A Fluorine-Containing Cryptand for the Complexation of Anions and the Utility of ^{19}F NMR Spectroscopy for the Determination of Host–Guest Association

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Z. Naturforsch. **50b**, 1075–1078 (1995); received January 20, 1995

Macrocycles, ^{19}F NMR Spectra, Fluorine, Anion Complexation

The first fluorine-containing cryptand $\text{F}_3\text{-TREN}$ **4** for the complexation of anions was prepared in the 3+2-condensation reaction of 2-fluoro-1,3-phthalaldehyde **3** with tris(2-aminoethyl)amine and subsequent reduction with NaBH_4 . Upon incorporation of anionic guests $4 \cdot 6\text{HClO}_4$ experiences shifts of its ^{19}F NMR resonances and thus demonstrates the advantages of studying host–guest association by ^{19}F NMR spectroscopy.

Introduction

We have recently described the first examples of fluorine-containing macrocycles [1] and a fluorinated relative of EDTA [2], which can form stable complexes with alkali and alkaline earth metal ions [3]. Due to the ability of covalently bonded fluorine to form σ -donor bonds with metal ions, the ^{19}F NMR resonances of these ligands experience large shifts of the NMR signals (relative to the free ligand) upon complexation of cations within the macrocycle. These NMR effects can be used to detect such metal ions by ^{19}F NMR spectroscopy and to monitor complexation reactions.

Inclusion and recognition of molecules or ions in the cavity of host molecules is one of the central topics of supramolecular chemistry [4]. To study such processes and to determine association equilibria especially of weak aggregates, NMR spectroscopy is an extremely useful tool [5]. The accuracy of such investigations crucially depends on two properties of the observed nucleus: intrinsic sensitivity and signal dispersion. However, ^1H and ^{13}C NMR which for obvious reasons have been used in most binding studies, each possess only one of the two desired properties.

Since the ^{19}F nucleus displays both a high sensitivity as well as a large signal dispersion in the NMR experiment [6], it was of interest to demonstrate that the study of association processes by ^{19}F NMR spectroscopy holds several advantages.

We became motivated therefore to synthesize fluorine-containing macrocycles which can incorporate anions into the macrocyclic cavity [7] and to find out whether such compounds experience substantial shifts of the ^{19}F NMR signals, even though a binding interaction between fluorine and the anion obviously is not possible.

Experimental

Experimentals were carried out under a nitrogen atmosphere. Solvents were purified and dried by standard methods. Starting materials were commercially available. NMR spectra were recorded at 300 K with a Bruker AC 200 F (^1H NMR 200 MHz, ^{13}C NMR 50 MHz) or a Varian Unity 300 (^1H NMR 300 MHz, ^{13}C NMR 75 MHz). ^1H NMR was referenced to residual hydrogen impurities in the solvent; ^{13}C NMR to the solvent signals: CDCl_3 (7.26 ppm, 77.0 ppm) or D_2O (TSP); ^{19}F NMR to CDCl_3 (CFCl_3) or D_2O ($\text{CF}_3\text{SO}_3\text{Na}$). Elemental analyses were performed by the Mikroanalytisches Labor der Chemischen Laboratorien, Universität Freiburg.

Potentiometric titrations

All titrations were performed under N_2 in thermostated vessels ($25 \pm 0.1^\circ\text{C}$). The fully automated pH titration unit consisted of a combined glass electrode (Metrohm UX), a digital pH-meter (Metrohm 652), a digital burette (Metrohm Dosimat 665), an interface unit (Twix 32 bit I/O), and a 80286 PC. The exact calibration was done daily by first using commercial buffer solutions of pH 4 and pH 7 and then titrating 50 ml of $8 \cdot 10^{-4}\text{ M}$ tris(hydroxymethyl)methylamine and HNO_3

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($1.3 \cdot 10^3$ M) with NaOH (0.200 M). Values of the apparent activity coefficient α (0.957), $\text{p}K_a$ of tris (8.167) and $\text{p}K_w$ were taken as reference from [8] and used for final readjustment of the experimental pH readings. All computations were done using the TITFIT program [9] which also handles the data acquisition.

1,3-Dimethyl-2-fluorobenzene (1)

200 ml (6.25 mmol, 37%) of HCl was cooled to 5 °C, the first portion of 1,3-dimethyl-2-aminobenzene (30 g, 0.25 mol) added while stirring vigorously, followed by dropwise addition of a solution of NaNO_2 (80 g, 1.16 mol) in water (100 ml), while maintaining the temperature of the reaction mixture below 10 °C. During the addition of the NaNO_2 solution more 2,6-dimethylaniline (total 100 g, 0.825 mol) was introduced stepwise (the hydrochloride always has to be present in excess = crystalline solid!). All remaining amine was added after more than half the NaNO_2 solution was in the flask. The diazotation is finished when the iodine-starch reaction for HNO_2 is positive. The reaction mixture was then cooled to 0 °C and ice-cooled HBF_4 (87 g, 1 mol) added rapidly (temperature must not rise above 10 °C). Stirring was continued for 30 min, the pale-brown residue filtered off and washed with ice water, methanol and ether (*ca.* 100 ml each) until the salt was nearly colorless. The diazonium tetrafluoroborate salt was dried in air overnight. Yield 110 g (0.5 mol, 60%).

The diazonium salt was filled into a 2 l flask connected to two cold traps (–20 °C) and carefully heated to initiate decomposition, which results in a rapid evolution of BF_3 (absorbed in aq. NaOH). After *ca.* 30 min the reaction had stopped and the mixture was reheated with a heat gun for 5 min. The liquid material in the flask and in the cold traps was collected and distilled over a short Vigreux column. Yield 55 g (0.44 mol, 53%). ^1H NMR (CDCl_3): δ = 2.67 (d, J = 2.3 Hz, 6H), 7.27–7.44 (m, 3H). ^{19}F NMR (CDCl_3): δ = –122.53 (s).

1,3-Bis(dibromomethyl)-2-fluorobenzene (2)

A mixture of 1,3-dimethyl-2-fluorobenzene (6.1 g, 50 mmol), N-bromosuccinimide (53.4 g, 300 mmol), AIBN (0.5 g) and 400 ml CCl_4 was heated under reflux for 6 h. The cold reaction mixture was filtered, the solvent evaporated *in vacuo* and the residue recrystallized from petroleum ether (60–70). Yield: 17.6 g (80%). ^1H NMR (CDCl_3): δ = 6.91 (s, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.84 (t, J = 7.5 Hz). ^{13}C NMR (CDCl_3): δ = 30.64

(d, $^3J_{\text{CF}}$ = 6.4 Hz), 125.44 (d, J_{CF} = 4.1 Hz), 129.32 (d, J_{CF} = 12.8 Hz), 131.79 (d, J_{CF} = 2.3 Hz), 151.18 (d, $^1J_{\text{CF}}$ = 253 Hz). ^{19}F NMR (COCl_3): δ = –121.54.

2-Fluoro-isophthaldialdehyde (3)

Into a mixture of 1,3-bis(dibromomethyl)-2-fluorobenzene (17.6 g, 40 mmol) and H_2SO_4 (125 ml) heated to 100 °C was bubbled N_2 to drive out the bromine, generated in the course of the reaction. Heating was continued (*ca.* 2 h) until bromine evolution had ceased. The cold reaction mixture was slowly added to water (1000 ml) and the product extracted with ether. The organic layer was separated, neutralized, dried over MgSO_4 , filtered, evaporated to dryness, and the residue recrystallized from petroleum ether (60–70). Yield: 4.4 g (75%). ^1H NMR (CDCl_3): δ = 7.41 (t, d, J = 7.6 Hz, 0.6 Hz, 1H), 8.11 (t, J = 7.2 Hz, 2H), 10.39 (s, 2H). ^{13}C NMR (CDCl_3): δ = 124.85 (d, J_{CF} = 7.9 Hz), 125.08 (d, J_{CF} = 4.2 Hz), 134.27 (d, J_{CF} = 2.4 Hz), 166.11 (d, $^1J_{\text{CF}}$ = 255 Hz), 185.57 (d, J_{CF} = 7.2 Hz). ^{19}F NMR (CDCl_3): δ = –132.84 (t, J_{HF} = 5.6 Hz).

F_3 -TREN (4)

To a stirred solution of tris(2-aminoethyl)amine (0.83 g, 5.7 mmol) in 250 ml CH_3CN was slowly added dropwise a mixture of 2-fluoro-isophthaldialdehyde (1.3 g, 8.5 mmol) in 150 ml CH_3CN . After 12 h the insoluble product was filtered off and dried *in vacuo*. The condensation product (1.3 g, 2 mmol) was suspended in 50 ml of ethanol and stirred with NaBH_4 (0.5 g, 13 mmol) for 12 h. The solvent was evaporated *in vacuo*, 10 ml of water added to the residue, and the suspension extracted with CH_2Cl_2 three times. The organic layer was separated, dried over MgSO_4 , evaporated, and the oily residue dried *in vacuo* for 12 h to give 1.2 g of a colorless oil. ^1H NMR (CDCl_3): δ = 3.69 (12H), 6.98 (t, J = 7.5 Hz, 3H), 7.19 (br, 6H). ^{19}F NMR (CDCl_3): δ = –126.49.

F_3 -TREN · 6 HClO_4 (4 · 6 HClO_4)

A suspension of 4 (1.2 g) in H_2O was acidified to pH 3 with HClO_4 . Most of the water was evaporated, the product filtered off, recrystallized from water twice, and dried *in vacuo*. Yield (including condensation, reduction and protonation) = 2.5 g (67%). ^1H NMR (CDCl_3): δ = 2.89 (t, J = 6.0 Hz, 12H), 3.35 (t, J = 6.0 Hz, 12H), 4.39 (s, 12H), 7.38 (t, J = 7.7 Hz, 3H), 7.65 (t, J = 7.4 Hz). ^{13}C NMR (D_2O , TSP): δ = 47.95, 48.52, 53.53, 121.26 (d,

$^2J_{\text{CF}} = 15 \text{ Hz}$), 128.45, 136.92 (d, $J_{\text{CF}} = 2.8 \text{ Hz}$), 162.52 (d, $^1J_{\text{CF}} = 249 \text{ Hz}$). ^{19}F NMR (D_2O , NaCF_3SO_3): -41.09 .

Analysis for $\text{C}_{36}\text{H}_{67}\text{N}_8\text{Cl}_6\text{F}_3\text{O}_{32}$ (1393.7)

Calcd C 31.14 H 4.32 N 7.74%,

Found C 31.03 H 4.85 N 8.04%.

Results and Discussion

The synthesis of the fluorine-containing host molecule **4**·6HClO₄ is illustrated in Scheme 1. 1,3-Dimethyl-2-fluorobenzene **1** was reacted with an excess of NBS to produce 1,3-bis(dibromomethyl)-2-fluorobenzene **2** in 80% yield. Treatment of **2** with concentrated H₂SO₄ at 100 °C for 2 h results in the formation of 2-fluoro-isophthalaldehyde **3** in 75% yield. The condensation of **3** with tris(2-aminoethyl)amine and subsequent reduction of the Schiff base with NaBH₄ yields the 3+2-addition product **4** which forms a colorless oil. Related macrocycles have first been described by Fenton *et al.* [10]. However, the procedure we used is modelled after a more recent preparation by Martell *et al.* [11] and does not require a templating metal ion. An aqueous solution of the octamine **4** was adjusted to pH 3 by addition of HClO₄, resulting in the formation of **4**·6HClO₄. The hexaprotonated ammonium salt is a crystalline solid which was purified by recrystallization from water.

Since related macrocycles had been utilized by Lehn *et al.* to coordinate anions within the positively charged cavity [12], we were intrigued whether this was also possible with fluorine-containing **4**·6HClO₄ and if incorporation of anions

Scheme 1. Reagents and conditions: (a) 6 equiv. NBS, CCl₄; (b) H₂SO₄ conc. 100 °C, 2 h; (c) N(CH₂CH₂NH₂)₃; NaBH₄; (d) HClO₄, pH 3.

into the positively charged cavity gives rise to significant shifts of the ^{19}F NMR signals. It is worth noting that in the classic paper by Lehn *et al.* on a closely related ligand, ^{13}C NMR titrations had to be used to establish coordination of anions and to determine the association constants, as the shifts of the ^1H NMR signals upon addition of anions were too small.

Since six protons attached to **4** are ideal for the formation of stable complexes with anions, potentiometric titrations were performed first to determine the optimum pH range for the ^{19}F NMR studies. It is evident from these experiments (Scheme 2) that binding studies should not be carried out at pH > 4.

^{19}F NMR titration experiments in water with SO_4^{2-} indicate formation of a stable 1:1 complex with a stability constant $K > 5 \cdot 10^3$. Upon addi-

Scheme 2. Species distribution for **4**. Successive pK values: 8.95, 8.50, 7.57, 6.74, 6.27, 5.50 (25 °C, NaCF₃SO₃ supporting electrolyte).

Scheme 3. Shifts of the ^{19}F NMR resonances of the complexes of **4** with the respective anions relative to **4**·6HClO₄ (solvent H₂O/D₂O 5:1).

tion of anions, the ^{19}F NMR resonances are shifted with respect to those of $4\cdot 6\text{HClO}_4$ (Scheme 3). In the series of the halides the complexation-induced shifts of the ^{19}F NMR signal are correlated to the size of the anions since iodide generates the largest effect on the position of the ^{19}F NMR signal, even though it is only weakly bonded. Nitrate is the only non-spherical, magnetically anisotropic anion in this series which might explain the different sign of the NMR shift. Due to the absence of a direct bonding to fluorine, the shifts of the NMR signals caused by inclusion of anions in $4\cdot 6\text{HClO}_4$ are considerably smaller than those produced by the complexation of metal ions in fluorinated crown ethers or chelating ligands [2, 3].

To complement our studies, the association constants for the complexes of I^- , Br^- and Cl^- were determined by ^{19}F NMR titrations using the method of Foster and Fyles [13]. The stability constants for the monovalent ions relative to perchlorate are as follows: $\log K$ 2.1 (Cl^-), 2.4 (Br^-), 1.4 (I^-). The values for Cl^- and Br^- are comparable to those determined for related ligands [12].

Conclusions

It is evident from the work described here, that the observation of association processes by ^{19}F NMR spectroscopy offers significant advantages compared to NMR of other nuclei (namely ^1H and ^{13}C), through a combination of properties such as high sensitivity, large signal dispersion, absence of a natural background, and the lack of overlapping signals.

The "discovery" of the element fluorine for host–guest chemistry will therefore facilitate the determination of equilibrium constants in weak aggregates by NMR spectroscopy in the future. This is even more significant since the properties of fluoroaromatic compounds are very similar to those of "normal" aromatics.

Acknowledgements

Financial assistance by Deutsche Forschungsgemeinschaft (DFG) and by Fonds der Chemischen Industrie (FCI) is gratefully acknowledged. Prof. Dr. H. Vahrenkamp is thanked for his generous support.

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