Theoretical Evidence for C-F Bond Activation by a Fluoro-calix[4]pyrrole-*tert*-amine Macrocycle

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Density functional theory as well as highly correlated ab initio molecular orbital theory was used to explore the possibility of activating C−F bonds in fluoroalkanes by organic macrocycles. The results indicate that the reaction between fluoro-calix [4]pyrrole-*tert*-amine and CH_3F via a Menshutkin displacement mechanism is highly favorable and competitive from a thermochemical point of view with the very efficient C−Cl activation by a simple macrocyclic amine recently reported in the literature (Stanger, L. J.; Noll, B. C.; Gonzalez, C.; Marquez, M.; Smith, B. D. *J. Am. Chem. Soc.* **2005**, *127*, 4184).

Introduction

Fluorine makes the single strongest bond to carbon (500−540 kJ/mol for aliphatic and olefinic C−F bonds) rendering fluorocarbons thermally stable and resistant to chemical degradation. These properties have resulted in fluorocarbons being widely used in many commercial areas including refrigerants, pesticides, and nonadhesive polymers. Despite their commercial value, fluorocarbons are known to be hazardous to the environment because of their negative impact on the ozone layer. Different methods making use of organometallic reactions involving lanthanide metals are currently available to degrade fluorocarbons.[1−6] However, these reactions require long reaction times and elevated temperatures.[7,8] Other methods entail the use of strongly electrophilic silylium species, which perform defluorination at room temperature,[9] and the use of tetrabutylammonium cyanide, which defluorinates hexafluorobenzene.[10] Despite these efforts, activation of the C−F bond using economically and environmentally friendly methods still remains a challenge. One possible approach to resolve this issue would be to develop a method of degradation that mimics nature. In nature, the fluroacetate dehalogenase enzyme from *Burkholderia* sp. FA1 activates the C−F bond using no metal cofactors.[11] The fluoride anion is removed from the carbon center of the fluoroacetate substrate presumably via an S_N2-like substitution reaction.[12] The related haloalkane dehalogenase enzyme from *Xanthobacter autotrophicus* GJ10 cleaves the C−Cl bond but not the stronger C−F bond.[13] The three-dimensional structure of this enzyme is known[14] and the reaction has been thoroughly studied using experimental techniques[15] as well as by theoretical methods.[16] The substitution reaction starts with an Asp^- residue making a nucleophilic attack on the chloride-bearing carbon. The leaving Cl^- is stabilized via the formation of two hydrogen bonds with the side-chain amines of two Trp residues. The Asp^- residue is subsequently liberated from the enzyme−substrate ester adduct via hydrolysis involving a acive site bound water molecule, and the enzyme becomes ready for another catalytic reaction cycle.

It has been suggested that enzymes bind their substrates to their active sites in a high-energy conformation (near attack conformation (NAC)) prior to the chemical reaction.[17] This strained substrate requires a small increase in free energy (mainly an increase in enthalpy) to cross the transition state. The unfavorable entropy decrease associated with the binding of the substrate in a NAC inside the active site is already “paid for” by the enzyme.[18]

Recently, we were able to demonstrate this concept using a macrocyclic amine (see Figure 1a).[19] This macrocycle consists of a tertiary amine connected to two amides that binds CH_2Cl_2 and displaces one of the chlorides via a Menschutkin displacement reaction, forming a tertiary ammonium salt. Calculations showed how CH_2Cl_2 is anchored in the cavity by forming hydrogen bonds to the two amides hydrogens. The carbon in CH_2Cl_2 is then in position for the nucleophilic attack by the amine nitrogen. The calculations confirmed that the substitution reaction is fast and that it is exothermic.[19] This reaction shows similarities with the haloalkane dehalogenase enzyme catalyzed reaction. The substrate is rescricted and positioned for a nucleophilic attack, and the two amide hydrogens analogous to the side-chain indole amine hydrogens of the two Trp residues stabilize the transition state. These interesting results open the possibility of designing macrocycles that can efficiently break the stronger C−F bond in fluorocarbons without the need of metallic cofactors. In this work, we perform highly correlated ab initio molecular orbital and density functional theory (DFT) calculations to explore this possibility.

Theoretical Calculations

To test the reliability of the methodology adopted in this work, we performed calculations using highly correlated ab initio molecular orbital methodologies as well as DFT on the corresponding Menschutkin reactions considering a smaller model consisting of H_2O and NH_3 and the substrates CH_2Cl_2,

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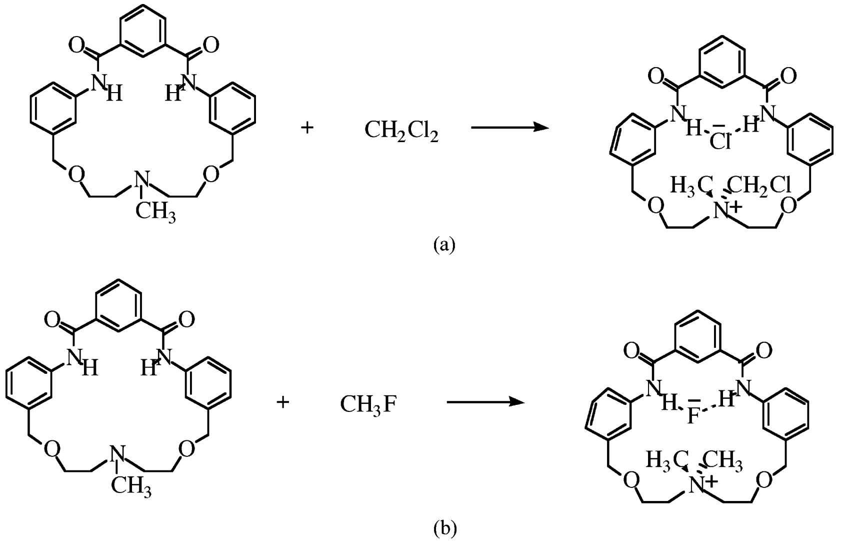

Figure 1. Schematic description of the reaction between the macrocycle MCA1 and (a) CH_2Cl_2,and (b) CH_3F.

CH_3F, and CH_3CH_2F:

$$NH_3 + H_2O + CH_2Cl_2 \rightarrow [CH_2ClNH_3]^+ + [HO-HCl]^- \quad (R1)$$

$$NH_3 + H_2O + CH_3F \rightarrow [CH_3NH_3]^+ + [OH-HF]^- \quad (R2)$$

$$NH_3 + H_2O + CH_3CH_2F \rightarrow [CH_3CH_2NH_3]^+ + [OH-HF]^- \quad (R3)$$

TABLE 1: Computed Relative Energies (with Respect to Separated Reactants) for Complexes, TS values, and Products in the Reactions between $H_2O + NH_3$ and the Substrates CH_2Cl_2, CH_3F, and CH_3CH_2F. All Energies in kJ/mol

species	Δ*EPBEPBE* + Δ*ZPE*	MP2 + Δ*ZPE*	CCSD + Δ*ZPE*	CCSD(T) + Δ*ZPE*
$H_2O-NH_3-CH_2Cl_2$	−41.7	−35.3	−42.6	−44.6
TS	98.7	118.7	109.6	100.2
prod	−117.3	−83.7	−86.7	−89.7
$H_2O-NH_3-CH_3F$	−32.3	−29.9	−20.8	−22.2
TS	135.8	169.6	187.2	180.6
prod	−95.8	−89.1	−72.2	−75.4
$H_2O-NH_3-C_2H_5F$	−52.0	−45.1	−32.5	−34.7
TS	133.4	169.7	187.0	179.0
prod	−83.6	−80.2	−31.4	−35.4

Numerous theoretical studies dealing with the energetics and mechanisms governing Menschutkin reactions similar to reactions R1−R3 have been reported in the literature.[20−23] Full geometry optimizations of reactants, prereactive complexes, transition states, and products for these reactions were performed with second-order Møller−Plesset perturbation theory (MP2),[24−27] coupled-cluster theory in the space of single, double electron excitations[28−31] (CCSD) and triple electron excitations[32−34] included in a perturbative manner (CCSD(T)), as well as with the PBE exchange-correlation DFT functional developed by Perdew, Burk and Ernzerhof.[35,36] In all geometry optimizations, the 6-31G* basis set was used. All calculations were performed with the Gaussian03 suite of programs.[37,38] The energetics for these reactions listed in Table 1 indicate a good agreement between the reaction barriers computed with MP2, CCSD, and CCSD(T). In addition, despite a reasonable agreement in the case of reaction R1, the barriers predicted by the PBE functional for reactions R2 and R3 are significantly lower than the corresponding ones computed with MP2, CCSD, and CCSD(T). This tendency of DFT to underestimate reaction barriers has been previously reported in the literature.[39] Becke[40,41] and collaborators have demonstrated that this problem arises from an inherent inability in most of the DFT functionals to properly describe the nonlocal character of the exchange-correlation “hole” in situations where odd electrons play an important role in the electronic structure of the systems under study, or in highly stretched situations such as the ones observed in transition states. The fact that a significant better agreement is found in the case of reaction R1 could probably be the result of fortuitous cancellations of errors or of a more localized exchange-correlation hole in the corresponding transition structure. Despite these differences, all theory levels used in this work predict that the intrinsic barriers for displacing F^- from the prereactive complex formed between the reactants and the substrates CH_3F and CH_3CH_2F are significantly higher than the corresponding intrinsic barrier involving the Cl^- displacement from the CH_2Cl_2 substrate. In contrast to the case of intrinsic barriers, the results in Table 1 indicate a better agreement between DFT and the rest of the ab initio results corresponding to the prereactive complexes binding energies as well as reaction energies. Given the significant relative computational efficiency of DFT when compared to MP2, CCSD, and CCSD(T), it would be desirable to use this methodology when treating the Menschutkin reactions involving the larger ligands considered in this study (see Figures 1−3). However, the results shown in Table 1 in the case of reactions R1−R3 cast some doubt regarding the reliability of the energetics computed with the PBE functional. Given that, as shown in the Supporting Information section, we have found no significant differences between the optimized geometries obtained with DFT and the highly correlated ab initio methodologies, we decided to perform geometry optimizations and frequency calculations using PBEPBE/6-31G* and single-point energy calculations using MP2 with the larger 6-311++G** basis set in the case of the larger ligands (MP2/6-311++G**//PBEPBE/6-31G* level). The use of a triple-ζ basis such as 6-311++G** that includes extra sets of diffusion and polarization functions provides enough flexibility in the basis to properly describe the nonbonded interactions in the macrocyclic systems studied in this work. To compare with the data previously reported for the C−Cl bond activation in CH_2Cl_2[19], the energetics of all reactions in this study also were computed in a CH_2Cl_2 solution using the polarizing continuum model

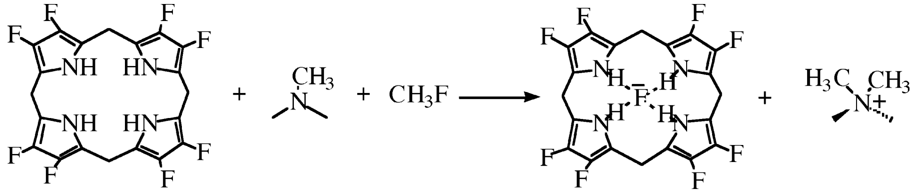

Figure 2. Schematic description of the reaction between fluorinated calix[4]pyrrole, the tertiaty amine $N(CH_3)_3$, and CH_3F.

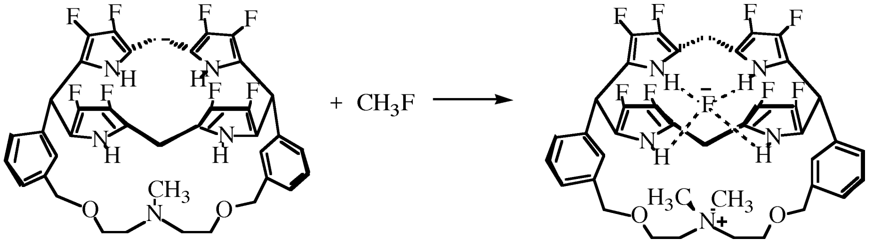

Figure 3. Schematic description of the reaction between the macrocycle MCA2 and CH_3F.

TABLE 2: Relative Energies (with Respect to Separated Reactants) Computed at the MP2/6-311++G//PBEPBE/6-31G* Level for the Reaction between CH_3F and CH_2Cl_2 with Fluorinated Calix[4]pyrrole and Macrocyclic Amines MCA1 and MCA2. All Energies in kJ/mol**

	Δ*EMP2*	Δ*ZPE*	$\Delta E_{\text{gasphase}}$	Δ*EPCM*	$\Delta E_{\text{solution}}$
MCA1−CH_2Cl_2	−103.1	6.2	−96.9	20.4	−76.5
TS	−9.3	9.0	−0.2	−7.5	−7.8
prod	−147.7	14.7	−133.0	−37.3	−170.3
MCA1−CH_3F	−52.4	9.7	−42.7	14.2	−28.5
TS	38.1	11.8	49.9	−11.0	39.0
prod	−70.5	18.9	−51.6	−29.1	−80.7
Fluoro-calix[4]pyrrole −$N(CH_3)_3$−CH_3F	−31.1	6.9	−24.2	27.2	3.0
TS	10.2	13.1	23.3	9.6	32.9
prod	−106.0	18.4	−87.6	−50.1	−137.7
MCA2−CH3F	−66.2	7.5	−58.7	2.2	−56.5
TS	−8.1	11.1	3.0	−16.2	−13.2
prod	−153.2	16.2	−137.0	−58.3	−195.3

(PCM)[42,43] as implemented in the Gaussian03 program. The relative gas-phase energy $\Delta E_{\text{gasphase}}$, reported herein (relative to separated reactants), was computed as the sum of the MP2 electronic energy $\Delta E_{\text{MP2/6-311++G**}}$ and the PBE zero-point energy, $\Delta ZPE_{\text{PBEPBE/6-31G*}}$, while in the CH_2Cl_2 solution, the solvation energy term Δ*EPCM* (computed at the PBEPBE/6-31G* level of theory using a dielectric constant of 8.93) was added to the gas-phase energy to compute the total relative energy in solution, $\Delta E_{\text{solution}}$. This approach provides a good compromise between reliability and computational expense, given that Δ*ZPE* and Δ*EPCM* calculations at the MP2/6-311++G** level can become taxing from the computational point of view.

Results

Figure 1a,b shows a schematic diagram of the reaction between the macrocyclic amine previously studied in ref 19 (MCA1 herein) and the CH_2Cl_2 and CH_3F substrates respectively. It is interesting to notice that in the case of the reaction between MCA1 and CH_2Cl_2, the all-electron calculations performed in this work (with the 6-311++G** basis set) predict an interaction energy in solution (see Table 2) for the MCA1−CH_2Cl_2 complex significantly larger than the one reported in our previous work (−76.5 kJ/mol vs −35.2 kJ/mol[19]), whereas the Los Alamos pseudopotential with a double-ζ basis was used (LANL2DZ herein). This significant discrepancy can be attributed to the fact that the double-ζ basis set used in the LANL2DZ calculation is not flexible enough to properly treat the nonbonded interactions in the MCA1−CH_2Cl_2 complex. This explanation seems to be supported by "single point" all-electron calculations (not shown) of the interaction energy at the MP2 level (not corrected by ZPE effects) using the double-ζ basis 6-31G basis and with the more extensive basis 6-311++G** adopted in the present work that show that even in the gas phase, the 6-31G results are significantly smaller than the corresponding interaction energy computed with the 6-311++G** basis (−5.9 kJ/mol vs −103.1 kJ/mol).

The results listed in Table 2 indicate that the gas phase prereactive complex between MCA1 and CH_3F lies 42.7 kJ/mol below the reactants. According to the PCM predictions, solvation makes this process less exothermic by 14.2 kJ/mol. This complex is connected to a transition state structure (TS) involving the breaking of the C−F bond, which exhibits an intrinsic barrier (going from the complex to the TS) of 92.6 kJ/mol (solvation brings down this barrier to 67.5 kJ/mol). This barrier is found to be 1.2 kJ/mol lower than the one corresponding to the reaction involving the same macrocyclic amine and CH_2Cl_2 (see Table 2). The subsequent gas-phase product lies 51.6 kJ/mol below reactants (80.7 kJ/mol in solution). Given these results, one would expect the Menschutkin reactions between MCA1 and the substrates CH_2Cl_2 and CH_3F to be competitive (at least from a thermochemical point of view), suggesting the possibility of using MCA1 for efficient C−F activation. However, contrary to the case of the reaction between MCA1 and CH_2Cl_2, characterized by a significantly stable prereactive complex and a TS that lies below reactants, the potential energy surface of the reaction between MCA1 and CH_3F exhibits a relatively less stable complex and a TS energy that lies above reactants, which would probably lead to significantly lower reaction rates. In addition, given that the intrinsic barrier computed for the reaction $NH_3 + H_2O + CH_3CH_2F \rightarrow [CH_3CH_2NH_3]^+ + [OH-HF]^-$ is about 15 kJ/mol higher than the corresponding barrier for $NH_3 + H_2O + CH_3F \rightarrow [CH_3NH_3]^+ + [OH-HF]^-$ (see Table 1), it is not clear how efficient this macrocycle would be in breaking C−F bonds in secondary and larger alkylfluorides. We reasoned that a more powerful F^- receptor would be needed to stabilize the transition state and make the reaction more exothermic and therefore decided to combine the nucleophilic strength of a tertiary amine with a fluorinated calix[4]pyrrole, which has been found to bind F^- strongly.[44,45] To test this premise, we performed full geometry optimizations of reactants, prereactive complex, TS, and products of the gas-phase reaction: fluorinated calix[4]-

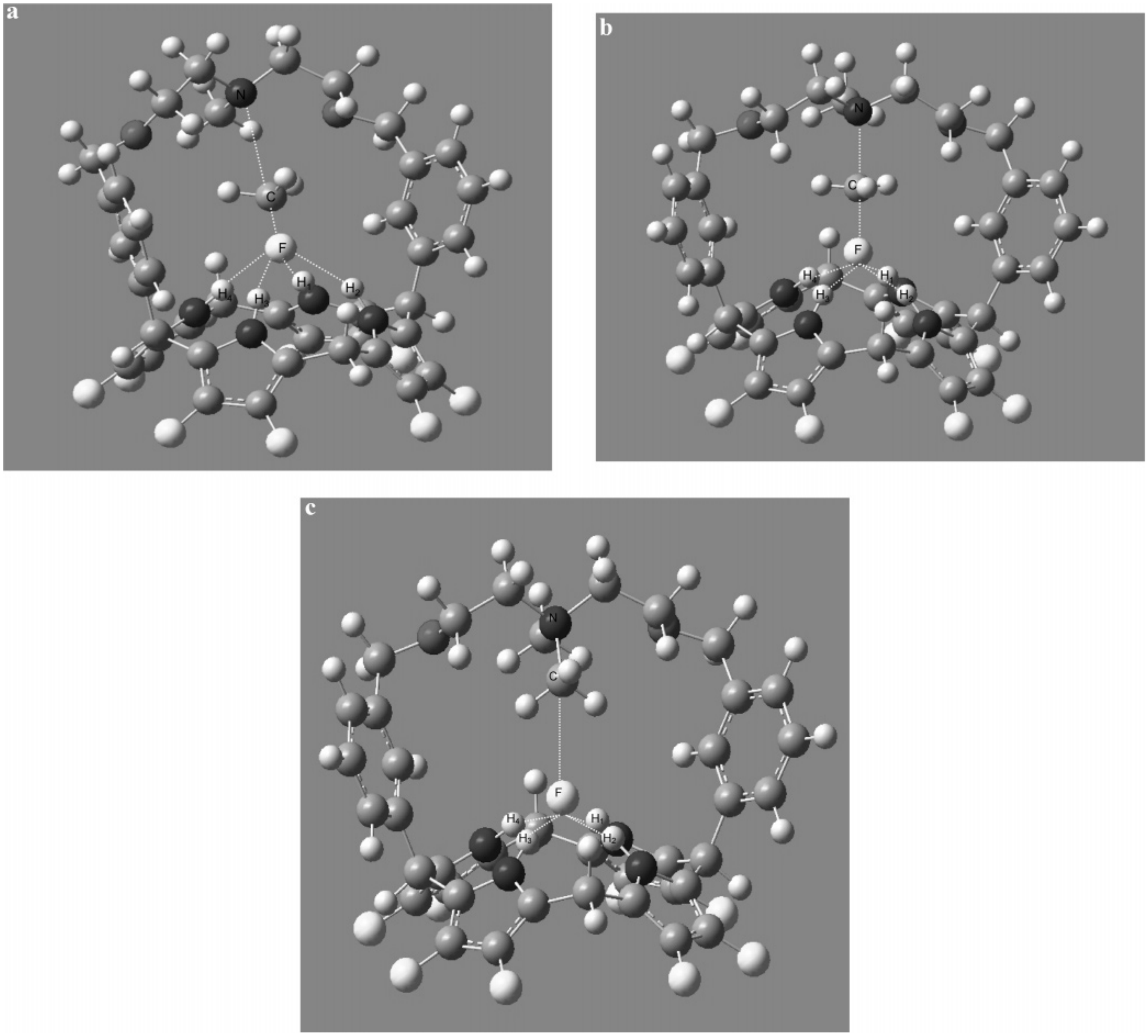

Figure 4. (a) Optimized geometry (at the PBE/6-31G* level of theory) for the complex between the macrocycle MCA2 and CH_3F. $R_{C-N} = 3.093$ Å; $R_{C-F} = 1.455$ Å; $R_{F-H1} = 2.026$ Å; $R_{F-H2} = 2.188$ Å; $R_{F-H3} = 2.181$ Å; $R_{F-H4} = 2.026$ Å. The Mulliken charges (in au) computed at the same level of theory are: $Q_F = -0.262$, $Q_{H1} = 0.327$, $Q_{H2} = 0.321$, $Q_{H3} = 0.321$, $Q_{H4} = 0.327$, $Q_{CH3} = 0.360$ and $Q_N = -0.357$. (b) Optimized geometry (at the PBE/6-31G* level of theory) for the transition structure for the reaction between the macrocycle MCA2 and CH_3F. $R_{C-N} = 2.155$ Å; $R_{C-F} = 1.810$ Å; $R_{F-H1} = 1.861$ Å; $R_{F-H2} = 1.897$ Å; $R_{F-H3} = 1.904$ Å; $R_{F-H4} = 1.859$ Å. The Mulliken charges (in au) computed at the same level of theory are: $Q_F = -0.336$, $Q_{H1} = -0.717$, $Q_{H2} = -0.717$, $Q_{H3} = -0.716$, $Q_{H4} = -0.717$, $Q_{CH3} = 0.342$, and $Q_N = -0.368$. (c) Optimized geometry (at the PBE/6-31G* level of theory) for the products of the reaction between the macrocycle MCA2 and CH_3F. $R_{C-N} = 1.508$ Å; $R_{C-F} = 2.808$ Å; $R_{F-H1} = 1.698$ Å; $R_{F-H2} = 1.706$ Å; $R_{F-H3} = 1.706$ Å; $R_{F-H4} = 1.695$ Å. The Mulliken charges (in au) computed at the same level of theory are: $Q_F = -0.443$, $Q_{H1} = 0.348$, $Q_{H2} = 0.345$, $Q_{H3} = 0.345$, $Q_{H4} = 0.348$, $Q_{CH3} = 0.287$, and $Q_N = -0.337$.

pyrrole + $N(CH_3)_3$ + CH_3F → Products (see Figure 2). The intrinsic barrier in gas phase was computed to be 47.5 kJ/mol (35.9 kJ/mol in solution), showing a significant reduction in the intrinsic barrier when compared to the reaction between CH_3F and MCA1. In addition, the reaction was found to be exothermic by 87.6 kJ/mol in gas phase and 137.7 kJ/mol in solution. These results suggest the thermochemical possibility of breaking the C−F bond in CH_3F by a macrocycle containing an amine and fluorinated calix[4]pyrrole. To construct this macrocycle (MCA2 herein), the amine moiety and the fluorinated calix[4]pyrrole were connected by two linkers similar to the ones found in MCA1 (see Figure 3). As with the previous cases, geometries and relative energies of all the stationary points involved in the reaction between MCA2 and CH_3F were computed. Figure 4 shows the geometries of these stationary points in which a summary of the most relevant geometric parameters is listed. The results show that the complex between MCA2 and CH_3F is characterized by the formation of four hydrogen bonds between the F atom in CH_3F and the acidic protons on the calix[4]pyrrole fragment of MCA2. At the transition state (Figure 4b), these F−H bond lengths decrease by as much as 0.291 Å accompanied by a corresponding decrease in the C−N distance of 0.938 Å and an elongation of the C−F bond of 0.355 Å. In addition, the methyl group in the CH_3F moiety becomes completely planar in the TS. Figure 4c shows that in the product, while the C−F bond is broken, the methyl group binds to the tertiary amine of MCA2. In addition, the incipient F^- ion gets “trapped” by the nonbonded interactions with the four acidic protons on the calix[4]pyrrole fragment. These strong interactions between the acidic protons in calix-

[4]pyrrole and fluoride anions has been previously discussed by Sessler et al.[44,45] In this way, the macrocycle provides the right environment to stabilize the fluoride anion resulting from the Menschutkin reaction between MCA2 and CH_3F, making the whole process significantly exothermic (see below). The increasing Mulliken charge for the F atom being cleaved as the reaction proceeds from the complex to the products (see Figure 4) supports this conclusion. As shown in Table 2, the complexation energy of MCA2 and CH_3F was computed to be −58.7 kJ/mol in the gas phase and −56.5 kJ/mol in solution. The gas-phase intrinsic barrier was computed to be 61.7 kJ/mol, and the reaction is exothermic by 137.0 kJ/mol. Comparison with the results obtained in the case of the prototype reaction between fluorinated calix[4]pyrrole, the tertiary amine $N(CH_3)_3$ and CH_3F indicate that the molecule fragments connecting the fluorinated calix[4]pyrrole and the tertiary amine must adjust slightly to accommodate the transition state, adding strain energy to the intrinsic barrier. Nevertheless, the results suggest that MCA2 would be much more efficient in degrading CH_3F than MCA1 does. Synthesis of the non-fluorinated analogue of MCA2 is currently in progress.

Conclusions

Highly correlated ab initio molecular orbital theory and density functional theory have been used to probe the possibility of designing organic macrocycles able to activate strong C−F bonds in fluoroalkanes without the need of metal cofactors. The results show that the macrocycle fluoro-calix[4]pyrrole-*tert*-amine is very effective in breaking the C−F bond in CH_3F (at least from a thermodynamics point of view) via a Menshutkin reaction mechanism in which the charge separation in the products is stabilized by the formation of four hydrogen bonds between the F^- ion being formed and the acidic protons of the calix[4]pyrrole-*tert*-amine. These encouraging results suggest the possibility of using quantum chemistry calculations in the rational design of potential C−F activating ligands.

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Supporting Information Available: Geometry-optimized structures and energies of the stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373.

(2) Edelbach, B. L.; Kraft, B. M.; Jones, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 10327.

(3) Maron, L.; Werkema, E. L.; Perrin, L.; Eisenstein, O.; Andersen, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 279.

(4) Werkema, E. L.; Messines, E.; Perrin, L.; Maron, L.; Eisenstein, O.; Andersen, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 7781.

(5) Cornehl, H. H.; Hornung, G.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 9960.

(6) Hertwig, R. H.; Koch, W. *Chem. --Eur. J.* **1999**, *5*, 312.

(7) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber. Recl.* **1997**, *130*, 145.

(8) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373.

(9) Scott, V. J.; Çelenligil-Çetin; Ozerov, O. V. *J. Am. Chem. Soc.* **2005**, *127*, 2852.

(10) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(11) Kurihara, T.; Yamauchi, T.; Ichiyama, S.; Takahata, H.; Esaki, N. *J. Mol. Catal. B: Enzyme* **2003**, *23*, 347−355.

(12) Ze-Sheng Li, Y. Z.; Sun, M.; Wu, J. Y.; Zheng, Q.-C.; Sun, C.-C. *Biochem. Biophys. Res. Commun.* **2004**, *325*, 414−420.

(13) Pries, F.; Kingma, J.; Pentenga, M.; van Pouderoyen, G.; Jeronimus-Stratingh, C. M.; Bruins, A. P.; Janssen, D. B. *Biochemistry* **1994**, *33*, 1242−1247.

(14) Verschueren, K. H. G.; Seljée, F.; Rozeboom, H. J.; Kalk, K. H.; Dijkstra, B. W. *Nature* **1993**, *363*, 693.

(15) Schanstra, J. P.; Ridder, I. S.; Heimeriks, G. J.; Rink, R.; Poelarends, G. J.; Kalk, K. H.; Dijkstra, B. W.; Janssen, D. B. *Biochemistry* **1996**, *35*, 13186.

(16) Lau, E. L.; Kahn, K.; Bash, P. A.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9937.

(17) Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139.

(18) Page, M. L.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678.

(19) Lee, J.-J.; Stanger, K. J.; Noll, B. C.; Gonzalez, C.; Marquez, M.; Smith, B. D. *J. Am. Chem. Soc.* **2005**, *127*, 4184.

(20) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 154.

(21) Gao, J. *J. Am. Chem. Soc.* **1991**, *113*, 7796.

(22) Gao, J.; Xia, X. *J. Am. Chem. Soc.* **1993**, *115*, 9667.

(23) Castejon, H.; Wiberg, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 2139.

(24) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(25) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503.

(26) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275.

(27) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281.

(28) Cizek, J. *Adv. Chem. Phys.* **1969**, *14*, 35.

(29) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910.

(30) Scuseria, G. E.; Janssen, C. L.; Schaefer, H. F., III. *J. Chem. Phys.* **1988**, *89*, 7382.

(31) Scuseria, G. E.; Schaefer, H. F., III. *J. Chem. Phys.* **1989**, *90*, 3700.

(32) Bartlett, R. J.; Watts, J. D.; Kucharski, S. A.; Noga, J. *Chem. Phys. Lett.* **1990**, *165*, 513.

(33) Watts, J. D.; Gauss, J.; Bartlett, R. J. *J. Chem. Phys.* **1993**, *98*, 8718.

(34) Pople, J. A.; Head-Gordon, M.; Raghavachari, K. *J. Chem. Phys.* **1987**, *87*, 5968.

(35) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.

(36) Perdew, J. P.; Burke, K.; Enrzenhof, M. *Phys. Rev. Lett.* **1997**, *78*, 1396.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.02; Gaussian, Inc: Wallingford, CT, 2004.

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(39) Johnson, B. G.; Gonzalez, C.; Gill, P. M. W.; Pople, J. A. *Chem. Phys. Lett.* **1994**, *221*, 100.

(40) Becke, A. D. *J. Chem. Phys.* **2005**, *122*, 064101.

(41) Dickson, R. M.; Becke, A. D. *J. Chem. Phys.* **2005**, *123*, 111101.

(42) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253.

(43) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43.

(44) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140.

(45) Wu, Y.-D.; Wang, D.-F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739.