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SUBSTRATE DEPENDENT SOLVENT EFFECTS IN NUCLEOPHILIC FLUORINE TRANSFER REACTIONS

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SUMMARY

The rate of fluorination of organic substrates by potassium fluoride in aprotic solvents is subject to substrate dependent solvent effects.

INTRODUCTION

Of the very many ways of introducing fluorine into an organic molecule the nucleophilic fluorine transfer method using an alkali metal fluoride is probably the most important [1-3]. Two of the most significant developments in this area have concerned the choice of solvent and the use of catalysts. Protic solvents which often led to non-fluorine containing products [4] have been superceded by aprotic solvents and the new generation of dipolar aprotic solvents such as sulpholane and N-methylpyrrolidone in particular [2,5]. It is generally accepted that dipolar aprotic solvents do not solvate F^- to any significant extent and this characteristic along with their high boiling points and good thermal stabilities make them obvious choices for bulk solvents in reaction using alkali metal fluorides.

Finger first recognised the advantages of using such solvents in nucleophilic fluorine transfer reactions using potassium fluoride [1] and he subsequently discovered that the rate of conversion of aryl chlorides to aryl fluorides was sensitive to the identity of the dipolar aprotic solvent

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with dimethylsulphoxide giving faster rates of reaction than dimethylsulphone which in turn gave faster rates than dimethylformamide [5]. Other factors and especially solvent breakdown can be important in determining the choice of solvent and this has led to the widespread use of solvents such as sulpholane which are less easily decomposed in high temperature fluorination reactions. Despite the obvious importance of the correct choice of solvent and the possibility of the solvent playing less than a passive role in nucleophilic fluorine transfer reactions, we are not aware of any reported attempt to carry out a reasonably comprehensive study of solvent effects in these reactions. We now report our results from such a study.

RESULTS AND DISCUSSION

Important target aromatic substrates for fluorination include heterocyclic as well as carbocyclic molecules and nucleophilic fluorine transfer can involve fluorodenitration as well as fluorodehalogenation. The sensitivity of the rate of fluorination to the type of solvent is qualitatively the same for model reactions that fall in all of these classes, namely the fluorinations of 2,3,5,6-tetrachloronitrobenzene and 2-chloro-6-nitrobenzonitrile (both fluorodenitrations) [6,7], 1-chloro-2,4-dinitrobenzene, 2-chloro-5-nitropyridine and 4-chloro-3-nitrobenzotrifluoride (all fluorodechlorinations). The rate curves for the conversion of 2-chloro-6-nitrobenzonitrile are shown as an illustration of the solvent dependence in Fig. 1.

For all of the aromatic substrate fluorinations investigated the rates of reaction under exactly the same experimental conditions are very much faster in polar aprotic protophilic solvents such as sulpholane or dimethylsulphoxide than in other types of solvent such as acetonitrile or 1,2-dimethoxyethane. The best solvent in all cases is dimethylsulphoxide despite the fact that this is a relatively poor solvent for KF (*ca.* 0.6 mmolar at 82°C). In general there is a poor correlation of rates of reaction of aromatic substrates with the solubility of KF.

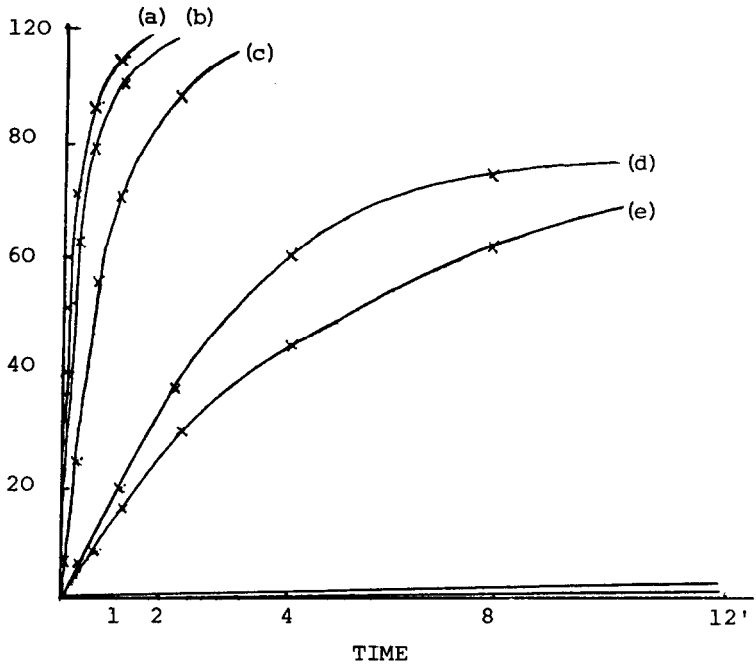

Fig. 1. Rate of production of 2-chloro-6-fluorobenzonitrile from 2-chloro-6-nitrobenzonitrile with KF (1 mol. equivl.) at 82°C using (a) dimethylsulphoxide; (b) tetramethylenesulphoxide; (c) N,N-dimethylacetamide; (d) N-methylpyrollidone; (e) sulpholane; (f) acetonitrile; and (g) dimethoxyethane.

In contrast to the aromatic substrates, we have found that the rates of fluorination of simple aliphatic substrates show quite different sensitivities to the type of solvent. The rates of fluorination are generally rather less solvent dependent and correlate much better with the solubility of KF. Reagents that are known to improve the solubility of KF such as glycols and 18-crown-6 also result in a corresponding increase in the rate of aliphatic substrate fluorination [8,9]. Thus the rate of fluorination of benzyl bromide for example, using a solution of 18-crown-6 in acetonitrile (KF solubility ca. 3.5 mmolar) [8] is about twice that using dimethylacetamide (KF solubility ca. 2.5 mmolar). The observed rates of fluorination of benzyl bromide at 82°C with KF follow the order 18-crown-6-acetonitrile > dimethylacetamide > 1,2-dimethoxy-

ethane > sulpholane > acetonitrile > N-methylpyrrolidone. The reversal of the order for 1,2-dimethoxyethane and N-methylpyrrolidone on going from aromatic substrate fluorinations to aliphatic substrate fluorination is particularly striking.

The magnitude of the increase in rate of fluorination of the aromatic substrates on going from acetonitrile to the polar protophilic solvent sulpholane for example, is itself substrate dependent and provides an important clue concerning the nature of these non-KF solubility related solvent effects. The ratio of the initial rates of fluorination of the aromatic substrates in sulpholane to those in acetonitrile follow the order 2,3,5,6-tetrachloronitrobenzene (ca. 580) > 2-chloro-6-nitrobenzonitrile (ca. 280) > 4-chloro-3-nitrobenzotrifluoride (ca. 170) >> 2-chloro-5-nitropyridine (ca. 28) > 1-chloro-2,4-dinitrobenzene (ca. 22). The order of solvent dependent rate enhancements correlates well with the degree of resonance stabilisation in the corresponding anionic reaction (Meisenheimer) intermediates. The greatest rate enhancement is observed for the substrate that will have no effective -M groups operating in the corresponding Meisenheimer intermediate whereas the smallest rate enhancements are observed for those substrates where two -M groups are operative in the respective intermediates. We believe that these results strongly suggest that the stability of the Meisenheimer intermediate produced in nucleophilic fluorine transfer reactions with aromatic substrates is solvent sensitive and that the less intrinsically stable the Meisenheimer intermediate the greater is this sensitivity. The stabilisation of the Meisenheimer intermediate is clearly of major importance in determining the overall rate of fluorination and for more stubborn substrate fluorinations, the correct choice of bulk solvent is clearly of considerable importance. The precise nature of the solvent stabilisation of Meisenheimer intermediates is not immediately obvious since optimum stabilisation is obtained with those solvents that possess high polarisability (π^*) and protophilicity (β) but zero hydrogen bond donating ability (α) [10] and it is the last property which can be most easily associated with specific association with anionic species.

We do believe however that specific association of solvent molecules with the Meisenheimer complexes is likely to be relevant since the difference in polarisabilities between the solvent acetonitrile (π^* = 0.75) and the much more effective polar protophilic solvents (π^* = 0.88-1.00) is not large. We have recently reported a similar effect where the solvent stabilisation of a hydrogen bonded anionic complex can be best explained by consideration of a combination of the π^* and solvatochromic parameters rather than π^* alone [11,12]. We suggest that specific association involving a Meisenheimer complex and a polar aprotic protophilic solvent may be achieved by interaction of the complex with the positive ends of the polarisable SO, SO_2 or CO functions in the solvents - a type of interaction that is not allowed for in the principle Taft parameters [10]. The accessibility of these positive sites will then be a relevant factor and this may explain why the rate of fluorination of 2-chloro-6-nitrobenzonitrile for example, follows the order dimethylsulphoxide > tetramethylene sulphoxide > sulpholane as well as dimethylacetamide > N-methylpyrrolidone.

EXPERIMENTAL

All halogen exchange and fluorodenitration reactions were carried out in exactly the same way. Potassium fluoride (0.725 g, 0.0125 mole) which had been previously dried at ca. 280°C for one week was vigorously stirred with a solution of the substrate (0.0125 mole) in the dried solvent (30 cm^3) at 82°C. The reactions were monitored by g.l.c. and/or ^1H n.m.r. spectroscopy. The identities of the products were confirmed by g.l.c.-mass spectrometry.

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