The synthesis of the largest perfluoro macrocycles; perfluoro [60]-crown-20 and perfluoro [30]-crown-10†

Han-Chao Wei and Richard J. Lagow*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, TX 78712-1167, USA.
E-mail: rjlagow@mail.utexas.edu

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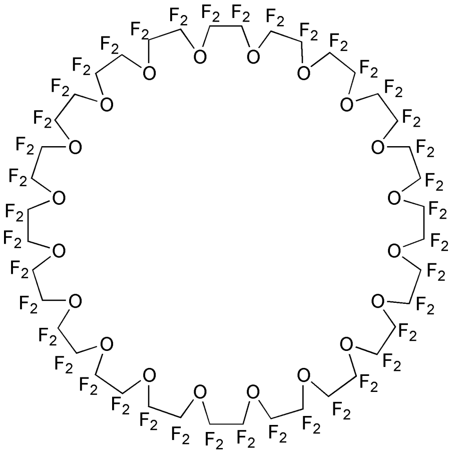
The largest perfluoro macrocycles, perfluoro [60]-crown-20 and perfluoro [30]-crown-10, have been synthesized using the new continuous addition solution phase direct fluorination technique and characterized using ^{19}F NMR and mass spectrometry.

The syntheses of perfluoro crown ethers were first reported in 1985.[1] Perfluoro macrocycles have important medical applications such as ^{19}F NMR imaging and oxygen carrier applications.[2,3] Perfluoro crown ethers generally do not form stable complexes with cations because the basicities of perfluoro crown ethers dramatically decrease as the amount of fluorine substitution increases.[4,5] However, perfluoro crown ethers form complexes with anions, such as O_2^- and F^-, in gas phase reactions.[6] Prior to 1997, only thirteen perfluoro macrocycles were reported and all were synthesized by members of our fluorine research group using low temperature, below room temperature, direct fluorination synthetic techniques.[1,3,7–9] In this paper, we have explored the possible synthesis of perfluorinated organic compounds at higher temperature, above room temperature, during the initial stage of fluorination. The largest perfluoro macrocycles, perfluoro [60]-crown-20 **1** and perfluoro [30]-crown-10 **2**, have been successfully synthesized by using a new continuous addition solution phase direct fluorination technique. In the future, the synthesis of higher molecular weight perfluoro macrocycles will enable us to further explore the chemistry of the perfluoro macrocycles, such as ion complex chemistry and oxygen carrier applications.

In general, the rate of fluorination must be slow enough to allow vibrational energy relaxation processes to occur by collisions in an inert solvent. Many direct fluorination reactions are performed below room temperature during the initial stage of fluorination because reaction rates are so fast that excessive fragmentation occurs and a much lower temperature is required. We initially lowered the fluorination temperature to minimize possible ring opening reactions during fluorination of [60]-crown-20. Several first attempts to perfluorinate [60]-crown-20 at lower temperatures, 0, −10, −20 and −30 °C, during the initial stage of fluorination were unsuccessful. Interestingly, as the temperature of the initial stage of fluorination decreased, the degree of fluorination decreased and only partial fluorination occurred. These observations were confirmed by ^{1}H, ^{19}F NMR spectroscopy and mass spectrometry. Therefore, we increased the initial stage reaction temperature to 26 °C and succeeded in the synthesis of perfluoro [60]-crown-20 **1**.

At room temperature, [60]-crown-20 molecules are conformationally flexible[8] and hydrogen atoms can be replaced by fluorine even at sites which are sterically protected by the configuration of the carbon skeleton of [60]-crown-20 during fluorination. In contrast, the [60]-crown-20 molecules are less flexible at lower temperatures. Once the 'surface' hydrogen atoms of [60]-crown-20 are replaced by fluorine, the nonbonding electron cloud of the fluorine atoms tends to repel the oncoming fluorine molecules as they approach the [60]-crown-20 molecules and only partially fluorinated products are obtained. Under such vigorous fluorination conditions, higher temperature solution phase fluorination, fragmentation products were also obtained and the yield of perfluoro [60]-crown-20 was 14%. However, perfluoro [30]-crown-10 **2** was synthesized in 50% yield using the direct fluorination method with reaction temperatures escalating from −20 to 26 °C, as described in the literature.[9,10] The spectral data were in agreement with the structural assignments of perfluoro [60]-crown-20 **1** and perfluoro [30]-crown-10 **2**.[11]



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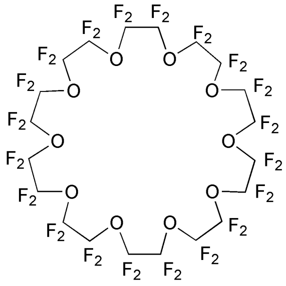

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In conclusion, the largest perfluoro macrocycle, perfluoro [60]-crown-20 **1** and perfluoro [30]-crown-10 **2**, were synthesized by direct fluorination and characterized using ^{19}F NMR spectroscopy and mass spectrometry. Perfluoro [60]-crown-20 **1** and perfluoro [30]-crown-10 **2** are expected to be biologically inert, in contrast to their hydrocarbon analogues, and may be useful in biological or medical applications where physiologically inert or oxygen carrying fluids are required. Perfluoro [60]-crown-20 **1** has also shown potential as a very clean, high mass compound for use as a mass spectral marker material in the chemical ionization negative mode.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b0/b004168h/

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Notes and references

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11 The starting materials, [60]-crown-20 and [30]-crown-10, were synthesized by the following procedures from the literature (ref. 8). *Synthesis of perfluoro [60]-crown-20.* In a typical reaction, the direct fluorination reaction was performed in a similar manner to the reactions that have been described in the literature (ref. 9 and 10). [60]-Crown-20 (1 g) was dissolved in 1,1,2-trichloro-1,1,2-trifluoroethane (300 mL) and chloroform (3 mL), then the solution was slowly introduced into a stainless steel reactor which contained 1,1,2-trichloro-1,1,2-trifluoroethane (600 mL), sodium fluoride (100 g) and a fluorine–helium mixture. During the next 72 h the relative fluorine concentration was slowly increased. Filtration of the solution and removal of 1,1,2-trichloro-1,1,2-trifluoroethane by simple distillation produced a white waxy solid and a viscous oil. The product was purified by preparative gas chromatography on an OV-210 column at 200 °C. Pure perfluoro [60] crown-20 was collected by preparative GC as white waxy solid in 14% yield. Negative chemical ionization mass spectrometry: *m/z* (formula, identification, intensity) 2320 ($C_{40}F_{80}O_{20}$, M^-, 100). The elemental compositions were studied by high resolution mass spectrometry in chemical ionization negative mode. The results were consistent with $C_{40}F_{80}O_{20}$ (Calc.: 2319.7706; Found: 2319.7688). ^{19}F NMR ($CFCl_3$) δ -89.45 (s, 80F). *Synthesis of perfluoro[30]-crown-10.* Perfluoro [30]-crown-10 was synthesized in a similar manner to perfluoro [60]-crown-20. The product was purified by preparative gas chromatography on a OV-210 column at 150 °C. Pure perfluoro [30]-crown-10 was collected by preparative GC as a colorless liquid in 50% yield. Fast atom bombardment (FAB) mass spectral analysis (negative mode): *m/z* (formula, identification, intensity) 1159 ($C_{20}F_{40}O_{10}$, M^-, 100). The elemental compositions were studied by high resolution mass spectrometry in FAB negative mode. The results were consistent with $C_{20}F_{40}O_{10}$ (Calc.: 1159.8853; Found: 1159.8844). ^{19}F NMR ($CFCl_3$) δ -89.48 (s, 40F). More experimental details are described in ESI.†