increased range of compounds (several 2-substituents included) meant we were successful in improving our ability to predict labelling conditions. Corrected $RCWE_X$ values (Table 1), which allow for the deviations due to the effects of inhibition of resonance, are thus used when the KF–cryptand system is employed.

In summary, our correlations, suitable for the prediction of [^{11}C]methyl-labelling conditions, show evidence that confirms charge localisation, previously inferred from theoretical and gas-phase studies of fluoride H-bonded solvates, does operate in dipolar aprotic solution to modify reactivity. The consequences of the localisation by strong H-bonding are shown for the improved rapid labelling of deactivated phenolic compounds in a KF–cryptand system. Although NaOH is quite suitable for rapid [^{11}C]methyl-labelling of many simple phenolic substrates, fluoride ion H-bond assisted methylation is of use for labelling less reactive compounds, including biologically important tracers.

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‡ Structures of the free anions were obtained by energy minimization, without counter-ion or solvent interactions.

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