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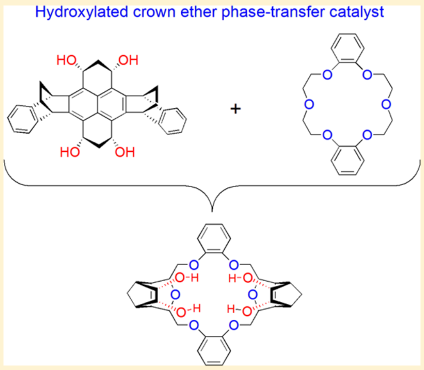
Theoretical Design and Calculation of a Crown Ether Phase-Transfer-Catalyst Scaffold for Nucleophilic Fluorination Merging Two Catalytic Concepts

Nathália F. Carvalho and Josefredo R. Pliego, Jr.*

Departamento de Ciências Naturais, Universidade Federal de São João Del-Rei, São João del-Rei 36301-160, MG, Brazil

Ⓢ *Supporting Information*



ABSTRACT: Fluorinated organic molecules are playing an increased role in the area of pharmaceuticals and agrochemicals. This fact demands the development of efficient catalytic fluorination processes. In this paper, we have designed a new crown ether with four hydroxyl groups strategically positioned. The catalytic activity of this basic scaffold was investigated with high levels of electronic structure theory, such as the ONIOM approach combining MP4 and MP2 methods. On the basis of the calculations, this new structure is able to solubilize potassium fluoride in toluene solution much more efficiently than 18-crown-6 (18C6). In addition, the strong interaction of the new catalyst with the S_N2 transition state leads to a very important catalytic effect, with a predicted free energy barrier of 23.3 kcal mol^{-1} for potassium fluoride plus ethyl bromide reaction model. Compared with experimental data and previous theoretical studies, this new catalyst is 10^4 times more efficient than 18C6 for nucleophilic fluorination of alkyl halides. The catalysis is predicted to be selective, leading to 97% of fluorination and only 3% of elimination. Catalytic fluorination of the aromatic ring has also been investigated, and although the catalyst is less efficient in this case, our analysis has indicated further development of this strategy can lead to more efficient catalysis.

INTRODUCTION

The incorporation of a fluorine atom into organic molecules alters their properties such as pK_a, lipophilicity, and conformational structure. In fact, the presence of fluorine in biologically active molecules often leads to higher metabolic stability, efficiency, and bioavailability.[1−7] These effects are attributed partly to the electronegativity of this element and its small radius.[8−13] As a consequence of these unique effects, at least one fluorine atom is present in about 20% of pharmaceuticals and 30−40% of agrochemicals.[2,14,15] Many of these compounds are fluorinated aromatics. Moreover, the radiolabeling of some molecules with ^{18}F enables the use these compounds in positron emission tomography (PET), a helpful technique in early diagnosis of various illnesses such as Parkinson's and Alzheimer's disease.[9,16,17] For the cited reasons, the organic fluorine chemistry is one of the most exciting areas of current research in chemistry.[18−31]

Nucleophilic substitution reactions are widely used routes for obtaining organofluorine compounds. Among the available nucleophilic methodologies for fluorination of aromatics, diazotizations with BF_4^- (Balz−Schiemann reaction)[32] or with HF/pyridine are the most relevant routes for obtaining fluorinated aromatic compounds on a large scale.[10] However, these methods have the drawback of using hazardous and toxic reagents. Another important methodology is the halogen exchange or Halex reaction. This method requires the activation of the halogen atom by other moieties on the ring such as nitro groups or elevated temperatures. Furthermore, there is a predominance of byproducts in the reaction mixture.[10] Although usually considered unreactive toward nucleophilic attack, gas-phase experimental studies have shown that aromatic rings are intrinsically highly reactive for nucleophilic substitution even for unactivated aromatics.[33] In fact, theoretical calculations have indicated that the low reactivity found in liquid-phase reactions is due to a substantial solvent effect.[34]

Fluorinating reagents commonly utilized in nucleophilic fluorination via S_N2 or S_NAr reactions include alkali-metal fluorides and tetraalkylammonium fluorides. Alkali-metal fluorides have low solubility in dipolar aprotic solvents, and the use of common protic solvents leads to low reactivity. The tetrabutylammonium fluoride (TBAF) salts are hygroscopic and only in the past decade have been obtained in anhydrous form.[35,36] Although useful in aromatic fluorination, TBAF acts as a strong base that can cause elimination reactions in aliphatic compounds, leading in general to poor chemoselectivity.[17,37] In addition, anhydrous TBAFs are difficult to employ. Tetramethylammonium fluoride (TMAF) is a similar reactant and has been recently proposed to be a better alternative in aromatic nucleophilic substitution.[38]

Despite the importance of fluorine in organic chemistry and the meaningful advances undertaken,[37] selective and efficient introduction of this element into poorly activated compounds

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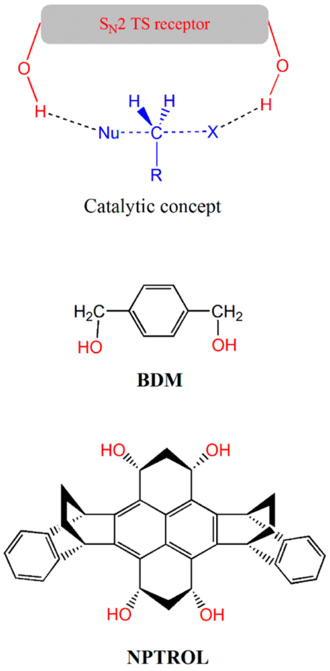
remains an ongoing problem in fluorine chemistry.[9,17] For example, although the use of Selectfluor is successful in many fluorination reactions, electrophilic fluorination of aromatics using Selectfluor or other F^+ sources requires activated aromatics.[18,39] Thus, there is a high demand for new methods to synthesize fluorinated compounds in a quick and selective procedure. Catalytic methods based on transition metals have received increased attention recently due to important advances in this area.[2,40−45] Other possibile route is to control the reactivity of the fluoride ion by designing a supramolecular catalyst or structured nanoenvironment around the ion.[46−50] This approach has been explored in this paper through computational chemistry. Hereafter, we will discuss key studies and ideas that led us to design the new catalyst scaffold proposed in this work. It is worthwhile to emphasize the increased role of theoretical methods in the design of new catalysts, with successful outcomes.[51−53]

Role of H-Bonding in S_N2 and E2 Reactivity and Selectivity. The fluoride ion is a small and highly reactive anion in the gas phase.[33,54] In the liquid phase, it is one of the most solvated single-charged anion. For example, its solvation free energy is −116.7 kcal mol^{-1} in water and −109.2 kcal mol^{-1} in methanol, which are two classical polar protic solvents.[55,56] This high solvation leads to small reactivity, which can be enhanced in polar aprotic solvents like dimethyl sulfoxide and acetonitrile. In these cases, its solvation free energy becomes −96.1 and −88.4 kcal mol^{-1}, respectively. Considering that these four solvents have high dielectric constants, the difference in solvation and reactivity is owing to the solvation shell close to the ion. In other words, the hydrogen bonds involving the fluoride ion and the first solvation shell in protic solvents are critical for controlling its reactivity.[47,57]

Almost 30 years ago, Landini et al. reported that nucleophilic activity of $\text{hexyl}_4N^+F^-(H_2O)_n$ in apolar solvents can be decreased by a factor of 10^3 when n increases from 0 to 8.5 water molecules.[58] In addition, they have observed that the effect on basicity (E2 reaction) is even greater, decreasing the reaction rate by a factor of 10^7 for six water molecules. Thus, although the reactivity is decreased for both S_N2 and E2 processes, the higher effect on the elimination favors the selectivity of the reaction toward the S_N2 process in the presence of hydrogen bonds. Subsequent studies reported in 1998 have indicated that for secondary alkyl halides the amount of alkenes produced is high, indicating that is need further developments for an efficient fluorination.[59]

The effect of hydrogen bonding and steric hindrance on the fluoride reactivity was also investigated by Yonezawa and coworkers[60] with a series of hydrogen-bonded TBAF complexes. For the S_N2 reaction of bromide benzyl with these complexes, they observed that the reaction rate was related directly to steric bulk and to number of groups able to form hydrogen-bonding present in the alcohol complexed with TBAF (*t*-BuOH ≫ *i*-PrOH > *n*-BuOH ∼ *n*-PrOH > H_2O). More recently, Kim et al.[61−63] have investigated the reactivity of CsF directly in bulky alcohol solvents and showed that the selectivity of the S_N2 process is enhanced in relation to E2. In addition, the TBAF(*t*-BuOH)$_4$ complex was isolated and characterized in 2008 by the same group. This complex is more selective for the nucleophilic fluorination and easier to handle than TBAF (hydrated or anhydrous).[20] Extending these studies, Gouverneur and coworkers have shown that the TBAF(*t*-BuOH)$_4$ complex is very efficient in Pd- and Ir-catalyzed fluorination of allylic *p*-nitrobenzoates and carbonates,[44,64] while other fluoride sources are ineffective for these reactions. In 2015, the Gouverneur group synthesized and characterized several fluoride−alcohol complexes varying from two to four alcohol molecules, depending on the steric hindrance and branching of each alcohol. The selectivity was up to 4-fold S_N2 products in relation to the E2 products, although the reaction became slower.[49]

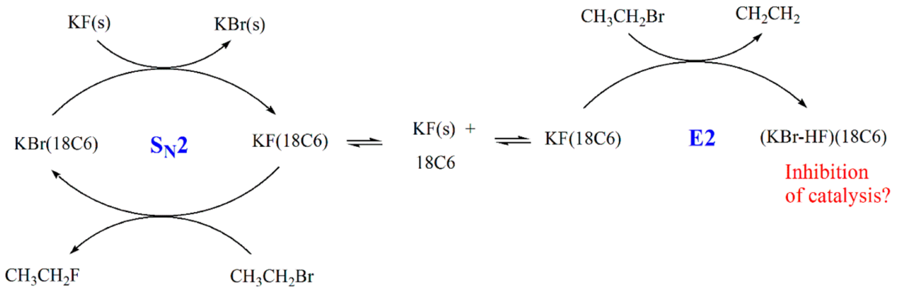
Scheme 1. Transition-State Receptors for S_N2 Reactions



Although hydrogen bonding retards anion−molecule S_N2 reactions, the possibility of using hydrogen bonds to selectively stabilize the S_N2 transition state was hypothesized by Pliego in 2005 (Scheme 1).[65] Theoretical calculations have indicated that this stabilization is possible and could lead to higher reactivity and selectivity toward an S_N2 process. The 1,4-benzenedimethanol (BDM) was theoretically investigated as a potential catalyst in nucleophilic fluorination.[57] However, the possibility of forming the $(F^-)_2(BDM)_2$ complex in DMSO solvent could eliminate any catalytic effect.[47] In order to overcome this shortcoming, Pliego proposed the use of hydroxylated molecular cavities.[47] Theoretical calculations have indicated that a molecular cavity with four hydroxyls and a relative steric hindrance is effective for excellent selectivity toward S_N2 reaction.[46] Thus, it was found that the NPTROL structure (Scheme 1) is able to complex with the reactants and to make the S_N2 transition state 5 kcal mol^{-1} more stable than the E2 transition state. Additionally, the predicted free energy barrier for the S_N2 process in DMSO solvent has remained as low as 18 kcal mol^{-1}, indicating a rapid kinetics. These findings support the view that a molecular cavity with strategically positioned hydroxyl groups can selectively accelerate nucleophilic fluorinations using free fluoride ions.

Crown Ether Catalysis. The use of KF as reagent in nucleophilic fluorination is very desirable since this salt is inexpensive and easily available. However, it requires a solid−liquid phase-transfer catalyst. With the discovery of crown ethers by Pedersen[66] in 1967, the potential use of crown ethers

Scheme 2. Proposed Catalytic Cycles through S_N2 and E2 Pathways: Solubilization of KF by 18C6, Reaction between KF Complexed with 18C6, KF(18C6), and the Alkyl Bromide; Regeneration of Complex KF(18C6)[a]



[a] In the E2 mechanism, the release of HF could inhibit the catalysis.

as phase-transfer catalysts has been explored. As early as 1974, Liotta and Harris[67] observed that 18C6 is able to catalyze the reaction of primary alkyl bromides with KF in benzene, leading to 92% of S_N2 product. However, the reaction takes several days to complete at high temperature, which makes it less useful.

The interest in crown ethers (and similar species) as catalysts in nucleophilic fluorination has resurged in past 10 years. In 2007, Stuart and Vidal investigated a new diaza-18-crown-6 derivative for fluorination of 2,4-dinitroclorobenzene and found it to be slightly superior to dibenzo-18-crown-6.[68] In 2009, Lee et al. reported that tri- and tetraethylene glycol are efficient solvents for nucleophilic fluorinations.[69] This property was attributed to the ability of these hydroxylated polyethers to interact with both the potassium cation and the fluoride ion, facilitating its solubilization and decreasing the fluoride basicity. Additional studies with penta- and hexaethylene glycol have shown these species are even more efficient.[70] Furthermore, those authors have found that methylation on the hydroxyl groups of pentaethylene glycol decreases the reactivity.

With the aim of understanding how crown ethers work at a molecular level, Pliego and Riveros have recently reported a theoretical study of the model reaction between ethyl bromide and KF catalyzed by 18C6.[71] The proposed mechanism is presented in Scheme 2. The initiation step is the dissolution of the KF by the 18C6 in apolar solvent. In the next step, which initiates the catalytic cycle, there is a nucleophilic attack of the complexed fluoride ion to the substrate (alkyl halide). The strong complexation of the crown ether with the potassium cation makes the fluoride anion highly reactive, and the calculated activation free energy barrier was as low as 14 kcal mol^{-1}. However, the next catalytic step is the exchange reaction between the solid KF and the KBr(18C6) complex, regenerating the KF(18C6) species. Unfortunately, this step requires 11 kcal mol^{-1} and leads to a slow final kinetics. Another important result was the observation that the crown ether makes the E2 mechanism less favorable and the main product is the alkyl fluoride.

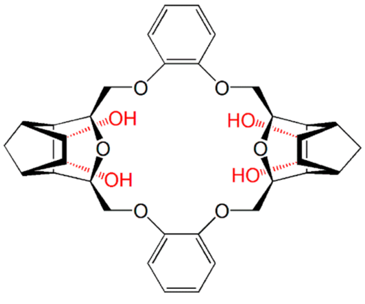
In the past year, the Kim group evaluated the reactivity of the KF(18C6) toward an alkyl mesylate.[72] In this case, they found the reactivity was much lower than that of bromide as the leaving group. Since the reaction takes place in benzene, they observed only 13% conversion after 12 h at 100 °C. These kinetics findings correspond to a free energy barrier of 31 kcal mol^{-1}.

The idea of combining crown ether and hydroxyl groups was further explored by Kim and co-workers.[48] An interesting example was the combination of 18C6 with calix[4]arene (BACCA), generating a species able to complex with CsF. The idea behind this approach is to complex the cesium ion with the crown ether moiety while the fluoride ion complexes with two *tert*-alcohol groups of the BACCA molecule. In the view of those authors, the separation of Cs^+ and F^- ions would promote the higher reactivity of the fluoride ion, even considering its interaction with hydroxyl groups. Thus, the fluorination of an alkyl mesylate in acetonitrile solvent and using KF led to 42% conversion in 24 h at 100 °C. On the basis these data, an activation free energy barrier of 30 kcal mol^{-1} can be estimated.

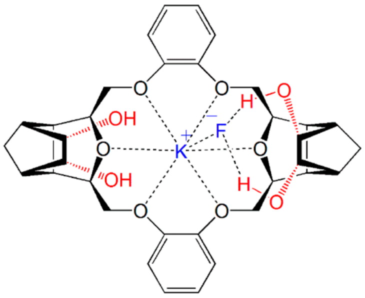
Merging the Catalytic Concepts. The use of crown ether and hydrogen bonds has proved to be a useful approach for creating new molecules able to promote or catalyze nucleophilic fluorination. In particular, we think that hydroxyl groups should be placed in distant positions as shown in Scheme 1 to stabilize the transition state. In the case of crown ethers, the problem of an exchange reaction as in Scheme 2 indicates the need to stabilize the fluoride ion more than the bromide ion to favor this step. Because it known that the fluoride ion has a stronger interaction with a water molecule than the chloride (and bromide), the introduction of hydroxyl groups in crown ether would favor this exchange. Therefore, the new hydroxylated crown ether presented in Scheme 3 was designed. The idea is that this structure will favor the exchange reaction and would stabilize the S_N2 transition state. Thus, this report presents a theoretical study the reaction between KF and CH_3CH_2Br in toluene, exploring the new designed molecule as a potential catalyst. Its structure, based on dibenzo-18-crown-6 and four hydroxyl groups strategically positioned, was named DB18C6-4OH. The use of a reliable level of theory can provide important insights and predictions on this process and be useful in the development of this new class of catalysts.

Ab Initio Calculations. The reaction of KF(DB18C6-4OH) with ethyl bromide was studied by electronic structure methods. Full geometry optimization and harmonic frequency calculations were carried out with the X3LYP[73] functional and 6-31(+)G(d) basis set. This basis corresponds to the 6-31G(d) basis set for C, H, and K atoms and the 6-31+G(d) basis set for N, O, F, and Br atoms. The choice of the X3LYP functional is based on its good performance for obtaining geometries and describing hydrogen bonds. In addition, it performs better than the widely used B3LYP functional.[74,75] The solvent effect (toluene) was included by means of an integral equation formalism polarizable continuum model (IEF-PCM)[76−79] and the SMD method,[80] which includes a non-electrostatic solvation contribution. In this case, we have used X3LYP/6-31(+)G(d) electronic density.

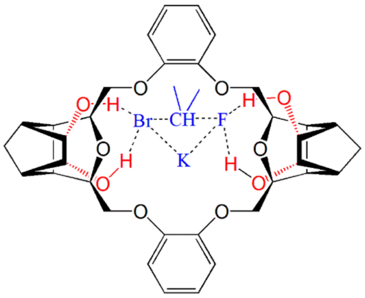
Scheme 3. DB18C6-4OH Phase-Transfer Catalyst Designed in This Work and Its Action Mechanism



Catalyst



Catalyst complexed with KF



Catalyst interacting with the S_N2 transition state

To obtain reliable electronic energies, single-point energy calculations were performed with the ONIOM method.[81] This is a composed approach, and a part of the system, named model system, is described by a higher level of theory, while the whole system is treated by a lower level of theory. The energy of the ONIOM method is obtained through eq 1:

$$E_{\text{ONIOM}} = E^{\text{lower level}}_{\text{real system}} + (E^{\text{higher level}}_{\text{model system}} - E^{\text{lower level}}_{\text{model system}}) \quad (1)$$

In the present study, the model system is the species KF + CH_3CH_2Br and the real system includes the catalyst. The MP4 method was used for the model system and the MP2 method for the complete system, and both of these calculations used the Ahlrichs def2-TZVPP basis set[82] extended with sp diffuse functions on F, Cl, N, O, and Br with exponents 0.07, 0.05, 0.05, 0.06 and (0.055(s)/0.033(p)), respectively. These basis sets are similar to the minimally augmented Karlsruhe basis sets of Truhlar and co-workers.[83] Therefore, our calculations correspond to the ONIOM (MP4/TZVPP+diff: MP2/TZVPP+diff) level.

Another system investigated was the S_NAr reaction between the KF(DB18C6-4OH) complex and *p*-bromobenzonitrile in toluene solution. The level of theory was the same as that used for the S_N2 reaction.

The free energy for reaction and activation steps was calculated by eqs 2 and 3

$$\Delta G^*_{\text{g}} = \Delta E_{\text{elet}} + \Delta G^*_{\text{vrt}} \quad (2)$$

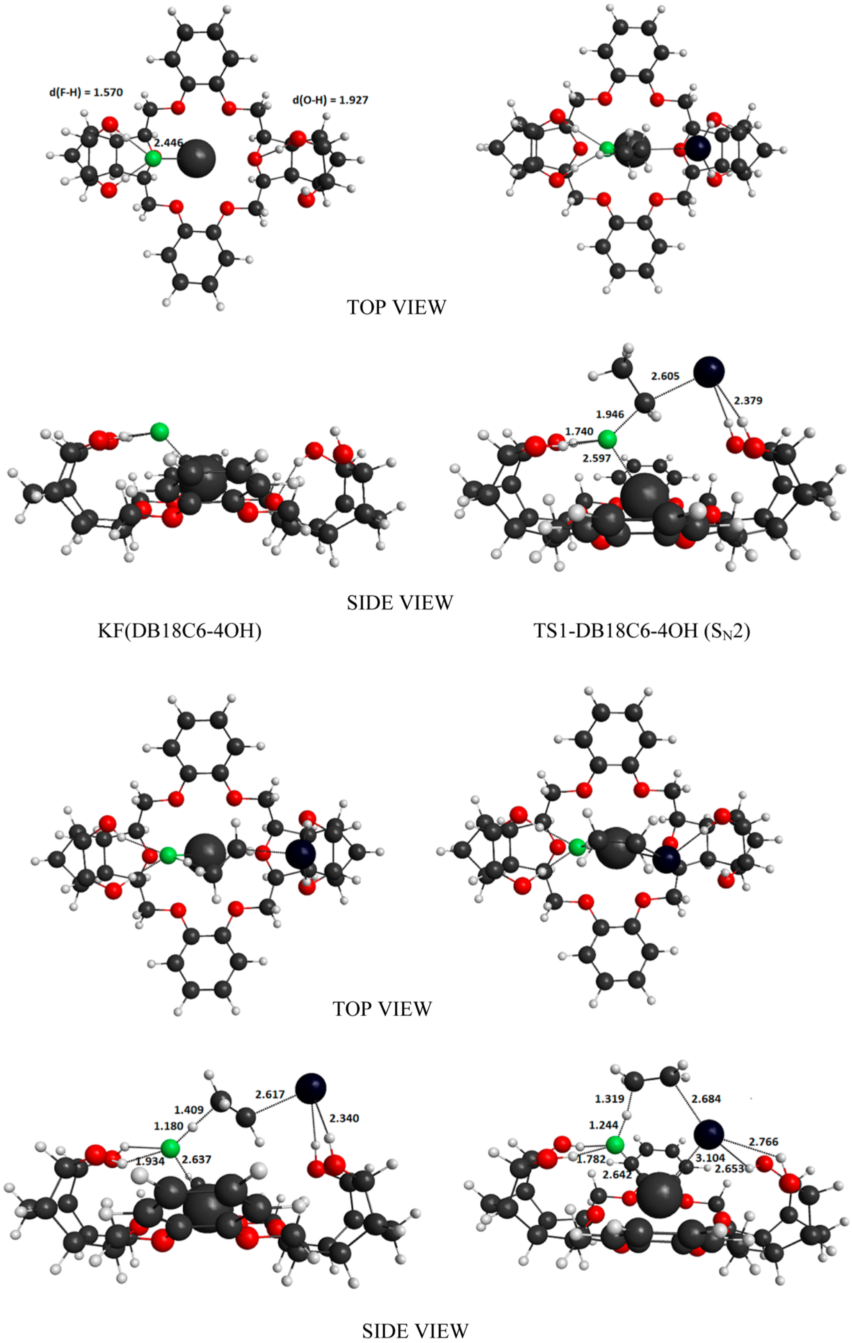
$$\Delta G^*_{\text{sol}} = \Delta G^*_{\text{g}} + \Delta\Delta G^*_{\text{solv}} \quad (3)$$

where ΔE_{elet} is the electronic energy contribution and ΔG^*_{vrt} is vibrational, rotational, and translational contributions obtained through calculations of harmonic vibrational frequencies. The sum of these terms leads to the gas-phase free energy contribution. The $\Delta\Delta G^*_{\text{solv}}$ term was obtained from the calculation of the solvation free energy using the SMD solvation model. For all of these processes, the standard state of 1 mol L^{-1} was used for both gas and solution phases as indicated by an asterisk. All calculations were carried out with the GAMESS[84] and FIREFLY[85] programs.

■ RESULTS AND DISCUSSION

Stability of the KF(DB18C6-4OH) and KBr(DB18C6-4OH) Complexes. An important step in the solid−liquid phase-transfer catalysis is the solubilization of the salt via formation of the KF(catalyst) complex. The structure of this complex, named KF(D18C6-4OH), is presented in Figure 1, and it can be seen that the fluoride ion interacts with both the potassium ion and the two hydroxyl groups. The bond length between the fluoride ion and the hydroxyl hydrogen is 1.57 Å, suggesting a very strong interaction. The thermodynamics data are presented in Table 1. The interaction energy of the KF with DB18C6-4OH is 56.2 kcal mol^{-1}, while the interaction with 18C6 is only 42.3 kcal mol^{-1}. Considering the solid KF, we have combined experimental thermodynamics data with theoretical values to estimate the standard free energy for solubilization of KF in toluene using DB18C6-4OH (process 11, Table 1). A value of 1.6 kcal mol^{-1} was calculated for this process using processes (3), (5), and (6), indicating an enhanced ability of the new crown ether to solubilize the KF salt. For comparison, in the case of 18C6, this free energy is 15.3 kcal mol^{-1} (using processes (1), (5), and (6) to obtain the process (9)). This high value points out that the new catalyst scaffold is much more efficient than 18C6 for solubilizing KF. The same analysis was performed for KBr. In this case, the bond length between the Br atom and the hydroxyl hydrogen is 2.33 Å. The free energies for solubilization of KBr (calculated using processes (2), (7), and (8) for obtaining the process (10) and applying processes (4), (7), and (8) for obtaining the process (12)) are 1.2 and 3.8 kcal mol^{-1} with DB18C6-4OH and 18C6 in toluene, respectively. These results show the higher affinity of the new catalyst with KF and a small effect for KBr if compared to 18C6. Such a property is very important for the efficiency of the catalyst because it facilitates the solubilization of KF, while the KBr generated in the process does not inhibit the reaction.

In the above analysis, a point not taken in consideration in our previous study on crown ether catalysis can be observed.[71] The free energy for solubilization of KBr by 18C6 is positive by 3.8 kcal mol^{-1}, meaning that the KBr released in the reaction forms solid KBr and free 18C6. As a consequence, the exchange reaction in Scheme 2 does not contribute to the overall barrier. Rather, the solubilization of solid KF by the 18C6 is a critical step. This fact increases the overall activation free energy



KF(DB18C6-4OH) TS1-DB18C6-4OH (S_N2)

TS2-DB18C6-4OH (E2-anti) TS3-DB18C6-4OH (E2 syn)

Figure 1. Structures of the complexes and transition states involving the DB18C6-4OH catalyst and the KF + CH_3CH_2Br system (bond lengths in angstroms).

barrier and makes our predicted value closer to the experimental one. This point will be discussed ahead along with the reaction free energy profile (Figure 2).

S_N2 and E2 Reactions of KF(DB18C6-4OH) with CH_3CH_2Br. The reaction between KF complexed with DB18C6-4OH and ethyl bromide was studied in toluene solution. This analysis can provide the effect of the new crown ether catalyst on the reactivity and selectivity. The reaction pathways are presented in Scheme 4. The fluorination takes place through the S_N2 mechanism, while the E2 process occurs via both syn and anti transition states. The optimized structures are presented in Figure 1. We can notice the TS1-cat structure corresponds to the S_N2 transition state interacting with the DB18C6-4OH catalyst and supports our conceptual view of the mode of action envisioned in Scheme 3. The activation free energy barrier is 21.7 kcal mol^{-1}. Considering that the solubilization free energy is only 1.6 kcal mol^{-1}, the final barrier becomes 23.3 kcal mol^{-1}, indicating that the DB18C6-4OH catalyst is able to promote efficiently nucleophilic fluorination.

The other two pathways via E2-anti and E2-syn are also able to interact with the new crow ether. However, the respective barriers involving the solubilized KF(DB18C6−4OH) are 23.9 and 26.9 kcal mol^{-1}. The difference of 2.2 kcal mol^{-1} for E2 anti in relation to the S_N2 mechanism indicates an important selectivity toward nucleophilic fluorination, which should

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Table 1. Reaction and Activation Data for Fluorination Catalyzed by DB18C6-4OH and 18C6 Using KF in Toluene Solution[a]

	relative data[b]	ΔE	ΔG_g	$\Delta\Delta G_{solv}$	ΔG_{sol}
	TS1-DB18C6-4OH (S_N2)	6.34	17.17	4.54	21.71
	TS2-DB18C6-4OH (E2 anti)	14.02	20.03	3.82	23.85
	TS3-DB18C6-4OH (E2 syn)	16.09	22.03	4.82	26.85
	CH_3CH_2F + KBr(DB18C6-4OH)	−8.39	−8.05	0.24	−7.81
	CH_2CH_2 + (KBr-HF)(DB18C6-4OH)	−10.08	−13.11	2.88	−10.23
	CH_2CH_2 + HF + KBr(DB18C6-4OH)	8.37	−3.05	−0.69	−3.74
	homogeneous processes	ΔE	ΔG_g	$\Delta\Delta G_{solv}$	ΔG_{sol}
(1)	KF(tol) + 18C6 → KF(18C6)[c]	−42.30	−31.45	5.98	−25.45
(2)	KBr(tol) + 18C6 → KBr(18C6)[c]	−48.38	−37.26	6.12	−31.14
(3)	KF(tol) + DB18C6-4OH → KF(DB18C6-4OH)	−56.16	−45.68	6.56	−39.12
(4)	KBr(tol) + DB18C6-4OH → KBr(DB18C6-4OH)	−48.51	−38.49	4.78	−33.71
	heterogeneous processes				ΔG
(5)	KF(s) → KF(g)[c]				48.3
(6)	KF(g) → KF(tol)				−7.59
(7)	KBr(s) → KBr(g)[c]				42.0
(8)	KBr(g) → KBr(tol)				−7.07
(9)	KF(s) + 18C6 → KF(18C6)				15.3
(10)	KBr(s) + 18C6 → KBr(18C6)				3.8
(11)	KF(s) + DB18C6-4OH → KF(DB18C6-4OH)				1.6
(12)	KBr(s) + DB18C6-4OH → KBr(DB18C6-4OH)				1.2

[a] Units in kcal mol^{-1}. Standard state of 1 mol L^{-1} for both gas and solution phases. Geometry optimizations at the X3LYP/6-31(+)G(d) level. Single-point energies at ONIOM(MP4/TZVPP+diff: MP2/TZVPP+diff) level and solvent effect using the SMD method. [b] Data relative to the CH_3CH_2Br + KF(DB18C6-4OH) reactants in toluene solution. [c] Taken from ref 71.

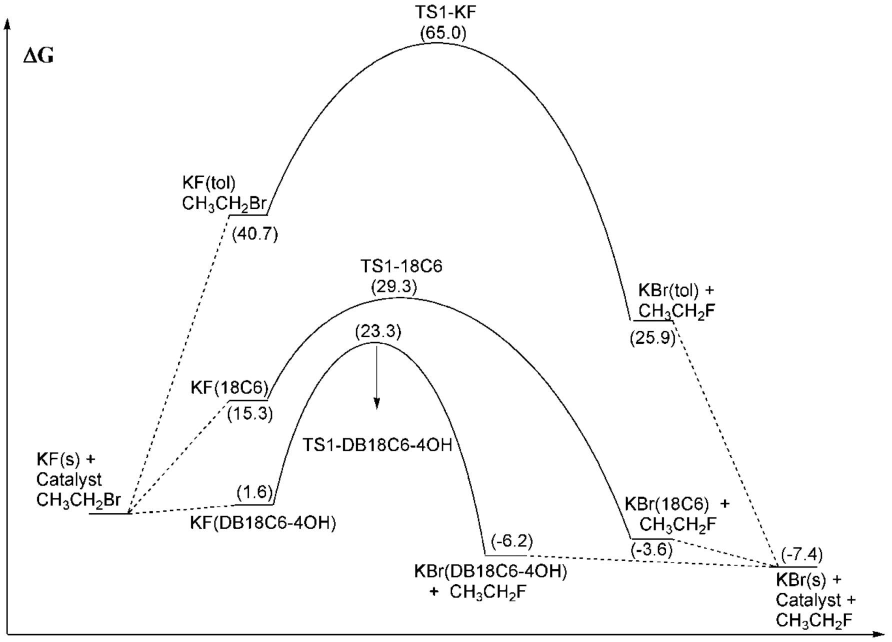

Figure 2. Free energy profile for S_N2 reaction of KF(s) with ethyl bromide in toluene solution involving solubilized potassium fluoride (KF(tol)), KF complexed with 18-crown-6, and KF complexed with DB18C6-4OH. (Values for activation and reaction of KF(s) + CH_3CH_2Br and KF(18C6) + CH_3CH_2Br processes were taken from ref 71.)

correspond to 97% of the products. Similar to 18C6, the formation of HF in the E2 pathway leads to a stable (KBr-HF)(DB18C6-4OH) complex, which probably inhibits the catalysis.

The data presented in Table 1 allow us to build a free energy profile of the reaction. For a better appreciation of the catalytic property of the new molecule, the free energy data for the reaction of free KF with ethyl bromide and the effect of the 18C6 catalyst reported in a previous study are included.[71] The free energy profile for these three processes is presented in Figure 2. In the analysis of the reaction of free KF in toluene, the solubilization of this species require 40.7 kcal mol^{-1} and its reaction through the S_N2 mechanism requires more 24.3 kcal mol^{-1},[71] leading to a final barrier of 65 kcal mol^{-1}. This is a very high barrier, and no reaction by this pathway will be observed. In fact, it is possible that the reaction of CH_3CH_2Br with the solid KF, taking place on its surface, is more favorable.

The other process is the reaction catalyzed by 18C6. The solubilization of KF by 18C6 requires a free energy of 15.3 kcal mol^{-1}, which is 25.4 kcal mol^{-1} lower than solubilization of free

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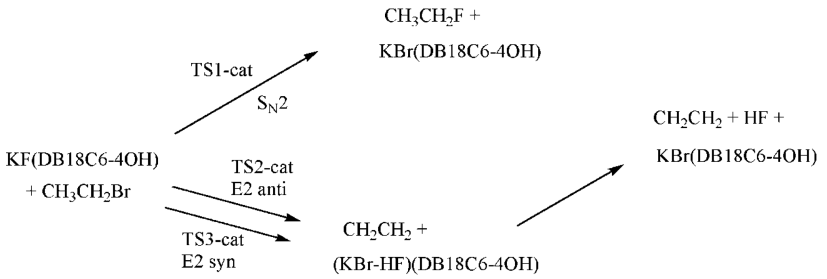
Scheme 4. Reaction Steps of the KF Complexed with the Catalyst (cat = DB18C6-4OH)



KF. The barrier for the S_N2 process is 14.0 kcal mol^{-1}, and adding these two steps, the final barrier becomes 29.3 kcal mol^{-1}. The KBr(18C6) complex is 3.8 kcal mol^{-1} above the KBr(s) + 18C6 products. Therefore, following the catalytic cycle of Scheme 2, the KBr(18C6) species formed leads to KF(18C6), which releases the 18C6 catalyst and initiates the process again. At 25 °C, the calculated free energy of activation is 29.3 kcal mol^{-1}, while the experimental value was estimated as 30.3 kcal mol^{-1} at 90 °C. This excellent agreement is an important support for the mechanism proposed in this work. In addition, we can notice the catalytic effect is very high, decreasing the overall barrier by 35.7 kcal mol^{-1}!

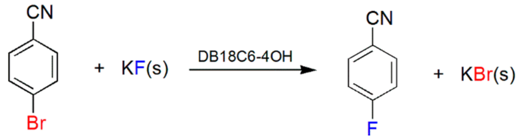
The new catalyst designed in this work overcomes an important limitation of the 18C6 species: the solubilization of the KF. The free energy for this process is only 1.6 kcal mol^{-1}, indicating that the interaction of the fluoride ion with the two hydrogen bonds is very effective. In the activation step, the reaction of ethyl bromide with the KF(DB18C6-OH4) has a barrier of 21.7 kcal mol^{-1}. The sum of these two steps leads to the overall barrier of only 23.3 kcal mol^{-1}. Compared with the 18C6, the barrier decreases by 6 kcal mol^{-1}, amounting to a rate acceleration effect of 10^4! This very meaningful catalytic effect should make this catalyzed process very effective and useful. For a more quantitative evaluation, we can write a kinetic model. Based on the free energy profile, the reaction rate is given by eq 4

$$\frac{d[\mathrm{EtBr}]}{dt} = -k_2 K_{\mathrm{sol}} C_{\mathrm{cat}}[\mathrm{EtBr}] \tag{4}$$

where k_2 (7.7×10^{-4} L mol^{-1} s^{-1}, at 25 °C) is the solution-phase bimolecular reaction rate constant, K_{sol} (0.067, 25 °C) is the solubilization equilibrium constant, and C_{cat} is the catalyst concentration. Considering the last value is 0.10 mol L^{-1}, the pseudo-first-order rate constant becomes 5.2×10^{-6} s^{-1}. Using the same free energy values at 70 °C, it can estimated that 98% of the reaction takes place within 1 h. If these data are correct, the DB18C6-4OH is the most efficient phase-transfer catalyst designed for nucleophilic fluorination to date. For comparison, two previous reports[48,72] have presented catalysts with activation barriers around 30 kcal mol^{-1}. In the case of the new catalyst investigated in this paper, the barrier is predicted to be only 23.3 kcal mol^{-1}. In addition, many prior studies require CsF as substrate, while the present catalyst is able to work with KF. In our view, this difference is due to the strategically positioned hydroxyl groups, which interact with the center of negative charge of the transition state. Thus, the combination of hydrogen bond with the crown ether seems to be a very effective strategy for fluorination of alkyl halides.

S_NAr Reaction of KF(DB18C6-4OH) with *p*-Bromobenzonitrile. It is worthwhile to analyze the possibility of the new catalyst being active for aromatic fluorination. Thus, we also studied the catalytic effect of DB18C6-4OH for aromatic nucleophilic substitution (S_NAr) reactions. The studied reaction is the fluorination of *p*-bromobenzonitrile as indicated in Scheme 5 below. The reaction was evaluated with and without the catalyst. The results are shown in Table 2 and Figure 3.

Scheme 5. S_NAr Reaction Investigated in This Work



The transition state related to the reaction of the potassium fluoride in toluene, KF(tol), (without catalyst) has a free energy barrier of 22.8 kcal mol^{-1}, which can be compared with the barrier of 24.3 kcal mol^{-1} for the previously investigated S_N2 process. Nevertheless, the free energy of 40.7 kcal mol^{-1} for solubilization of the KF(s) makes this pathway unviable.

In the case of a catalyzed S_NAr process, represented by Scheme 5, the free energy barrier involving the soluble complex is 25.2 kcal mol^{-1}, whereas the S_N2 reaction has a barrier of 21.7 kcal mol^{-1}. Adding the 1.6 kcal mol^{-1} for solubilization of KF(s) through complexation with DB18C6-OH4, the final barrier for the S_NAr process becomes 26.8 kcal mol^{-1}. Considering the reaction takes place at 90 °C and that the free energy barrier does not change with the temperature, a time of 24 h can be estimated for 99% conversion. Looking at both transition states, a more efficient hydrogen bond between the catalyst and the S_N2 transition state than for the S_NAr one is noticed. In fact, the more compact S_NAr transition state would benefit from less distant hydroxyl groups.

For comparison, Sanford and co-workers[38] have investigated the reactivity of tetramethylammonium fluoride (TMAF) in dimethylformamide solvent. They have reported that the reaction between 2-bromobenzonitrile with anhydrous TMAF provide 48% of product at 25 °C, within 24 h. Considering a bimolecular kinetics, this translate to a free energy barrier of 24.3 kcal mol^{-1}, a few kcal mol^{-1} below of our catalyzed barrier. A similar reaction was theoretically investigated by Pliego and Pilo-Veloso.[34] They have calculated a barrier of 26.3 kcal mol^{-1} for S_NAr reaction of TMAF with *p*-chlorobenzonitrile in dimethyl sulfoxide solvent at 25 °C. If the present calculations are accurate, the process simulated has an advantage over that with TMAF one, once it makes use of KF reagent and toluene solvent. Furthermore, it is evident that a more efficient catalyst can be designed for the S_NAr reaction. The new catalyst should have the hydroxyl groups in opposed positions closer each other to better stabilize the S_NAr transition state.

Table 2. Thermodynamics Data for S_NAr Reaction[a]

processes	ΔE	ΔG^*_g	$\Delta\Delta G^*_{solv}$	ΔG^*_{sol}
p-bromobenzonitrile + KF(tol) → TS4[b]	9.97	17.87	4.88	22.75
p-bromobenzonitrile + KF(tol) → *p*-fluorobenzonitrile + KBr(tol)	−16.26	−15.75	2.20	−13.55
p-bromobenzonitrile + (KF) (DB18C6-4OH) → TS4-cat	12.41	22.57	2.64	25.21
p-bromobenzonitrile + (KF) (DB18C6-4OH) → *p*-fluorobenzonitrile + (KBr) (DB18C6-4OH)	−8.61	−8.55	0.42	−8.13

[a] Units in kcal mol^{-1}. Standard state of 1 mol L^{-1} for both gas and solution phases. Geometry optimizations at X3LYP/6-31(+)G(d) level. Single-point energies at ONIOM(MP4/TZVPP+diff: MP2/TZVPP+diff) level and solvent effect using the SMD method. [b] TS4 is the transition state for the uncatalyzed reaction.

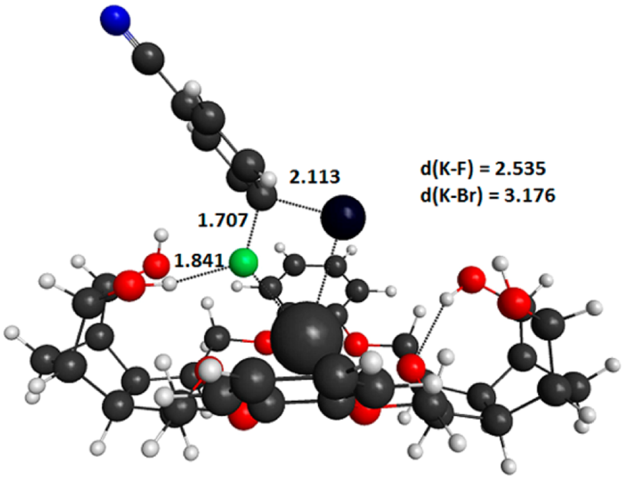


Figure 3. Structure of the TS4-DB18C6-4OH transition state relative to the catalyzed S_NAr reaction of KF(DB18C6-4OH) with *p*-bromobenzonitrile.

CONCLUSIONS

A new crown ether scaffold based on dibenzo-18-crown-6 with strategically positioned four hydroxyl groups has been designed and computationally evaluated for catalytic activity. On the basis of this high level of theory, the proposed catalyst is much more efficient than 18-crown-6 ether for solubilizing KF in toluene solution. In addition, the strong interaction of the new catalyst with the S_N2 transition state for fluorination of ethyl bromide leads to a free energy barrier 6 kcal mol^{-1} lower than that calculated for 18C6, resulting a reaction rate 10^4 times higher. The calculations have also indicated that the catalyst is selective toward the fluorination and the competitive E2 process is 2.2 kcal mol^{-1} less favorable, resulting in 97% of selectivity for fluorination of a primary halide. The feasibility of the catalyst to be active for fluorination of aromatics via the S_NAr process has also been investigated. In this case, the interaction of the catalyst with the S_NAr transition state is less effective, although the catalysis is also feasible. In summary, a new crown ether scaffold was designed with very promising catalytic activity, which can be very useful in selective nucleophilic fluorination using the cheap, green, and available KF as the reagent.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01624.

Coordinates of the optimized structures (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: pliego@ufsj.edu.br.

Notes

The authors declare no competing financial interest.

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