^{19}F NMR Indicator for Protons and Metal Ions with Direct Fluorine–Metal Interactions

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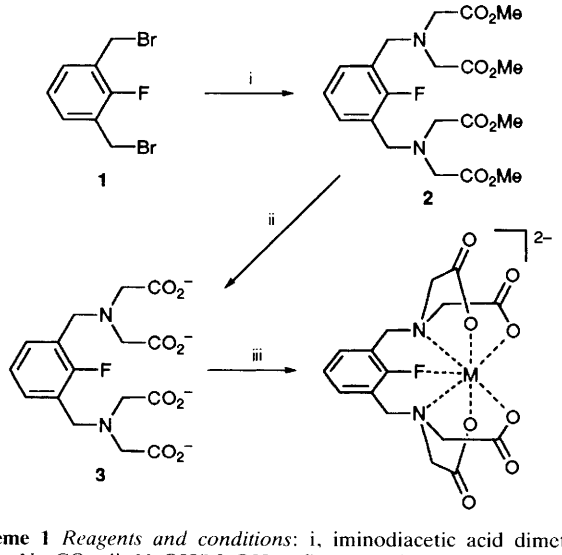
A ^{19}F NMR indicator for protons and metal ions, 1-fluoro-2,6-bis(methylene-iminodiacetate)benzene is prepared which experiences large shifts of the ^{19}F NMR resonances upon protonation or complexation of metal ions, probably owing to metal–fluorine σ-donor bonds.

Donor atoms such as nitrogen, oxygen, sulfur and phosphorus are essential for the binding of metal ions in crown ethers, cryptands, cyclams and numerous other chelating ligands such as edta, cdta or nta.[1] Even though fluorine is known to bind to metal ions in the solid state[2] and in solution,[3] it is hardly ever used as an active donor atom in the complexation of metal ions.[4] This is all the more surprising since fluorine is one of the most useful NMR nuclei,[5] being ideally suited for sensor applications due to its high sensitivity, large signal dispersion and lack of a natural background.[6]

We were therefore interested in synthesizing a relative of edta[7] which has a carbon–fluorine bond that is directed towards the site of potential metal complexation. It was expected that once metal ions were coordinated, a metal–fluorine σ-donor bond would form and give rise to large shifts of the ^{19}F NMR resonances.

The synthesis of such a ligand was achieved in the reaction of 1-fluoro-2,6-bis-(bromomethyl)benzene **1** with iminodiacetic acid dimethyl ester in acetonitrile, followed by cleavage of the ester **2** with NaOH in MeOH. This two-step procedure affords the tetrasodium salt of 1-fluoro-2,6-bis-(methylene-iminodiacetate)benzene (fxdta–Na_4) **3** in 61% overall yield (Scheme 1).†

The ^{19}F NMR resonance of **3** is highly sensitive to changes of proton concentration in the pH region of 6.0–11.0, with the shifts varying between −36.3 and −44.4 ($\Delta\delta$ = −8.1 ppm). This strong pH-dependency of the ^{19}F NMR signals makes **3** an interesting candidate for the determination of pH values by NMR spectroscopy. We have therefore potentiometrically determined the pK values of **3** (pK_2 2.81, pK_3 7.97, pK_4 9.24). Since the useful range for pH determination is centred around the pK value of the respective basic centre, it is quite advantageous that **3** has two basic nitrogen atoms close to fluorine (Fig. 1).



Scheme 1 *Reagents and conditions*: i, iminodiacetic acid dimethyl ester, Na_2CO_3; ii, NaOH/MeOH, reflux 4 h; iii, M^{2+} (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}). The same sequence was used for the nonfluorinated analogue **3**(H).

To evaluate the effect of metal coordination, a tenfold excess of metal salt was added to solutions containing 1 mg of **3** in 0.5 ml of D_2O. Large shifts of the ^{19}F NMR resonances are observed upon complexation of metal ions such as Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Tl^+ (+δ 4.8) and Zn^{2+} (+δ 4.4). The ^{19}F NMR titration curves of **3** with different alkaline earth metal ions are plotted in Fig. 2 (internal reference $NaCF_3SO_3$). From the viewpoint of charge density, it is surprising that the least hard ion, Ba^{2+}, produces the largest shift of the NMR resonances. We ascribe this to a σ-donor bond of fluorine to the largest ion among the alkaline earth metals.‡ This feature makes ligand **3** unique among other ligands which have been used for the detection of metal ions.[8] Ba^{2+}, Sr^{2+} and Ca^{2+} form 1 : 1 complexes as evidenced by the negligible shifts of the ^{19}F NMR resonances upon addition of metal salt beyond a 1 : 1 stoichiometry. In the case of Mg^{2+}, a bismetallic complex is formed.§ However, with a view to the strong pH dependency of the NMR shifts, it is essential to ensure a constant pH value during the determination of metal ion concentration.

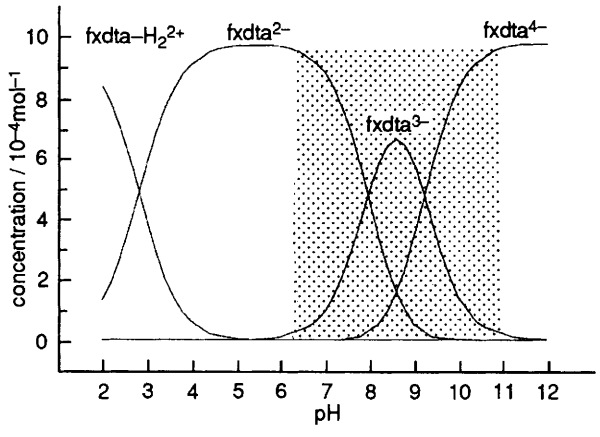


Fig. 1 Distribution curves of the protonated forms of fxdta depending on the pH value. The useful range (<95% saturation) for pH determination is shaded. fxdta–H_2^{2+} represents H_4fxdta–H_2^{2+}, H_3fxdta–H_2^{2+}, H_2fxdta–H_2^{2+} and Hfxdta–H_2^{2+}.

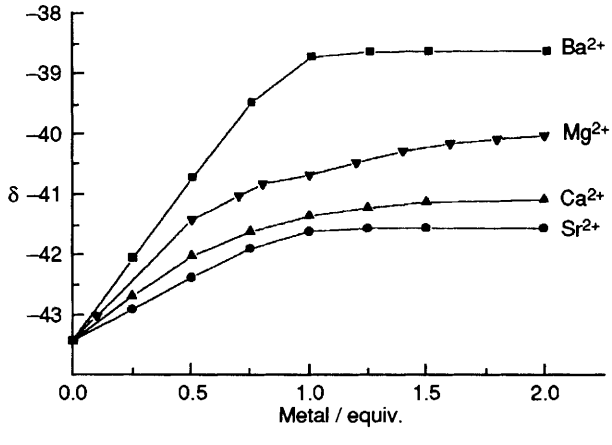


Fig. 2 ^{19}F NMR titration of fxdta–Na_4 with alkaline earth metal ions in H_2O–D_2O

To determine the useful concentration range for such investigations, we have potentiometrically determined the complex stability of **3** with Ca^{2+}, Sr^{2+} and Ba^{2+}. Evaluation of the titration curves using TITFIT[9] gives the following stability constants: pK(Ca^{2+}) 4.52, pK(Sr^{2+}) 4.21, pK(Ba^{2+}) 4.02. Very much in contrast to other edta derivatives and edta itself, Ba^{2+} has almost the same stability constant as Ca^{2+}. This is caused by the large bite imposed through 1,3-substitution of the chelating atoms linked to the aromatic ring.

Furthermore, it was important to find out whether fluorine–cation contacts have a stabilizing effect on metal complexes, or if the higher steric bulk of the fluorine, as compared to hydrogen, decrease complex stability. We therefore synthesized **3**(H), the nonfluorinated analogue of **3** using the same procedure as for **3**. A competition experiment was carried out in 0.004 N NaOH with equimolar amounts of **3** and **3**(H), which were titrated with Ba^{2+}. Since the ^{1}H NMR resonances are overlapping, the ratio of the complexes of **3** and **3**(H) with Ba^{2+} had to be determined indirectly *via* ^{19}F NMR. It is evident from these experiments that the fluorine-containing ligand **3** forms slightly more stable complexes with barium salts than does **3**(H). This can only be ascribed to a stabilizing effect of a metal–fluorine bond, which is strong enough to compensate for the adverse steric effects of fluorine.

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Footnotes

† All new compounds gave satisfactory spectroscopic and analytical data in accordance with assigned structures. Data are quoted for a selection of the compounds. For **2**: ^{1}H NMR (200 MHz; $CDCl_3$) 3.56 (s, 8 H), 3.69 (s, 12 H), 3.96 (4 H), 7.09 (t, J 7.6 Hz, 1 H), 7.38 (t, J 7.3 Hz, 2 H); ^{13}C NMR (50.3 MHz; $CDCl_3$) 50.87 (d, $^3J_{CF}$ 3.3 Hz), 51.50, 54.33, 123.96 (d, J_{CF} 4.0 Hz), 124.74 (d, $^2J_{CF}$ 20 Hz), 130.49 (d, J_{CF} 4.7 Hz), 159.90 (d, $^1J_{CF}$ 247 Hz), 171.48. ^{19}F NMR ($CDCl_3$, $CFCl_3$) −124.28.

For **3** ^{1}H NMR (200 MHz; D_2O, TSP): 3.01 (s, 8 H), 3.70 (s, 4 H), 7.18 (t, J 7.3 Hz, 1 H), 7.35 (t, J 7.2 Hz, 2 H). ^{13}C NMR (50.3 MHz; D_2O, TSP): 54.00, 60.90, 126.55 (d, $^2J_{CF}$ 17 Hz), 126.60 (d, J_{CF} 3.4 Hz), 135.07 (d, J_{CF} 5.1 Hz), 163.37 (d, $^1J_{CF}$ 242 Hz), 182.12. ^{19}F, (188 MHz; D_2O, CF_3SO_3Na) −43.4.

‡ No coupling of an alkaline earth metal ion to fluorine was observed. To the best of our knowledge no such couplings have been described in the literature.

§ The ^{19}F NMR resonances observed for the fxdta–Mg^{2+} complex are very broad $\nu_{1/2} > 200$ Hz, 188 MHz, 293 K).

References

1 *Comprehensive Coordination Chemistry*, ed. G. Wilkinson, R. D. Gillard and J. A. McCleverty, Pergamon, Oxford, 1987.
2 P. Murray-Rust, W. C. Stallings, C. T. Monti, R. K. Preston and J. P. Glusker, *J. Am. Chem. Soc.*, 1983, **105**, 3206 and references therein.
3 J. A. Samuels, E. B. Lobkovsky, W. E. Streib, K. Folting, J. C. Huffman, J. W. Zwanziger and K. G. Caulton, *J. Am. Chem. Soc.*, 1993, **115**, 5093.
4 A. S. F. Boyd, J. L. Davidson, C. H. McIntosh, P. C. Leverd, E. Lindsell and N. F. Simpson, *J. Chem. Soc., Dalton Trans.*, 1992, 2531; H. W. Roesky, M. Sotoodeh and M. Noltemeyer, *Angew. Chem.*, 1992, **104**, 869; *Angew. Chem., Int. Ed. Engl.*, 1992, **21**, 864.
5 *Multinuclear NMR Spectroscopy*, ed. J. Mason, Plenum, New York, 1987; S. Berger, S. Braun and H. O. Kalinowski, *NMR-Spektroskopie von Nichtmetallen*, vol. 4, *^{19}F-NMR Spektroskopie*, Thieme Verlag, Stuttgart, 1994.
6 M. J. W. Prior, R. J. Maxwell and J. R. Griffiths, *In Vivo Magn. Reson. Spec. III; NMR Basic Principles and Progress*, Springer Verlag, Berlin, 1992, vol. 28, p. 102.
7 H. Plenio, D. Burth and P. Gockel, *Chem. Ber.*, 1993, **126**, 2585.
8 M. Ochsner-Bruderer and T. Fleck, *Nachr. Chem. Tech. Lab.*, 1993, **41**, 997; G. A. Smith, P. G. Morris, T. R. Hesketh and J. C. Metcalfe, *Biochim. Biophys. Acta*, 1986, **889**, 72; L. A. Levy, E. Murphy, B. Raju and R. E. London, *Biochem.*, 1988, **27**, 4041; G. A. Smith, H. L. Kirschenlohr, J. C. Metcalfe and S. D. Clarke, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1205; G. A. Smith, R. T. Hesketh, J. C. Metcalfe, J. Feeney and P. G. Morris, *Proc. Natl. Acad. Sci. USA*, 1983, **80**, 7178.
9 A. Zuberbühler and T. A. Kaden, *Talanta*, 1982, **29**, 201.