The Coordination Chemistry of Fluorine in Fluorocarbons

Herbert Plenio*[a]

1. Introduction

Organofluorine compounds have received considerable interest in recent years due to their growing importance in the Life Sciences, especially for drug development and crop protection.[1] The inclusion of a fluorine atom in a bioactive compound can alter the physicochemical properties (bond strength, lipophilicity, conformation, electrostatic potential, dipole, pK_a) and the pharmacokinetic properties (tissue distribution, route and rate of metabolism) in distinct ways.[2] Fluorine often replaces a hydrogen atom, even though its properties are more closely related to those of oxygen. Both atoms (F and O) share a very high electronegativity, have comparable van der Waals radii, similar bond lengths to carbon and both possess lone pairs. Consequently the isosteric replacement of -OH by an -F group is a common strategy in medicinal chemistry.[3]

Despite the obvious similarities of oxygen and fluorine, one aspect concerning the interaction of organic fluorine with metals has escaped the attention of most chemists for a long time.

In 1970 the crystal structure of Rb$^+$-fluorocitrate revealed close F⋯M contacts. Consequently it was proposed by Glusker et al. that such interactions might be responsible for the high toxicity of fluorocitrate (fluoroacetate) due to an efficient inhibition of the active iron centre of aconitase.[4, 5] It took another thirteen years until a landmark publication, again by Glusker et al.,[6] reported on the results of a Cambridge Structural Database (CSD) search (Figure 1) looking for molecules which display exceptionally short F⋯M contacts.

A detailed analysis of all seven crystal structures known then led Glusker to finally conclude: "We believe that the C—F bond is capable of significant, if not prominent interactions with both alkaline metal cations and proton donors".[6] Consequently, for the solid state, there was little doubt left on the existence of F⋯M interactions. At this point it was, however, far from clear whether such contacts were simply the result of packing forces within the crystal or whether F⋯M contacts could have a significant stabilizing effect in metal complexes.

Several years ago we decided to initiate studies to firmly establish the existence of F⋯M interactions in solution and in the solid state, to work towards a detailed understanding of the coordination chemistry of fluorocarbons and to obtain a deeper knowledge of F⋯M interactions.[7]

2. Ligands that Coordinate through Organic Fluorine

In order to test the idea of fluorine as an efficient donor atom towards metal ions, one has to first decide which metal cations could be the most suitable candidates for such interactions and next what kind of ligands are best suited to allow coordination of metal ions via organic fluorine.

Due to the similarity between fluorine and oxygen it was reasonable to assume that fluorine atoms should be classified as Pearson-type hard donors[8] which preferentially coordinate correspondingly hard metal cations, that is, those from groups I and II. However, such metals are known to form reasonably stable complexes exclusively with carefully preorganized ligands of the crown ether and of the cryptand type as first shown by Petersen and Lehn.[9]

Consequently, we proceeded to synthesize macrocyclic ligands in which one or more oxygen donors are replaced by fluorine atoms. This was done by treating 1,3-bis(bromomethyl)-2-fluorbenzene with various crown ethers or polyethyleneglycols in the presence of suitable templating bases, resulting in the formation of the fluorocryptands and fluorocrown ethers, respectively, in good yields (Scheme 1).[10, 11, 25a]

To be able to understand the effect of fluorine coordination in more detail, we also synthesized closely related crown ethers and cryptands, in which one fluorine atom is substituted by one hydrogen (Scheme 2). Hydrogen is an unlikely candidate for metal coordination and, on comparing the ligating properties of closely related ligands, the coordination properties of fluorine can be elucidated.

We have studied the coordination chemistry of the ligands depicted in Schemes 1 and 2 in great detail.[12, 13] By doing so, we have identified a number of effects observed in the presence of fluorine that can be explained only by assuming direct, attractive F⋯M interactions. In the following sections, I wish to present evidence obtained from various experimental techniques that supports the idea of fluorine's being an important coordination partner of group I and II metal ions.

While convincing evidence in favour of such interactions is available, the situation is much less clear cut when it comes to the heavily debated question of whether organic fluorine can participate in hydrogen bonding.[14] This topic will be dealt with by Dunitz in another review in this issue[15] and is therefore not discussed here. Our own results confirm the conclu-

[a] Prof. Dr. H. Plenio
Institut für Anorganische und Physikalische Chemie, TU Darmstadt
Petersenstrasse 18, 64287 Darmstadt (Germany)
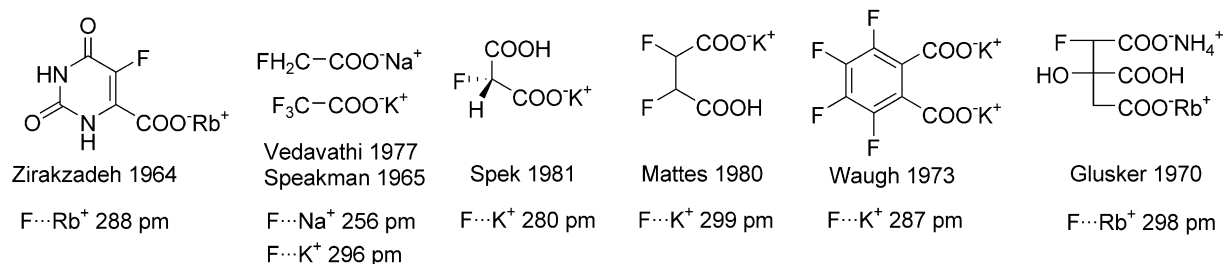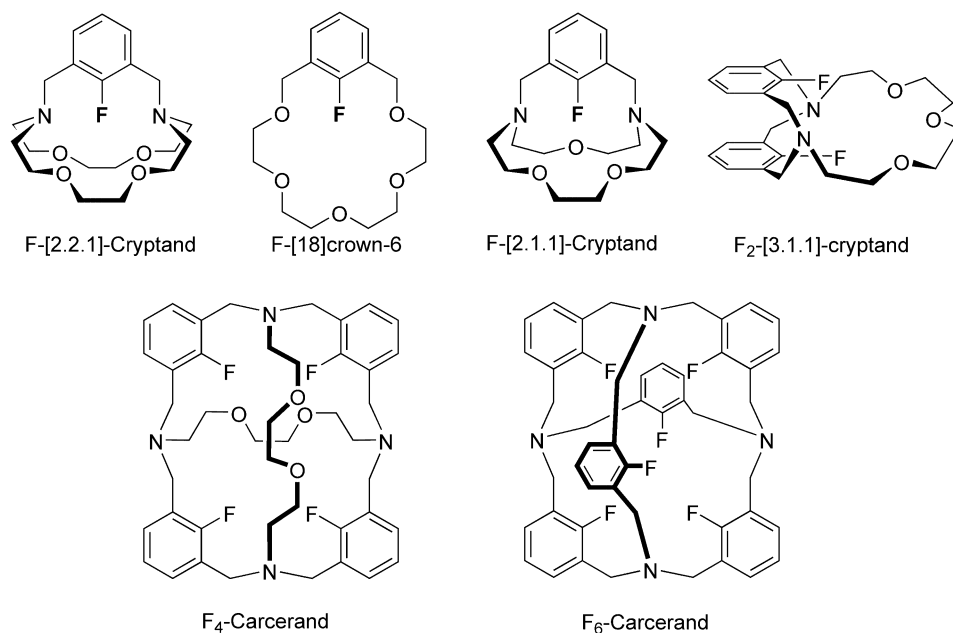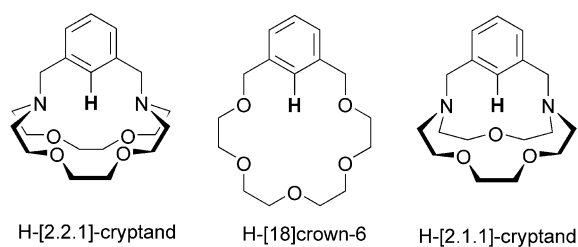Fax: (+49)6151-16-6040
E-mail: plenio@tu-darmstadt.de

Figure 1. *Alkali metal salts of fluorinated carboxylic acids.*

Zirakzadeh 1964   Vedavathi 1977 Speakman 1965   Spek 1981   Mattes 1980   Waugh 1973   Glusker 1970

$F\cdots Rb^+$ 288 pm $F\cdots Na^+$ 256 pm $F\cdots K^+$ 280 pm $F\cdots K^+$ 299 pm $F\cdots K^+$ 287 pm $F\cdots Rb^+$ 298 pm

   $F\cdots K^+$ 296 pm

F-[2.2.1]-Cryptand   F-[18]crown-6   F-[2.1.1]-Cryptand F_2-[3.1.1]-cryptand

F_4-Carcerand F_6-Carcerand

Scheme 1. *Representative examples of fluorinated cryptands and crown ethers.*

H-[2.2.1]-cryptand   H-[18]crown-6   H-[2.1.1]-cryptand

Scheme 2. *Representative examples of related flourine-free crown ethers and cryptands.*

3. Evidence in Favour of Attractive F···M Interactions

Based on the results of NMR spectroscopic studies, three independent sets of experimental results have been obtained all of which are indicative of fluorine acting as an efficient donor atom in the coordination sphere of hard metal ions.

NMR spectroscopy—^{19}F NMR

The incorporation of metal ions into the cavity of fluorine-containing ligands produces large downfield shifts in the ^{19}F NMR resonances of up to -28.5 ppm relative to the ^{19}F NMR signal of the free ligand. Typical shifts of the ^{19}F NMR signal are depicted in Figure 2 for metal complexes of the F-[2.2.1]cryptand. It is important to realize that such shifts are only qualitative signs of F···M interactions and that it is not possible to correlate the extent of the signal shift with the degree of F···M interaction.

sions drawn in there on the reluctance of organic fluorine to undergo hydrogen bonding.[16]

It is important to stress that the conclusions presented in the following paragraphs are based on results drawn from the analysis of a large number (> 100) of metal complexes. However, in order to be short and concise only a few carefully selected examples are presented here.
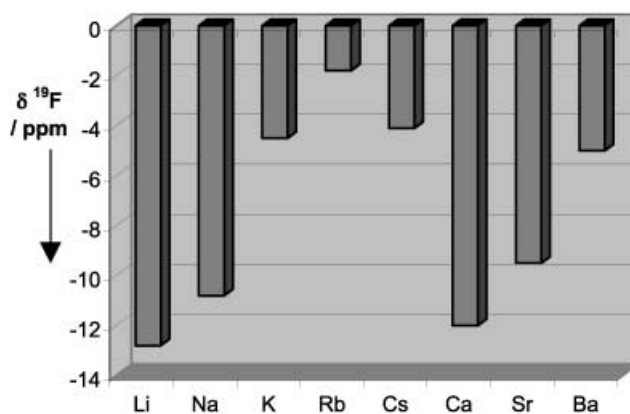

Figure 2. *Shifts of the ^{19}F NMR resonance upon complexation of metal cations relative to that of the reference ligand F-[2.2.1]cryptand.*

Based on the analysis of a large number of such complexes, we realized that at least two opposing effects appear to operate on the ^{19}F NMR signal: one that causes upfield shifts and another that results in downfield shifts. Consequently, in a few cases it is possible to observe shifts of the ^{19}F NMR resonance close to zero,[17] despite the fact that other analytical techniques are indicative of close F⋯M interactions.

NMR spectroscopy—^{13}C,^{19}F NMR coupling

The $^1J_{CF}$ coupling constant is a valuable diagnostic tool for probing F⋯M contacts because it appears to be directly correlated with the level of F⋯M interactions. Consequently, on complementarity of the size of the macrocyclic cavity and the size of the metal cation, strong F⋯M interactions result in decreased coupling constants relative to that of the free ligand. This can be understood in terms of competition for the lone pairs attached to the fluorine between the benzene ring and the metal cation coordinated to fluorine. The stronger the F⋯M interaction, the weaker the $+$M effect of fluorine and the less lone-pair electron density is present in the sp^2 C–F bond. As the lone pairs possess significant s character and because the Fermi contact term is important for spin–spin coupling, such a relationship makes sense.[18]

An instructive example to illustrate the dependency of the ^{13}C,^{19}F coupling constant on the interaction between fluorine and a metal ion would be the complexes of F-[18]crown-6 with various group I and II metal ions. The coupling constants of the ligand itself and of corresponding metal complexes are displayed in Figure 3.
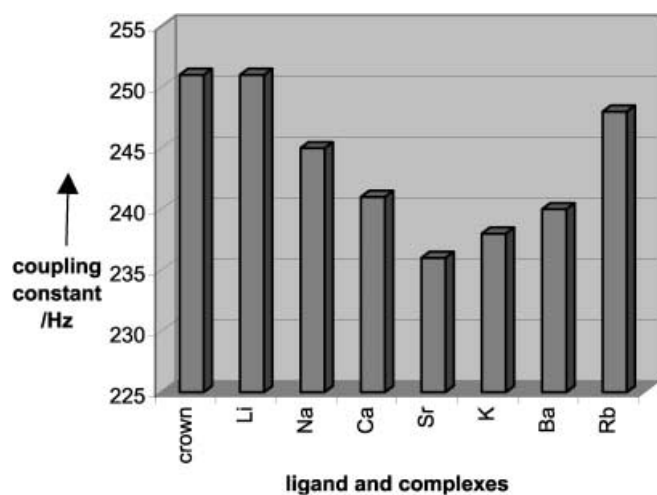

Figure 3. *^{1}J(^{13}C,^{19}F) coupling constants of F-[18]crown-6 and its metal complexes. Metal ions are sorted according to ionic radii.*

NMR spectroscopy—^{xx}M,^{19}F NMR coupling

Direct evidence for close interactions between NMR-active nuclei is the observation of spin–spin coupling between two nuclear spins. In the case of several complexes of metal ions with fluorinated ligands, spin–spin coupling has been ob-served. Known examples include complexes with ^{6,7}Li,[11] ^{107,109}Ag,[19] ^{133}Cs[20] and ^{205}Tl.[21]

Stability constants of metal complexes of fluorinated ligands.[11, 32]

Extensive studies by potentiometry, calorimetry, picrate extraction technique and NMR competition experiments demonstrate that the stability of the complexes of alkali and alkaline earth metal ions with partially fluorinated ligands is significantly higher than that of related complexes that have a hydrogen instead of the fluorine atom. To illustrate this, the stability constants for several metal complexes of F-[2.2.1]cryptand and H-[2.2.1]cryptand are listed in Table 1. For metal ions like Na$^+$,

Table 1. *Stability constants for metal complexes of F-[2.2.1]cryptand (log K_F) and H-[2.2.1]cryptand (log K_H) as determined by potentiometry.*

cation	log K_H	log K_F	Δ(log K)
Na$^+$	4.90	7.02	$+2.1$
K$^+$	5.56	6.71	$+1.1$
Rb$^+$	4.68	4.99	$+0.3$
Cs$^+$	4.76	4.70	$+0.1$
Ca^{2+}	2.15	4.36	$+2.2$
Sr^{2+}	4.44	6.55	$+2.1$
Ba^{2+}	5.94	7.63	$+1.7$

Ca^{2+} and Sr^{2+}, which are complementary in size to the F-[2.2.1]cryptand, the extra stabilization inferred by the fluorine donor can be higher than two orders of magnitude. In conclusion, there is unequivocal evidence in favour of attractive F⋯M interactions.

X-ray crystal structures

A more detailed insight into the nature of F⋯M interactions is provided by acquiring precise structural information on metal complexes with fluorinated ligands. Most important in this respect are the distances between fluorine and the respective metal cation, as well as the organization of the coordination sphere of the metal ion. Numerous crystal structures provide evidence for close F⋯M contacts.[7] The presentation here will be limited to a few representative examples. Two closely related complexes highlight the role of fluorine in the coordination sphere of lithium. In Figure 4[22] the crystal structures of Li$^+$·F-[2.1.1]cryptand and Li$^+$·H-[2.1.1]cryptand are shown. Chemically the only difference between those two complexes is the presence of fluorine in the former and its absence in the latter complex. This seemingly small difference, however, has drastic structural consequences on the coordination sphere of the metal cation. With the fluorinated ligand, Li$^+$ is coordinated in a tetrahedral FO$_3$ environment within the F-[2.1.1]cryptand. With the fluorine-free ligand, an unusual trigonal-planar O$_3$ coordination around Li$^+$ is observed, with an additional water molecule completing the coordination sphere of Li$^+$.[11] Evidently, in the H-[2.1.1]cryptand, a donor atom (fluorine!) is missing that is present in the F-[2.1.1]cryptand.
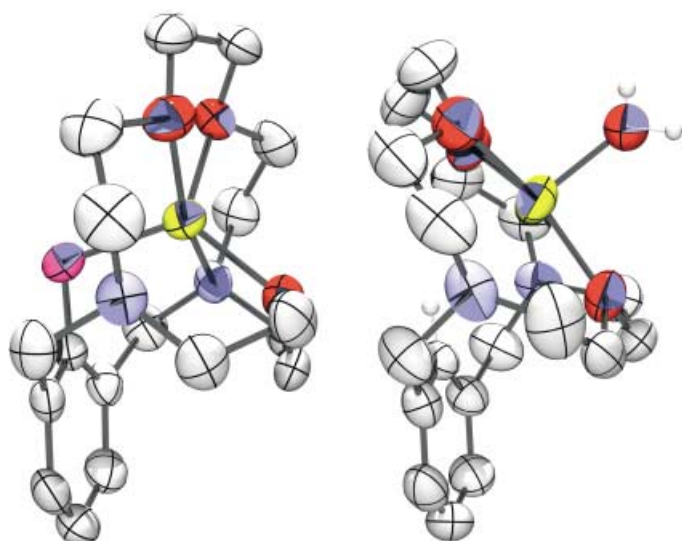
Figure 4. *Crystal structures of Li$^+$·F-[2.1.1]cryptand (left) and Li$^+$·H-[2.1.1]crypt-and (right) (Li yellow, O red, N blue, F pink). Coordination sphere of Li$^+$ in the F-[2.1.1]cryptand: F···Li$^+$ 203.5 pm, O···Li$^+$ 193.6, 201.3, 202.1 pm and in the H-[2.1.1]cryptand: O···Li$^+$ 200.5, 215.0, 210.2 pm, H$_2$O···Li$^+$ 192.8 pm.*

In order gain a better insight on the range of metal–ligand distances a few examples of F···Na$^+$ and O···Na$^+$ bond lengths observed in complexes of fluorinated macrocycles are given in Table 2. To avoid misunderstanding the large variations of metal–ligand distances, one should keep in mind that this is

Table 2. *Na$^+$–ligand bond lengths in complexes of fluorinated macrocycles.*[7]

Fluorinated macrocycle	F···Na$^+$ [pm]	O···Na$^+$ [pm]
F$_2$-[3.1.1]cryptand	229.8, 235.7	228.5, 242.0, 243.8, 247.6
FH-[3.1.1]cryptand	236.0	234.8, 239.3, 240.3, 240.6, 285.7
F-[18]crown-6	237.4	230.2, 240.2, 257.4
F-benzo-[2.1.1]cryptand	246.8	230.1, 234.6, 260.0
F-[2.1.1]cryptand	257.1	224.9, 233.0, 233.9, 243.3
F-[2.2.1]cryptand	267.1	242.6, 243.9, 246.2, 247.6, 248.6

typical in coordination chemistry in general, and even more so for group I metal ion complexes, which are all characterized by extremely shallow potential wells for metal–ligand interactions.

The coordination of metal ions by fluorine-ontaining ligands can be extended to complexes in which two (ligand displayed in Scheme 1),[23] four (F$_4$-carcerand in Scheme 1)[24, 20] or even six (F$_6$-carcerand in Scheme 1) fluorine atoms coordinate metal ions. The coordination chemistry of the F$_6$-carcerand, which allows the homoleptic coordination of metal ions by fluorine atoms, was studied in great detail by the Takemura group. Many hard metal cations (Na$^+$, K$^+$, Cs$^+$, La^{3+}, etc.) are coordinated exclusively through fluorine donors within the macrocyclic cavity.[25] It was further noted by Takemura et al. that in some crystal structures a small lengthening of the C–F bond is

observed.[26] Other more recent examples of F···M interactions show that, even in less preorganized ligands, organic fluorine can bind to group I cations.[27]

Cambridge structural database

Should an attractive interaction of the F···M type exist, statistical analysis of the distance distribution of all crystal structures involving organic fluorine and suitable metal cations should reveal a maximum in the number of F···M contacts at a certain fluorine–metal distance. This distance should correspond to the optimum interaction distance between two such atoms. However, as is typical for coordination chemistry, especially that of the group I metal ions, the potential surface for such an interaction will be rather shallow since the energy of interaction is fairly weak.[28] In Figure 5, a histogram with the result of the CSD search[29] for F···Na$^+$ contacts is displayed.[30, 31]

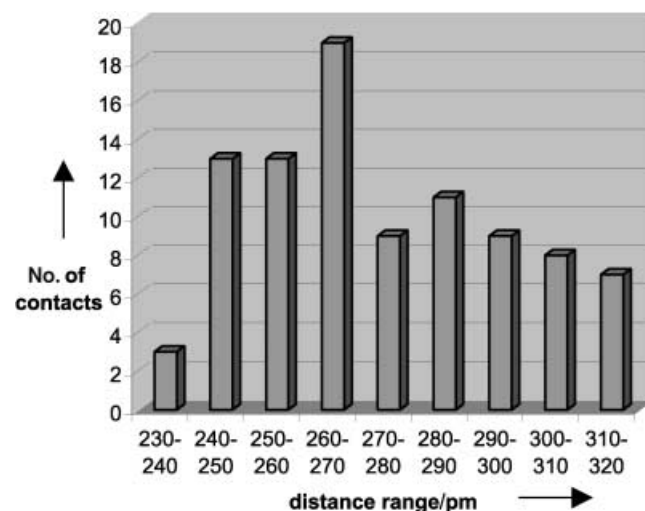**Figure 5.** *Histogram of F···Na$^+$ contacts from the CSD search.*

There can be little doubt about the maximum number of F···Na$^+$ contacts in the range of 250–270 pm, which gradually tails off towards longer distances. This observation further supports our view of attractive F···M interactions.

Calculations

In collaboration with Martin Kaupp, we determined the binding energy of a F···Li$^+$ interaction in the gas phase using DFT calculations.[32] For the model complexes Li(OMe$_2$)$_4$ and Li-(OMe$_2$)$_3$(C$_6$H$_5$F)$_1$, the binding energy of F···Li$^+$ was found to be about 64% of the O···Li$^+$ interaction, the F···Li$^+$ bond length was calculated to be 198.0 pm. It is interesting to note that in complexes of group I metal cations with fluorobenzene in the gas phase (according to DFT calculations at the B3LYP6-31G* level of theory), the lighter alkali metal ions prefer to coordinate to the π-face, while for the heavier ones an equilibrium between π-face and F···M coordination occurs.[33, 34]
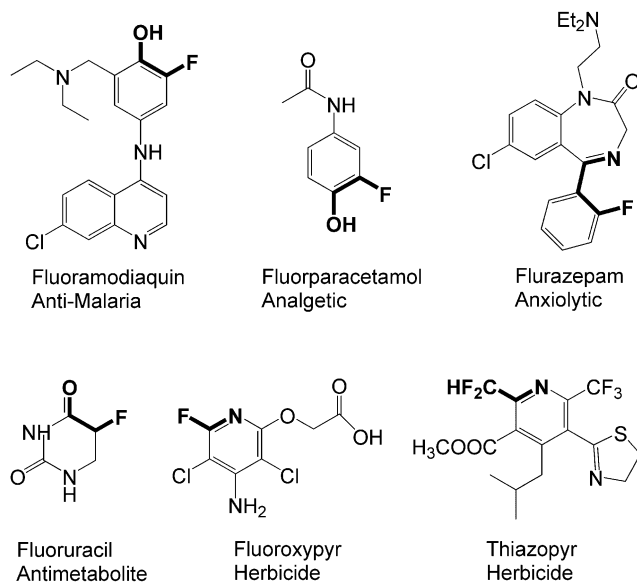
4. Where Else are F⋯M Contacts Found?

Interactions of fluorine with metals are not limited to the co-ordination chemistry of macrocyclic ligands, but occur more often. Some examples are summarized below:

a) In several CVD processes involving metal salts of fluorinated alkoxides, deposition of metal fluorides has been observed and shown to be due to significant F⋯M contacts in the alkoxides.[35]

b) CF activation by transition metal compounds is most likely preceded by coordination of metal ions to fluorine.[36]

c) In cationic catalysts of the type Cp_2ZrR^+, which are used in the Ziegler–Natta polymerization of α-olefins, the interaction of perfluorinated counter anions through fluorine is often observed. This interaction is postulated to be of significance for the control of catalyst reactivity through such hemilabile ligands.[37]

5. F⋯M Coordination in the Life Sciences?

This question could be of relevance in the future, since the use of fluorinated molecules in the Life Sciences is increasing and because there are several metals (Na^+, K^+, Mg^{2+}, Ca^{2+} and Zn^{2+}) that are highly abundant in living organisms and participate in numerous biological functions.[38] Based on our experience, we have selected a number of fluorine-containing compounds that are potential candidates as chelating ligands with fluorine participation (Scheme 3). There are good chances for such interaction to be of significance in biochemistry.[39]

Scheme 3. *Potential metal-ligating fluorinated drugs and herbicides.*

Fluoramodiaquin
Anti-Malaria

Fluorparacetamol
Analgetic

Flurazepam
Anxiolytic

Fluroruracil
Antimetabolite

Fluoroxypyr
Herbicide

Thiazopyr
Herbicide

Conclusion

It is my opinion that the data presented in the present Mini-review convincingly demonstrate that organic fluorine can be regarded as an efficient donor atom in the coordination chemistry of alkali and alkaline earth metal ions. It remains to be shown whether this interaction is strong enough to influence the biochemistry of bioactive, fluorinated compounds.

[1] T. Hiyama, *Organofluorine Compounds: Chemistry Applications*, Springer, Berlin, **2000**.

[2] B. K. Park, N. R. Kitteringham, P. M. O'Neill, *Ann. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443.

[3] a) R. Filler in *Organofluorine Compounds in Medicinal Chemistry* (Ed.: R. Filler), Elsevier, Amsterdam, **1993**, p. 1; b) "Biomedical Frontiers of Fluorine Chemistry" K. L. Kirk, R. Filler, *ACS Symp. Ser.* **1996**, *232*, 1; c) B. K. Park, N. R. Kitteringham, *Drug Metab. Rev.* **1994**, *26*, 605.

[4] H. L. Carrell, J. P. Glusker, J. J. Villafranca, A. S. Mildvan, R. J. Dummel, E. Kun, *Science* **1970**, *170*, 1412.

[5] A. Karipides, C. Miller, *J. Am. Chem. Soc.* **1984**, *106*, 1494.

[6] P. Murray-Rust, I. P. William, C. Stallings, C. T. Monti, R. K. Preston, J. P. Glusker, *J. Am. Chem. Soc.* **1983**, *105*, 3206.

[7] H. Plenio, *Chem. Rev.* **1997**, *97*, 3363.

[8] *Chemical Hardness, Structure and Bonding, Vol. 80* (Ed.: K. D. Sen), Springer, Berlin, **1993**.

[9] B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, **1993**.

[10] H. Plenio, R. Diodone, *Angew. Chemie.* **1994**, *106*, 2267; *Angew. Chem. Int. Ed.* **1994**, *33*, 2175.

[11] H. Plenio, R. Diodone, *J. Am. Chem. Soc.* **1996**, *118*, 356.

[12] H. Plenio, R. Diodone, *Chem. Ber.* **1997**, *130*, 963.

[13] a) H. Plenio, D. Burth, *J. Chem. Soc. Chem. Commun.* **1994**, 2297; b) H. Plenio, R. Diodone, *Z. Naturforsch.* **1995**, *50b*, 1075; c) H. Plenio, *Inorg. Chem.* **1994**, *33*, 6123.

[14] J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89.

[15] J. D. Dunitz, *ChemBioChem* **2004**, *5*, ■■.

[16] H. Plenio, R. Diodone, *Chem. Ber.* **1997**, *130*, 633.

[17] We believe that apart from coordination of the metal to fluorine, the orientation of the oxyethylene chains and that of the metal ion relative to the fluorine atom influence the ¹⁹F NMR shift.

[18] S. Berger, S. Braun, H.-O. Kalinowski, *NMR-Spektroskopie von Nichtmetallen*, ¹⁹F *NMR-Spektroskopie* Thieme, Stuttgart, **1994**

[19] H. Plenio, R. Diodone, *Chem. Ber.* **1996**, *129*, 1211.

[20] H. Takemura, N. Kon, M. Kotoku, S. Nakashima, K. Otsuka, M. Yasutake, T. Shinmyozu, T. Inazu, *J. Org. Chem.* **2001**, *66*, 2778.

[21] W. A. W. A. Bakar, J. L. Davidson, W. E. Lindsell, K. J. McCullough, K. W. Muir, *J. Chem. Soc. Dalton Trans.* **1989**, 991.

[22] Structural drawings were produced by using ORTEP-3, L. J. Farugia, University of Glasgow and POVRAY V3.5.

[23] H. Plenio, J. Hermann, R. Diodone, *Inorg. Chem.* **1997**, *36*, 5722.

[24] H. Plenio, R. Diodone, D. Badura, *Angew. Chem.* **1997**, *109*, 130; *Angew. Chem. Int. Ed.* **1997**, *36*, 156.

[25] a) H. Takemura, S. Nakashima, N. Kon, M. Yasutake, T. Shinmyozu, T. Inazu, *J. Am. Chem. Soc.* **2001**, *123*, 9293; b) H. Takemura, N. Kon, M. Yasutake, H. Kariyazono, T. Shinmyozou, T. Inazu, *Angew. Chem.* **1999**, *111*, 1012; *Angew. Chem. Int. Ed.* **1999**, *38*, 959.

[26] H. Takemura, *J. Syn. Org. Chem. Jpn.* **2002**, *60*, 963.

[27] Y. Habata, T. Saeki, S. Akabori, X. X. Zhang, J. S. Bradshaw, *Chem. Commun.* **2000**, 1469.

[28] B. P. Hay, J. R. Rustad, *J. Am. Chem. Soc.* **1994**, *116*, 6316.

[29] Cambridge Structural Database, Version November 22, 2002. F. H. Allen, W. D. S. Motherwell, *Acta Crystallogr.* **2002**, *B58*, 407.

[30] This metal was chosen because the number of known F⋯M$^+$ contacts (total number 79) is by far the largest among the group I and II metal ions.

[31] The CSD reference codes of the structures are as follows: BUXTAP, CUBYED, DENZAX, DOLJUJ; FPYRVH, HAGYAP, HAGYIX, HAGYOD, JIWVIU, NAVVAH, NEHCEI, NIQJAY, RAWXOC, REJBAJ, REJBEN, REZGEI, RUVFET, VOVDOZ, YOXTUA01, ZAQZII, ZAWMEP, ZOHYAW, ZOHYEA, ZUVQIQ, ZUVQOW.

[32] H. J. Buschmann, J. Hermann, M. Kaupp, H. Plenio, *Chem. Eur. J.* **1999**, *5*, 2566.

[33] R. Amunugama, M. T. Rodgers, *J. Phys. Chem. A* **2002**, *106*, 9092.

[34] E. S. Meadows, S. L. de Wall, L. J. Barbour, G. W. Gokel, *J. Am. Chem. Soc.* **2001**, *123*, 3092.

[35] J. A. Samuels, E. B. Lobkovsky, W. Streib, K. Folting, J. C. Huffman, J. W. Zwanziger, K. G. Caulton, *J. Am. Chem. Soc.* **1993**, *115*, 5093.

[36] a) J. Burdeniuc, B. Jedlicka, R. H. Crabtree, *Chem. Ber.* **1997**, *130*, 145; b) T. G. Richmond, *Angew. Chem.* **2000**, *112*, 3378; *Angew. Chem. Int. Ed.* **2000**, *39*, 3241.

[37] a) N. Kleigrewe, T. Brackemeyer, G. Kehr, R. Fröhlich, G. Erker, *Organometallics* **2001**, *20*, 1952; b) X. Yang, C. L. Stern, T. J. Marks, *Organometallics* **1991**, *10*, 840.

[38] J. J. R. Frausto da Silva, R. J. P. Williams, *The Biological Chemistry of the Elements*, Clarendon, Oxford, **2001**.

[39] H. Weychardt, H. Plenio, unpublished results.