

FORMATION AND REACTIVITY OF A STRONGLY HYDROGEN
BONDED FLUORIDE-4-CYANOPHENOL COMPLEX

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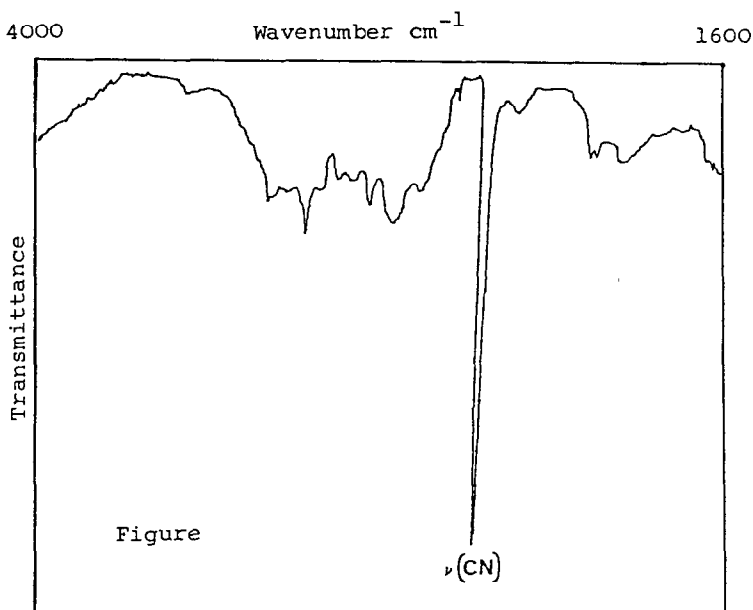
Summary - Potassium fluoride forms a thermally stable strongly hydrogen bonded complex with 4-cyanophenol. The complex is a very useful substrate for the formation of biaryl ethers via denitration or dechlorination.

Ionic fluorides are among the most versatile reagents in organic synthesis. Their use as bases has been the subject of a number of recent reviews¹⁻³ and their nucleophilicity is the basis for the synthesis of many selectively fluorinated molecules as well as other reactions in organofluorine chemistry.³⁻⁵ The combination of the properties of basicity and nucleophilicity can however lead to undesired complications in reaction systems and the selective suppression of one of these inherent characteristics is a subject of interest and importance. The pre-formation of a strongly hydrogen bonded complex between the substrate nucleophile and the fluoride is one possible way of reducing F⁻ nucleophilicity while achieving the desired activation of the organic nucleophile.¹ As part of our programme of research on the chemistry of F⁻ we recently reported the preparation and spectroscopic study of the strongly hydrogen bonded complex of 4-cyanophenol with tetrabutylammonium fluoride (TBAF).⁶ The apparent strength of the hydrogen bond and the ability to "tune" the complex into a form where the charge is highly localised on the phenolic oxygen (by control of the medium solvation characteristics)^{6,7} encouraged us to consider the possible use of such a complex as a highly selective and reactive in-situ source of 4-cyanophenoxide in the synthesis of substituted biaryl ethers. Unfortunately the thermal stability of the hydrogen bonded complex is quite low (TBAF can decompose to Bu₃N or Bu₃NHF at 100 °C or less)⁸ which would effectively preclude its use in all but a few facile reaction systems. In an attempt to overcome this problem while maintaining the synthetic advantages of the strong, localised hydrogen bond, we turned our attention to the preparation and synthetic utilisation of a potassium fluoride-4-cyanophenol complex which is less expensive and may be more thermally stable than the TBAF analogue.

Slow evaporation of a methanolic solution containing equimolar amounts of anhydrous potassium fluoride and 4-cyanophenol gave a white solid. Ether washing removed excess phenol and final drying under high vacuum gave a non-hygroscopic white solid. The infrared spectrum of this material show (Figure) a $\nu(\text{OH})$ pattern characteristic of strong, asymmetrical hydrogen bonding (broad, structured band in the $3200\text{--}1600\text{ cm}^{-1}$ region centred at ca. 2400 cm^{-1}) very similar to that of TBAF-4-cyanophenol.⁶ In addition to the $\nu(\text{OH})$ bands the KF-4-cyanophenol complex shows a strong, band at ca. 2220 cm^{-1} due to $\nu(\text{C}\equiv\text{N})$. The position of the $\nu(\text{C}\equiv\text{N})$ band is particularly significant since it suggests that the complex is in the localised (charge localised in the OHF hydrogen bond) rather than delocalised (charge partially delocalised on to the CN group) form.⁶ Further evidence in favour of this was obtained by running spectra of the pure phenol and KF-4-cyanophenol in dimethylsulphoxide (a solvent that generally favours delocalisation for hydrogen bonded complexes). The $\nu(\text{C}\equiv\text{N})$ bands for these species occurred at 2225 and 2223 cm^{-1} respectively which again suggests that the KF complex exists in the localised form (which should enhance regioselective reactivity) even in polar environments.

The thermal stability of the KF-4-cyanophenol complex was determined by thermogravimetric analysis and infrared spectroscopy. No weight loss was observed after heating the complex at $110\text{ }^{\circ}\text{C}$ for a period of two hours (reaction conditions - see later) and the infrared spectrum of the resulting material was effectively unchanged with less than 1% decomposition to HF_2^- (the expected decomposition product).

We may reasonably conclude therefore, that in dimethylsulphoxide at $110\text{ }^{\circ}\text{C}$ the KF-4-cyanophenol complex will maintain its OHF hydrogen bond with little delocalisation of charge away from the hydrogen bond. We can therefore expect high reactivity for the complex in nucleophilic substitution reactions run under these conditions.¹ So as to demonstrate this we ran reactions of the complex with four aromatic substrates susceptible to denitration or dechlorination (Table). Reactions were run at $110\text{ }^{\circ}\text{C}$ in dimethylsulphoxide with vigorous stirring (the complex is only slightly soluble under these conditions) and were regularly monitored by g.c. The products were isolated by standard ethoxyethane-water work-ups and their structures confirmed by mass spectrometry, ^1H n.m.r. and i.r. spectroscopy. In all cases the reactions proceeded rapidly and in high yield. No significant amounts of any other products were observed suggesting that the nucleophilicity of the F^- is effectively suppressed by complexation. KF itself will rapidly fluorodenitrate or fluorodechlorinate these substrates under these conditions,⁹ and that any side reactions such as attack at the ring carbons of the phenol resulting from delocalisation of charge do not occur. Interestingly when reactions were carried out using simple mixture of KF and the phenol rather than the pre-formed complex, fluorination of the substrate became a significant side-reaction.¹⁰



In conclusion we can say that the nucleophilicity of KF can be effectively suppressed by complexation with 4-cyanophenol. The resulting complex is a remarkably stable example of a charge localised, strong hydrogen bond which can be used as an efficient oxygen nucleophile for forming substituted biaryl ether: via denitration or dechlorination. Our method may well lend itself to the synthesis of some of the many biaryl ethers which find widespread application as physiologically active materials.

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<u>Substrate</u>	<u>Product</u>	<u>Yield^a</u>
		95
		95
		75
		88

^aYield by g.l.c. after 2h at 110 °C in DMSO.

References and Notes

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10. The reaction with a mixture of KF and 4-cyanophenol (not the pre-formed complex) and 1,2-dinitrobenzene for example, gave ca. 10% fluoro-2-nitrobenzene after 2h at 110 °C in DMSO (the pre-formed complex gave no detectable fluorination).

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