

# The solvated fluoride anion can be a good nucleophile

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**Computations show how the solvated fluoride ion can be a good nucleophile in spite of its high solvation energy.**

In the gas phase the fluoride ion,  $F^-$ , is a good nucleophile, but in aqueous solution it is the least reactive of the halides (tenfold less reactive than chloride, one hundredfold less reactive than bromide, towards iodomethane in water)<sup>1</sup> due to its large solvation free energy (439 kJ mol<sup>-1</sup>).<sup>2</sup> However, the discovery of a Fluorinase enzyme from *Streptomyces cattleya* has shown that aqueous fluoride can be converted to organic fluorine.<sup>3,4</sup> The actual enzymatic reaction involves nucleophilic attack at a saturated carbon centre bound to a positively charged sulfonium leaving group. This raises the intriguing question as to how this observation is reconciled with the magnitude of the fluoride ion solvation energy, which presumably must be overcome for nucleophilic attack to take place. To understand how such a reaction can occur under mild conditions, we here present electronic structure calculations of the nucleophilic attack at some model compounds by solvated fluoride.

We believe that central to this problem is the observation by us and others,<sup>5,6</sup> based on computations, that there can be a variable number of water molecules in the first solvation shell of solvated fluoride. This arises from the particularly large interaction (polarization and charge transfer) of the small  $F^-$  ion with these water molecules. These effects are non-additive, the polarization of individual water molecules being greater, the smaller the total number. For example, we previously<sup>5</sup> found that a structure with three water molecules in the first, and one in the second solvation shell, is more stable than one having four waters in the first solvation shell. In addition, different structures can occur having the same number of solvent molecules in the first solvation shell. For example, 16 water molecule clusters<sup>2</sup> with  $F^-$  have similar energies whether the anion is in the centre or at the surface. In the latter structure the surface fluoride should be more available for nucleophilic attack.

We have carried out electronic structure calculations on a number of model systems, using Gaussian,<sup>7</sup> to see if the exceptional solvation energetics of  $F^-$  do indeed lead to an energetically favourable nucleophilic attack. The reactants were chosen with the enzyme substrate, S-adenosyl-L-methionine (SAM) in mind, and are shown in Fig. 1. They involve sulfonium (I, II) and oxonium (III) leaving groups and do (I, III) or do not (II) have the potential to form hydrogen bonds. Due to the large interaction of the first solvation shell with  $F^-$ , a small cluster having only 4 water molecules was found to give a solvation enthalpy close to the experimental value, and only 33 kJ mol<sup>-1</sup> less

than a 16 molecule cluster.<sup>2</sup> We have thus modelled the nucleophilic attack of  $F^-$  solvated by 4 water molecules on the three substrates to give the corresponding organofluoride and dimethyl sulfide or dimethyl ether.

It has been found that density functional theory (DFT) calculations using the B3LYP functional in conjunction with a 6-31++G\*\* basis (B3LYP/6-31++G\*\*) gives a good description of the geometry of water clusters involving  $F^-$ .<sup>2</sup> However, to obtain solvation energies close to experimental values requires the use of a much higher level of theory (CCSD(T)), which is impracticable for the reaction we wish to study here. It is thus essential to identify any bias in the energetics of the reaction which might arise from the use of the B3LYP/6-31++G\*\* level of theory. To do this we have studied structure A ( $F^-(H_2O)_{16}$ ) of Zhan and Dixon,<sup>2</sup> which is predicted to lead to a solvation energy close to the experimental value. At our DFT level, the calculated binding energy of the fluoride ion in this cluster is overestimated by ~100 kJ mol<sup>-1</sup>. This would suggest that our level of theory does indeed bias the calculation, but in favour of the solvated ion. We have determined reactant and product minima, and transition states for a classical  $S_N2$  attack of  $F^-$  at the substitution centre (Fig. 2). For substrate I four water molecules were initially placed in the first solvation shell of  $F^-$ . However, two of these moved into the second solvation shell during the determination of the transition state and remained there for the calculation of the reactant and product. This solvent structure was maintained in the calculations for substrates II and III (Fig. 1).

The binding energy of the fluoride ion in the reactant structure of I (Fig. 1) is calculated to be 680 kJ mol<sup>-1</sup>, a value larger than that of  $F^-$  in the 16 water structure (517 kJ mol<sup>-1</sup>) at the same level of theory. Our calculation thus shows that in the small reactant complex having only four water molecules, the bulk solvation energy of  $F^-$  has been overcome by the interaction of  $F^-$  with the positively charged sulfur atom and the two remaining solvent hydrogen bonds. The hydrogen bond distances to the fluorine progressively increase as the reaction of all three substrates proceeds, and a covalent C–F bond forms (Table 1), in line with the considerable bond formation in the transition states (Fig. 2). Indeed, for the reaction of substrate I, in the transition state the

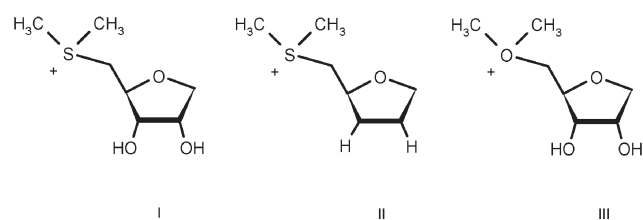
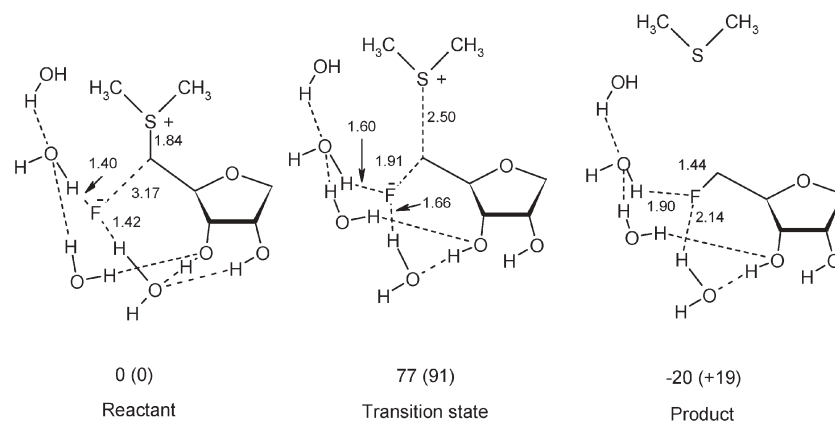


Fig. 1 Model substrates.

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**Fig. 2** The reactant, transition state and product structures (Å) for substrate **I**. The relative free energies and, in parentheses, enthalpies, at 298 K (kJ mol<sup>-1</sup>), are shown.

**Table 1** Structures (Å), charges (*e*) and free energies (kJ mol<sup>-1</sup>) for the reaction of solvated fluoride with substrates **I**, **II**, **III**

		<b>I</b> <sup>a</sup>	<b>II</b>	<b>III</b>
C–F bond length:	Reactant	3.17 (2.93)	2.95	2.94
	TS	1.91 (2.23)	1.91	2.03
	Product	1.45 (1.45)	1.41	1.45
Charge on F:	Reactant	-0.72 (-0.77)	-0.73	-0.72
	TS	-0.57 (-0.65)	-0.58	-0.62
	Product	-0.35 (-0.35)	-0.31	-0.35
Barrier to reaction		77 (172)	76	41
Reaction energy		-20 (26)	-66	-86

<sup>a</sup> Same side attack in brackets.

fluoride ion has lost 0.15*e* compared to its charge in the reactant. In this reaction the C–S bond has also lengthened considerably, from 1.84 to 2.50 Å and we find the barrier to reaction is not unduly high (77 kJ mol<sup>-1</sup>) and that overall the reaction is exothermic (by 20 kJ mol<sup>-1</sup>). Our calculations show that even using only a single configuration, entropic contributions (vibrational) are responsible for this exothermicity, the reaction being endothermic (by 19 kJ mol<sup>-1</sup>) considering only enthalpy changes. One particular entropic effect is that in the product the water molecules are held less rigidly (by covalent F) than in the reactant complex (by ionic F<sup>-</sup>), although additional entropy comes from breaking the C–S bond. For substrate **II**, which lacks hydrogen bonding groups, the barrier to reaction is similar although the reaction is more exothermic. For substrate **III**, which has a better leaving group, the barrier is now reduced and the transition state is earlier (Table 1).

For substrate **I**, we have also considered the attack of F<sup>-</sup> at the same side of the carbon atom as the leaving group. In this reactive configuration, the positive sulfur and negative fluorine are in close proximity and thus this minimum might be expected to be the favoured one. This alternative S<sub>N</sub>2 reaction in which the sulfur leaves and the fluoride attacks on the same side of the carbon atom has a high barrier to reaction (172 kJ mol<sup>-1</sup>), due to steric effects. The overall reaction is endothermic (Table 1) due to the closeness of the charged atoms in the reactant, although a bigger basis set (6-311++G\*\*) determined the reaction to be exothermic as we found for the initial S<sub>N</sub>2 reaction.

The aim of the calculations we have described is to shed light on the problem of how solvated F<sup>-</sup> can participate in nucleophilic

attack. We find that the charge on the organic moiety is critical both in stabilizing the fluoride ion as it becomes partially desolvated, and in giving a reactant conformation appropriate for nucleophilic attack. In addition, hydrogen bonding groups on the substrate, some distance from the centre of attack, have little effect on the barrier to reaction. However, substrates having different positively charged leaving groups can also undergo a similar reaction. In general the reaction should be entropically favoured so that the entropy increase on partially desolvating F<sup>-</sup> (as it becomes covalently bound) is maintained by solvation of a neutral product. Thus, although the high solvation energy of F<sup>-</sup> means that it is energetically unfavourable to completely desolvate it, nevertheless a reaction pathway, having a quite low barrier does indeed exist for a number of substrates.

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