Enhanced Transport of Fluoride Anion Effected using Protonated Sapphyrin as a Carrier

Jonathan L. Sessler,* Debra A. Ford, Michael J. Cyr and Hiroyuki Furuta

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

Sapphyrin, a pentapyrrole expanded porphyrin, acts as an efficient carrier for the transport of fluoride anion in a model three-phase H_2O–CH_2Cl_2–H_2O bulk liquid membrane system.

The binding and through-membrane transport of small anions plays an important role in many biological systems.[1] For instance, fluoride anion activation is important for a variety of enzymatic systems, including phosphatases, adenylate cyclase, and GTP-binding protein (G-protein).[2] In addition, mediated chloride anion transport is recognized as playing a crucial role in erythrocytes, where it serves to facilitate the excretion of CO_2 *via* a chloride–hydrogen carbonate exchange process.[3] It has also recently been implicated in the function of the so-called cystic fibrosis transmembrane conductance regulator protein, CFTR.[4] However, in spite of their obvious importance, mechanistic studies of such anion receptor interactions in nature have so far been limited. They have been hampered, at least in part, by the unavailability of suitable model systems for anion binding and transport. Although numerous elegant anion-binding receptors have been reported in recent years,[5] the number of synthetic systems capable of achieving both anion binding and transport remains limited at present.[6] In this communication, therefore, we report the through liquid membrane transport of fluoride anion effected using the protonated form (H_4Sap^+) of sapphyrin (H_3Sap, **1**), a highly lipophilic prophyrin-like 22 π electron macrocycle, as the carrier. To the best of our knowledge, such synthetic carrier-mediated fluoride transport is nearly without precedent in the anion recognition literature.[7]

Recently, we reported the solid state complexation of F^- by the diprotonated form (H_5Sap^{2+}) of sapphyrin **1**.[8] Specifically, from a single crystal X-ray analysis of the mixed F^-/PF_6^- salt, it was found that fluoride anion is encapsulated within the *ca.* 5.5 Å diameter core of the fully protonated macrocycle, being held there by five NH-to-F hydrogen bonds. This finding, and the apparent lipophilicity of this and other anion-containing sapphyrin salts,[9] led us to consider that this 'expanded porphyrin' could serve as a possible carrier for the through-membrane transport of F^-. As a test of this idea, we have explored F^- transport with H_5Sap^{2+} and H_4Sap^+ using a bulk liquid membrane system, Aq I–CH_2Cl_2–Aq II (Aq = aqueous), similar to that described earlier.[10,11]

The efficacy of F^- transport was first tested under con-

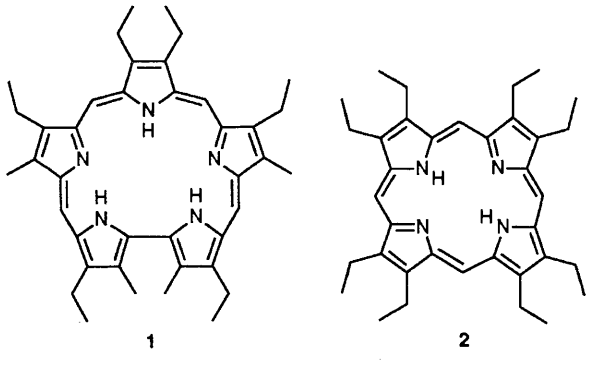


Table 1 Initial fluoride transport flux ϕ[a]

Expt.	pH(Aq I and Aq II)[b]	Sapphyrin **1** ϕ/ 10^{-8} mol h^{-1}	OEP **2** ϕ/ 10^{-8} mol h^{-1}	Control[c] ϕ/ 10^{-8} mol h^{-1}
1	3.0[d]	11.8	4.7	4.7
2	3.0[e]	17.6	0.8	0.1
3	5.0[f]	4.9	0.6	0.3
4	7.0[g]	9.5	0.3	0.1
5	7.0[h]	2.5	1.2	1.2
6	9.0[i]	10.7	0.6	0.3

[a] Transport experiments were performed in a manner similar to those reported in ref. 10. [NaF] = 0.25 mol dm^{-3}; [Carrier] = 1 mmol dm^{-3}. Initial transport flux (ϕ) were calculated from the linear region of concentration *vs.* time curve. Error is within ±10%. [b] Aq I containing NaF buffered at the specified pH; Aq II contained only buffer solution at the specified pH. [c] Transport experiments conducted under specified conditions in the absence of carrier. [d] Buffered at specified pH with trifluoroacetic acid–sodium trifluoroacetate solution. [e] Adjusted to specified pH with 0.1 mol dm^{-3} acetic acid–sodium acetate and a small amount of dilute HF. [f] Buffered at specified pH with 0.2 mol dm^{-3} acetic acid–sodium acetate solution. [g] Adjusted to specified pH with 1.5 mol dm^{-3} acetic acid–sodium acetate solution. [h] Buffered at specified pH with 0.2 mol dm^{-3} tris(hydroxymethyl)aminomethane–maleate solution. [i] Buffered at specified pH with 0.2 mol dm^{-3} glycine–NaOH solution.

ditions of an overall Aq I to Aq II proton gradiant (Aq I: pH 3, Aq II: pH 12).† Without an added carrier, slow uptake of F^- into Aq II by simple diffusion was observed (initial flux, $\phi = 4.0 \pm 0.4 \times 10^{-8}$ mol h^{-1}).‡ When sapphyrin (1.0 mmol dm^{-3}), however, was added to the central CH_2Cl_2 phase, F^- transport was enhanced strongly ($\phi = 86.0 \pm 8.6 \times 10^{-8}$ mol h^{-1}) (Fig. 1). On the other hand, no or little acceleration was observed when octaethylporphyrin (OEP, **2**), at the same concentration, was used as a 'control' carrier ($\phi = 4.0 \pm 0.4 \times 10^{-8}$ mol h^{-1}). As expected, a decrease in the pH of Aq II was observed during sapphyrin-mediated transport. This is consistent with F^- transport occurring *via* the so-called symport mechanism,[12] in which fluoride anions and protons are co-complexed and co-transported by sapphyrin (Scheme 1*A*).

In order to get a clearer picture of F^- binding and transport, we have carried out similar transport experiments in the absence of a proton gradient ($pH_{Aq\,I} = pH_{Aq\,II}$). Under the conditions of these experiments, which were carried out using several different buffer systems and at several different pH regimes, both F^- and a buffer counter anion were expected to be transported in a so-called antiport process (Scheme 1*B*).[12]

† The first and second pK_a values of diprotonated sapphyrin have been determined as being *ca.* 3.5 (Sap^{2+}/Sap^+) and 9.5 (Sap^+/Sap), respectively; see ref. 11.

‡ Initial flux values, ϕ, were calculated from the amount (μmol) of Cl^- and F^- transported per hour during the initial linear kinetic regime; see ref. 10.

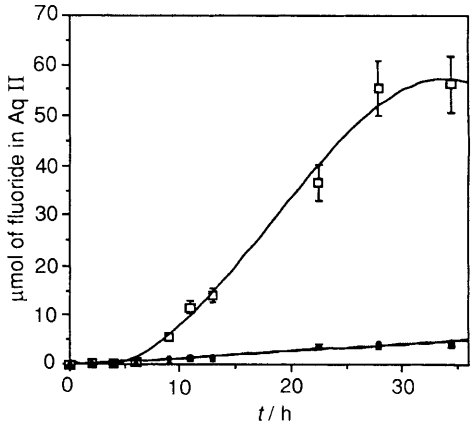
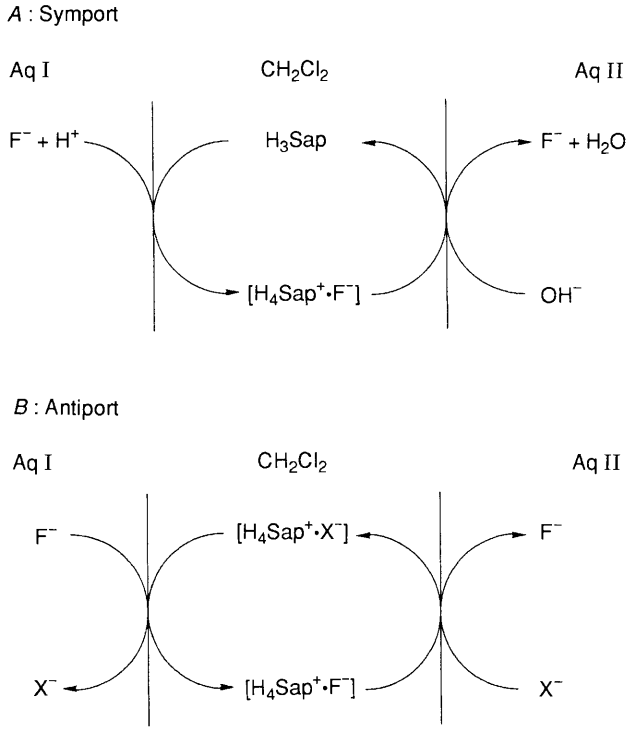


Fig. 1 Transport experiments were performed using a glass U-tube at 28 °C. *Conditions*: Aq I (1 cm^{-3}); 0.5 mol dm^{-3} HF, adjusted to pH 3.2 with NaOH. Membrane (10 cm^3); carrier: 1.0 mol dm^{-3} in CH_2Cl_2. Aq II (1 cm^3); NaOH (pH 12). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times using a fluoride combination electrode (Orion). In all cases, control experiments were performed in the absence of carrier. Error is within ±10%. □, sapphyrin **1**; ▲, OEP **2**; ●, control.



Scheme 1 Symport and antiport mechanisms; X = AcO^-, $CF_3CO_2^-$, $NH_2CH_2CO_2^-$ *etc*

Although counter anion antitransport was not specifically determined by the present experiments, the data from the sum total of these experiments (Table 1) are certainly consistent with this hypothesis: over the complete range of pH values investigated sapphyrin **1** was found to be an effective carrier for fluoride anion transport whilst its simple congener **2** was not. Interestingly, the latter system in general proved no more effective than 'pure' (carrier-free) CH_2Cl_2 in terms of enhancing the effective fluoride anion transport rate (Table 1). Presumably, this reflects the fact that protonated porphyrins (nitrogen-to-nitrogen core: size *ca* 4.0 Å[13]), protonated or otherwise, are too small for effective in-plane fluoride anion complexation, while, as noted above, diprotonated sapphyrin can and does bind F^- in the solid state.[8]

As might be expected, some dependence on the choice of buffer and pH is observed for the transport experiments summarized in Table 1. First, fluoride anion transport is enhanced, both for sapphyrin and the controls, when a more lipophilic buffer system is used to define the aqueous phase pH values. Secondly, as is consistent with the observed pK_a values for sapphyrin,† fluoride anion transport with this carrier was found to be enhanced at pH 3 (where H_5Sap^{2+} is the dominant species) and nearly independent of aqueous phase pH in the pH 5–9 regime (wherein H_4Sap^+ dominates among possible sapphyrin species). Taken together, these data provide further support for the proposed antiport mechanism (Scheme 1*B*) and confirm the efficacy of this particular 'expanded porphyrin' as a fluoride anion transport carrier.

Addition of chloride anion to the present transport system, under either symport or antiport conditions, caused a slight inhibition in the observed fluoride anion transport rates. Presumably, this reflects the effect of competitive chloride anion binding by sapphyrin and/or its protonated derivatives. At present, therefore, we are exploring the ability of sapphyrin and its protonated derivatives to function as a transport carrier agent for this and other small anions. In preliminary work§ we have found that chloride anion transport may be effected using monoprotonated sapphyrin, H_4Sap^+, as the carrier species§ whereas the corresponding diprotonated form, H_5Sap^{2+}, (only) acts as an efficient carrier for guanosine-5′-monophosphate dianion.[11] Full details of these and other transport-related studies will be reported in due course.

This work was supported by the Texas Advanced Research Program (grant no. 3658-016). J. L. S. also thanks the National Science Foundation (PYI 1986), the Camille and Henry Dreyfus Foundation (Teacher–Scholar 1988–1993), and the Sloan Foundation (Fellowship 1989–1991). D. A. F. thanks the United States Navy for the educational opportunity.

Received, 14th August 1991; Com. 1/04271H

§ For Cl^- transport at pH 7.0, an initial flux value, ϕ, of $48.0 \pm 0.5 \times 10^{-8}$ mol h^{-1} was obtained.

References

1 R. B. Gunn, in *Membrane Transport in Biology*, ed. G. Giebisch, D. C. Tosteson and H. H. Ussing, Springer-Verlag, Berlin, 1979, vol. II, p. 59.
2 J. Bigay, P. Deterre, C. Pfister and M. Chabre, *EMBO J.*, 1987, **6**, 2907.
3 R. B. Gennis, *Biomembranes. Molecular Structure and Function*, Springer-Verlag, New York, 1989, p. 270.
4 J. R. Riordan, C. E. Bear, J. M. Rommens, L. Tsui, E. F. Reyes, C. A. Ackerley, S. Sun, A. L. Naismith, T. T. Jensen, J. W. Hanrahan and N. Kartner, *Cell*, 1991, **64**, 681; M. J. Welsh, A. E. Smith, R. J. Gregory, D. P. Rich and M. P. Anderson, *Science*, 1991, **251**, 679; M. J. Welsh, A. E. Smith, R. C. Mulligan, D. W. Souza, S. Paul, S. Thompson, R. J. Gregory and M. P. Anderson, *Science*, 1991, **253**, 202; M. J. Welsh, A. E. Smith, P. Manavalan, M. P. Anderson, R. J. Gregory and D. P. Rich, *Science*, 1991, **253**, 205.
5 For overviews of anion binding receptors, see: L. F. Lindoy, *The Chemistry of Macrocyclic Ligands*, Cambridge University Press, Cambrige, 1989, ch. 5; E. Kimura, *Top. Curr. Chem.*, 1985, **128**, 113; E. Graf and J.-M. Lehn, *J. Am. Chem. Soc.*, 1976, **98**, 6403; E. Suet and H. Handel, *Tetrahedron lett.*, 1984, **25**, 645; B. Dietrich, J. Guilhem, J.-M. Lehn, C. Pascard and E. Sonveaux, *Helv. Chim. Acta*, 1984, **67**, 91. See also refs. 7*d*,*e*.
6 For examples of anion transport, see: B. Dietrich, T. M. Fyles, M. W. Hosseini, J.-M. Lehn and K. C. Kaye, *J. Chem. Soc., Chem. Commun.*, 1988, 691; J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89, and references cited therein; M. Huser, W. E. Morf, K. Fluri, K. Seiler, P. Schulthess and W. Simon, *Helv. Chim. Acta*, 1990, **73**, 1481.
7 For specific examples of fluoride binding and/or transport: (*a*) K. M. Kadish and R. K. Rhodes, *Inorg. Chem.*, 1983, **22**, 1090; (*b*) L. A. Bottomley and K. M. Kadish, *Inorg. Chem.*, 1981, **20**, 1348; (*c*) M. E. Jung and H. Xia, *Tetrahedron Lett.*, 1988, **29**, 297; (*d*) M. Newcomb and M. T. Blanda, *Tetrahedron Lett.*, 1988, **29**, 4261; (*e*) B. Dietrich, J.-M. Lehn, J. Guilhem and C. Pascard, *Tetrahedron Lett.*, 1989, **30**, 4125. See also ref. 8.
8 J. L. Sessler, M. J. Cyr, V. Lynch, E. McGhee and J. A. Ibers, *J. Am. Chem. Soc.*, 1990, **112**, 2811.
9 J. L. Sessler, M. J. Cyr and A. K. Burrell, *Synlett*, 1991, **3**, 127.
10 H. Furuta, K. Furuta and J. L. Sessler, *J. Am. Chem. Soc.*, 1991, **113**, 4707.
11 H. Furuta, M. J. Cyr and J. L. Sessler, *J. Am. Chem. Soc.*, 1991, **113**, 6677.
12 H. Tsukube, in *Liquid Membranes: Chemical Applications*, ed., T. Araki and H. Tsukube, CRC, Boca Raton, FL, 1990, p. 27.
13 W. R. Scheidt, in *The Porphyrins*, ed. K. M. Smith, Academic Press, New York, 1978, vol. III, p. 463.