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Origin of Octafluorocyclopentene Polyelectrophilicity

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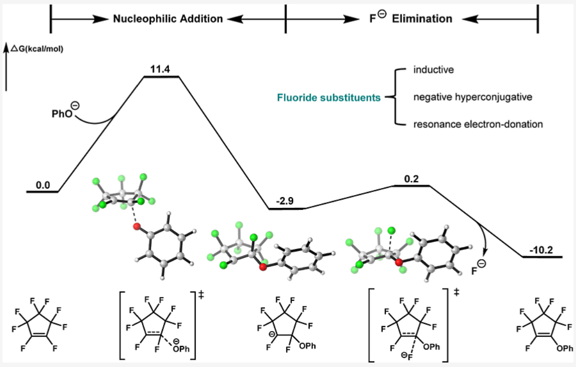
ABSTRACT: Octafluorocyclopentene (OFCP) has found utility as a polyelectrophile in substitution cascades that form complex macrocyclic compounds. The Harran group synthesis of macrocyclic polypeptides depends on OFCP as a linker, combining with four different nucleophilic units of a polypeptide. We report a computational investigation of the origins of OFCP reactivity and a rationale for controlled mono-, di-, tri-, and tetrasubstitution of fluoride ions by heteroatomic nucleophiles. The roles of inductive, negative hyperconjugative, and resonance electron-donation by fluoride substituents are explored for the reaction of OFCP, less-fluorinated analogues, and common electrophilic alkenes with several different nucleophiles.



1. INTRODUCTION

Octafluorocyclopentene (OFCP) is a potently electrophilic alkene that generally gives substitution rather than addition products (Figure 1A). Mono- and divinylic substitution reactions occur with hydroxide,[1] alkoxide,[1−3] thiolate,[4] and amine nucleophiles.[3] In addition, organolithium,[5] Grignard,[5] and heteroaromatic lithium[6] reagents have been found to react with OFCP, forming 1,2-disubstituted products. Enolates[6] and phosphonium ylides[6] have also been shown to form 1,3-disubstituted products. Shreeve et al. also demonstrated that OFCP can be tetrasubstituted with imidazoles or hexasubstituted with triazoles. This difference in reactivity is likely due to triazole being more electron withdrawing than imidazole.[7] OFCP reacts through a nucleophilic addition−elimination mechanism,[6] as illustrated in Figure 1A.

Given OFCP's polyelectrophilic nature, it has many potential applications. Yoshida[8] and Hell[9] both expanded upon Irie's[10] synthesis of photochromic diarylethenes. These compounds, formed by reacting OFCP with heteroaryllithium compounds, have significant potential for biological imaging and labeling and can be readily synthesized on a commercial scale (Figure 1B).

The Harran group has recently shown that OFCP reacts with nucleophilic peptides to form complex polycyclic derivatives.[11,12] Side chain and C-terminal nucleophiles engage OFCP in highly regioselective substitution cascades. Depending on the reaction conditions and substrate, up to four fluorine atoms of OFCP are replaced by peptidyl heteroatoms (Figure 2). The resulting macrobicyclic structures are being studied by the Harran group[11] as stable shape mimics of diverse loop structures that mediate intracellular protein−protein interactions. Moreover, the dynamic changes in the conformation of macrocycles, along with their high surface area in certain protein−protein interactions, make them promising candidates for potential therapies in the treatment of various diseases and conditions.[13]

Prompted by these successes, we have undertaken a more general overview of the reaction of OFCP with various nucleophiles. We have characterized the electrophilicity of OFCP in reactions with various nucleophiles and compared its electrophilicity with that of other common electron-deficient alkenes. In doing so, we show how the relative nucleophilicities of different peptide side chains lead to macrocyclic peptides, as generalized in Figure 2.

2. BACKGROUND

Wang and Borden previously compared the cycloaddition reactivity difference between tetrafluoroethylene (TFE) and ethylene. The high reactivity of TFE is attributed to its low π-bond strength stemming from the energetic cost of planarizing the two CF_2 groups.[14] OFCP differs from TFE in having two fluorines and two perfluoroalkyl substituents on the double bond. Although fluorine is an inductively electron-withdrawing group, it is also a resonance electron donor. In contrast, a perfluoroalkyl group acts only as a powerful electron withdrawer through both negative hyperconjugation and inductive effects.

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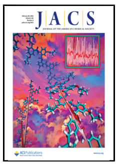

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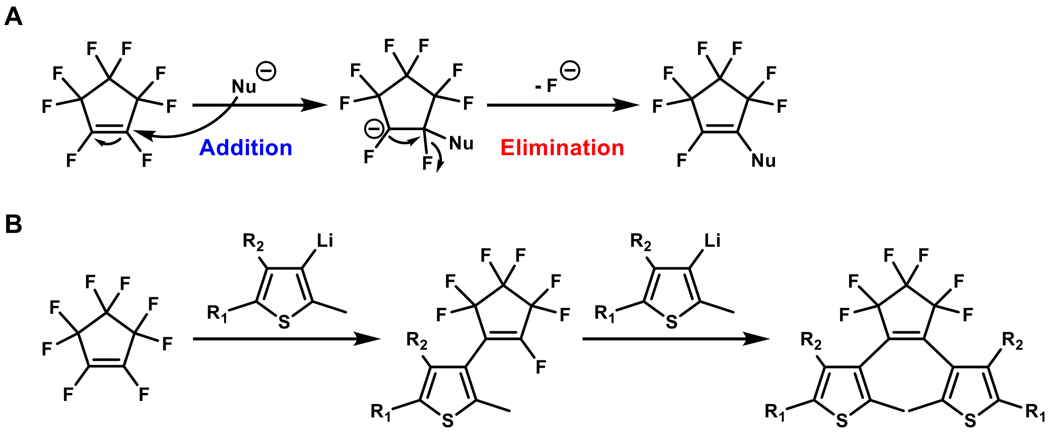


Figure 1. (A) OFCP addition−elimination reaction with nucleophiles. (B) Irie's[10] synthesis of photochromic diarylethenes.

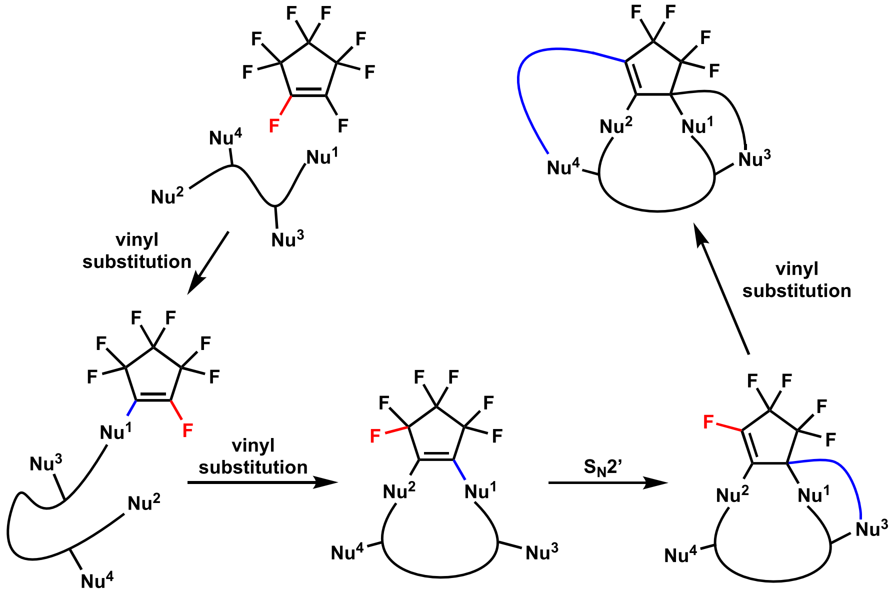


Figure 2. Harran synthesis of complex peptide macrocycles.[11,12]

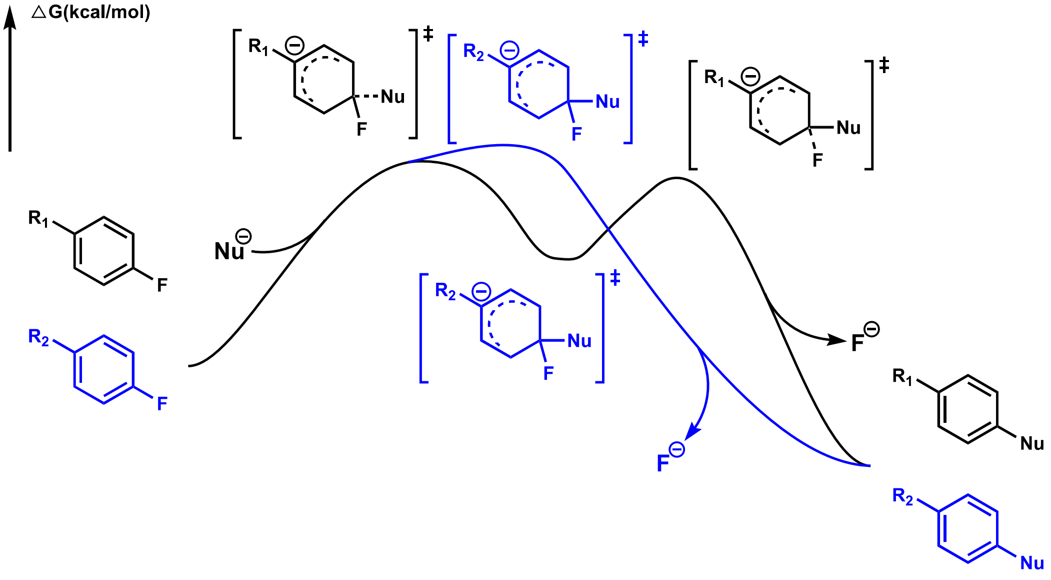


Figure 3. Stepwise and concerted mechanisms of aryl fluoride S_NAr reactions.

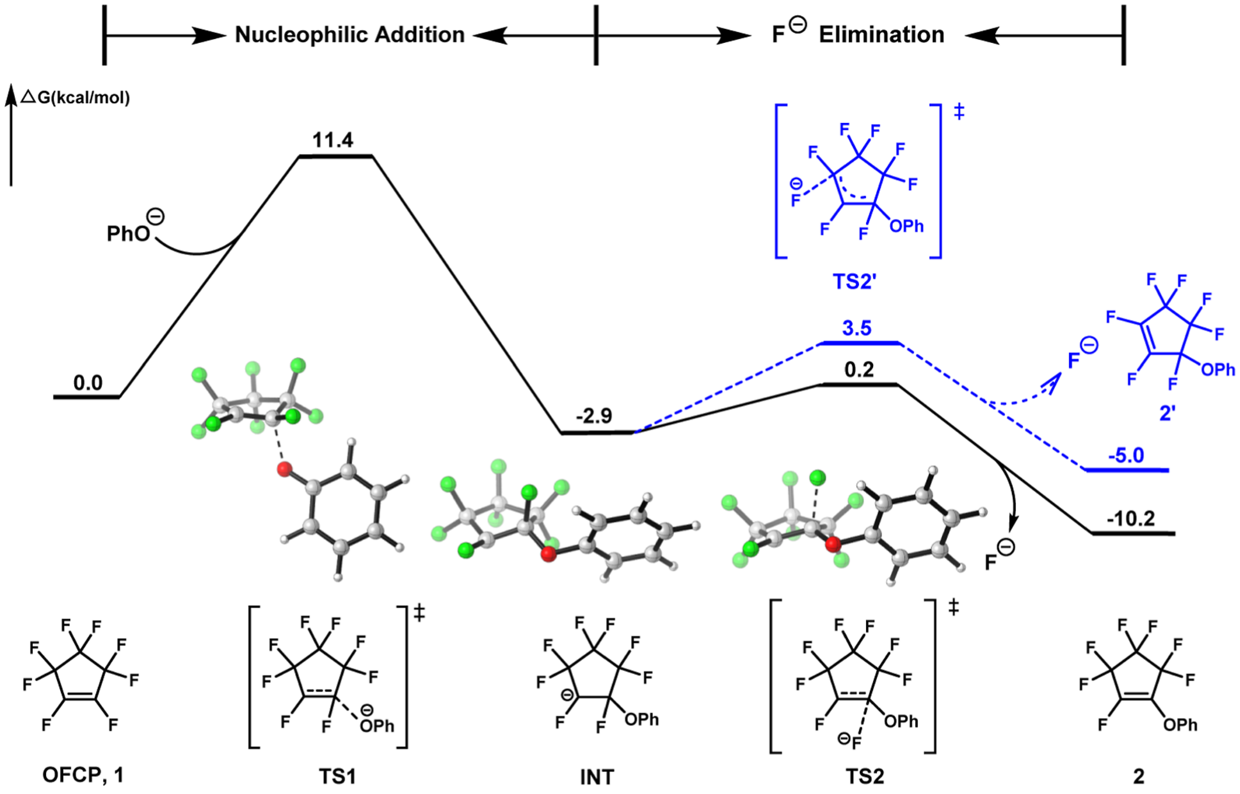


Figure 4. Free energy surface for the phenoxide reaction with OFCP.

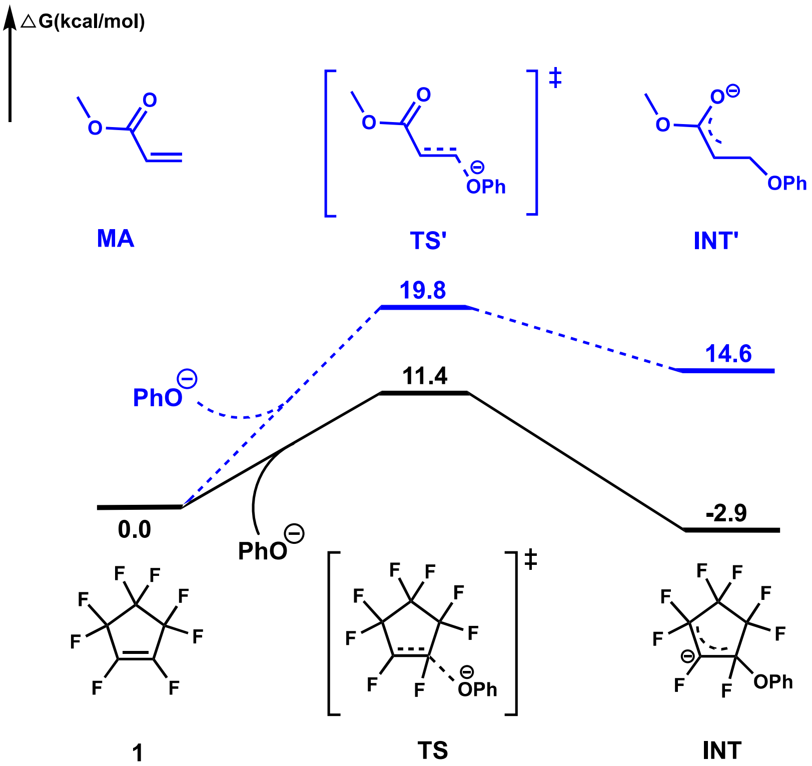


Figure 5. Nucleophilic addition reaction of phenoxide to methyl acrylate (MA) compared with that of OFCP.

Long et al. made energetic comparisons of OFCP and cyclopentene, giving possible reasons for why cyclopentene has a greater barrier to transition from an envelope shape to planar. They attributed this difference in energy to the electron-withdrawing fluorines of OFCP, which help to reduce the eclipsed torsion potential of its C−C bonds compared to those of cyclopentene.[15a] Zhang et al. characterized the thermal stability of polyfluorinated cyclopentene molecules by their bond orders, bond stabilization energies, strength of aromaticity, and AIMD simulations measuring bond deformation at 600

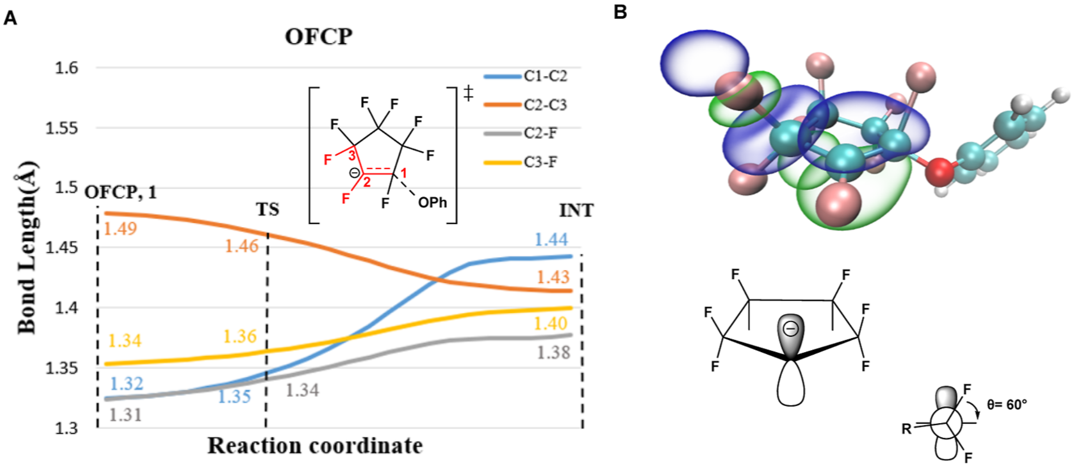


Figure 6. (A) Bond lengths during the nucleophilic addition of PhO^- to OFCP. (B) NBO orbital of the addition intermediate, which shows the n-σ*(C−F) hyperconjugation.

K.[15b] They found that the fluorination of the C═C bond increases OFCP's thermal stability compared to that of similarly fluorinated cyclopentene molecules such as hexa- and heptafluorocyclopentene, which lack two fluorine atoms on the C═C bond.[15b]

Liu and Zhang determined that C−C, C−N, C−O, C−S, and C−H bonds may be efficiently formed from polyfluoroarene compounds by nucleophilic replacement of a C−F bond.[16] However, the selectivity was difficult to control. The reaction shown in Figure 1A is related to S_NAr reactions of aryl fluorides. Rohrbach et al. found that for aryl fluorides undergoing S_NAr reactions, the electron affinity of the fluoroarene molecule was the greatest determinant of whether it would undergo a stepwise or concerted mechanism.[17] Specifically, an aryl fluoride with an electron affinity less than 10 kcal/mol was found to favor a concerted mechanism in which nucleophilic attack and fluoride loss proceed in one step.[16] On the other hand, an aryl fluoride with an electron affinity larger than 25 kcal/mol was found to prefer a stepwise mechanism in which a Meisenheimer intermediate is formed by nucleophilic attack.[17] (Figure 3). The region between 10 and 25 kcal/mol can occur by either of the —or both—mechanisms. Calcualtions show that electron affinity, rather than choice of nucleophile, is the primary determinant of the mechanistic pathway.[17]

3. RESULTS AND DISCUSSION

3.1. Mechanistic Studies. At the outset, we should mention that all of the reactions of nucleophiles with OFCP studied here do follow stepwise mechanisms, although the second step, loss of fluoride, may have a low barrier. In comparison to the results of Rohrbach et al.[17], we compute an electron affinity of 60 kcal/mol so the stepwise mechanism is expected and found.

We computed the energetics and mechanism of the reaction of phenoxide with OFCP using the M06-2X density functional and the def2-TZVP basis set using an SMD model for the DMF solvent (see Computational Methods). The energetics, transition states, and intermediates are shown in Figure 4.

OFCP is attacked by the nucleophile to generate carbanion intermediate INT. This can undergo elimination of the fluorine atom substituted on either the alkene carbon or the allylic carbon. There is a lower activation energy for elimination at the site of attack, presumably related to the greater stability of the alkene formed.

3.2. Origin of OFCP Electrophilicity. *3.2.1. OFCP vs a Common Electrophile, Methyl Acrylate.* We compared the reaction of a common electrophilic alkene, methyl acrylate (MA), with that of OFCP.

Figure 5 compares the barriers for these two reactions and shows that OFCP is much more electrophilic than MA, resulting in a product that is more stable than the reactants. We also explored the LUMO energies of these electrophilic alkenes. Their comparison is shown in Table 1. The lower LUMO energy of OFCP corresponds to the lower activation energy of its reaction (Table 1).

3.2.2. Effect of Vinylic and Allylic Fluoro Substituents. We also explored the addition of phenoxide to 1,2-difluorocyclopentene (1,2-diFCP) and to the hexafluoro compound.

Table 2 shows that substitution on the alkene slightly lowers the activation barrier for nucleophilic attack. Fluorine is resonance electron-donating and increases the LUMO energy. Nevertheless, it lowers the energy of the TS for nucleophilic addition of phenoxide slightly but lowers the energy of the intermediate substantially. This arises due to the electronegativity of F, which stabilizes both the anionic TS and the intermediate.

By contrast, allylic fluorides present in HFCP and OFCP decrease the LUMO energy substantially and also significantly stabilize both the TS and anion product. This very large stabilization by allylic fluorides is due to hyperconjugation, namely, the interaction of the occupied orbital of the carbanion lone-pair orbital with the σ* orbital of the CF bond, as shown in Figure 6B. Apart from vinylic and allylic fluoro substituents, it should be also noted that the other two additional fluorine substituents also help decrease the LUMO energy and stabilize the negative charge. Other electron-withdrawing substituents, such as a carbonyl group, give similar results (see Table S2).

Moreover, the Yu group reported a straightforward FMO method to quantify the electrophilicity by correlating reactivities from the Mayr equation with LUMO energies.[18] If electronic effects are the dominant factor affecting the reactivity, there should be a linear relationship between activation energies and LUMO energies. We also found a good linear relationship in our case when we changed the number of fluorine atoms (see Figure S2), which indicates that those fluorine atoms mainly act as electron-withdrawing anion stabilizers.

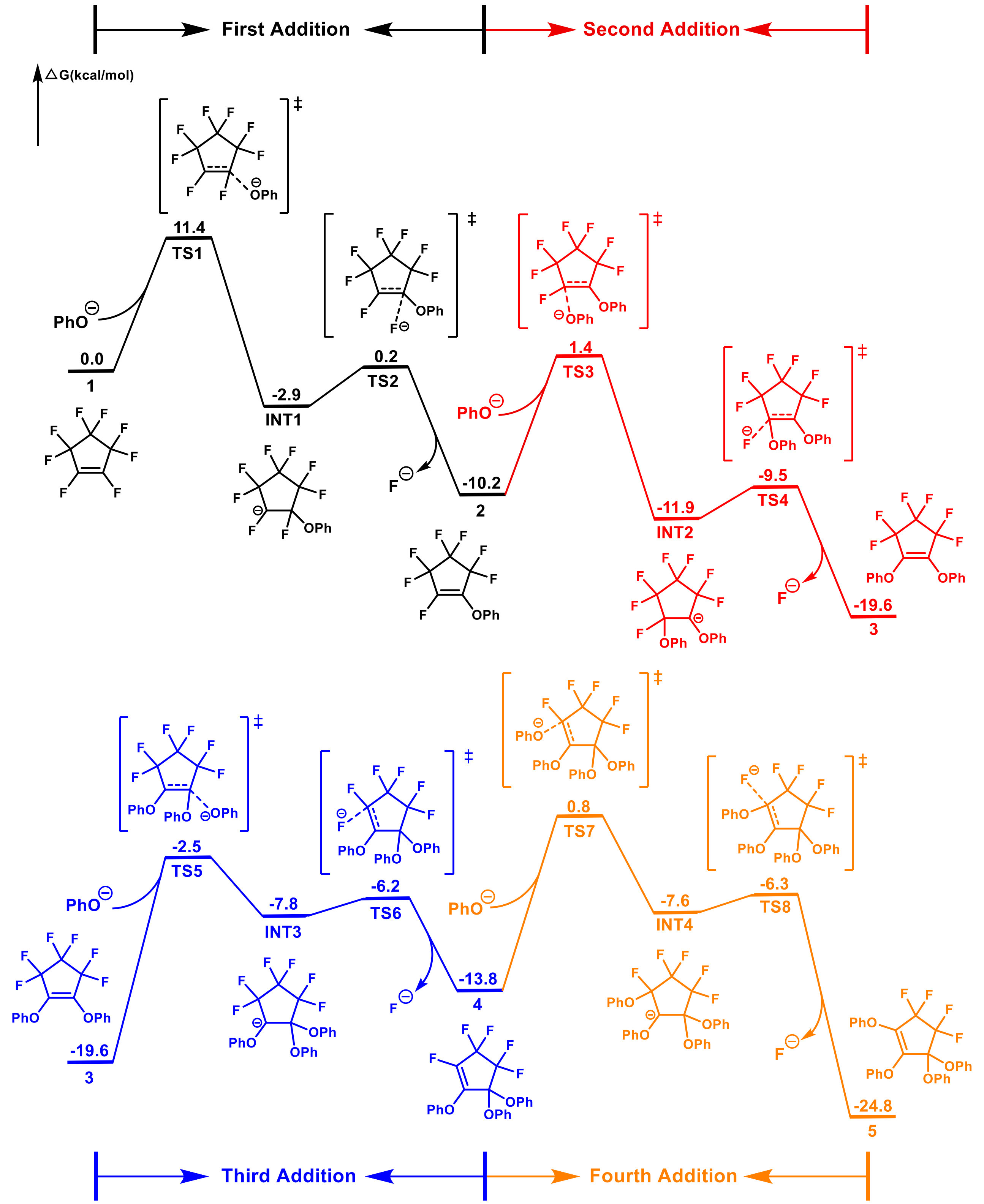


Figure 7. Energy profiles of the cascade reactions using multiple PhO^-s.

Figure 6A is a plot of the bond lengths during the nucleophilic addition step. C1−C2 stretches to 1.44 Å after nucleophile addition. C2−C3 shortens to 1.43 Å because of the rehybridization of C2 and hyperconjugative stabilization of the anion. Also, because of lone pair donation into the C−F σ^* orbital, the C2−F bond length increases to 1.40 Å. There is no pyramidalization at C_2, which maximizes hyperconjugation with the two allylic C_3F σ^* orbitals.

3.3. Other Nucleophiles.

Table 3 shows the energetics of the reactions of six nucleophiles with OFCP.

As shown in Table 3, the rate-determining step with all nucleophiles is the nucleophilic addition step, with the activation

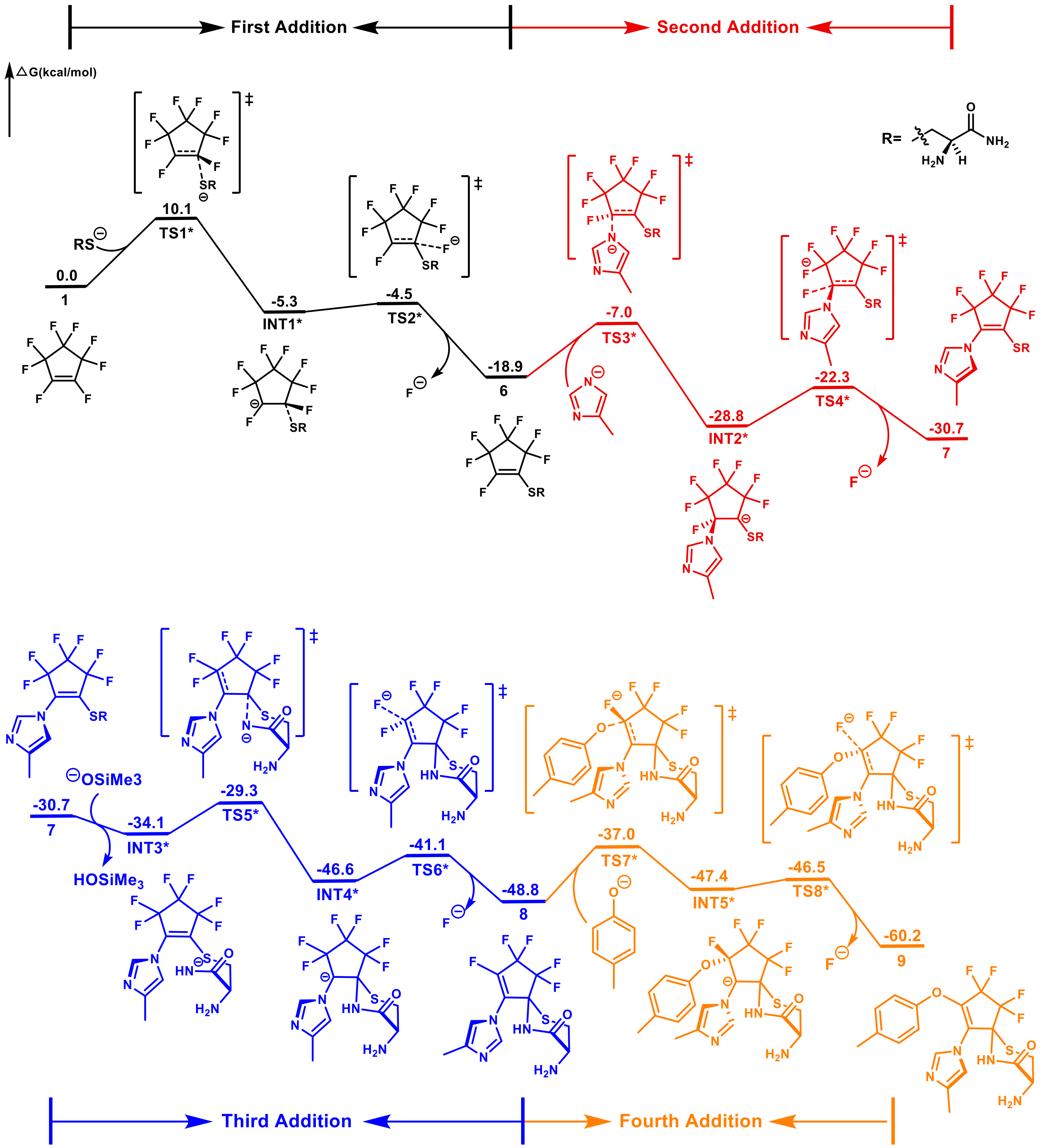


Figure 8. Energy profiles of the Harran's[11] cascade reactions using model nucleophiles.

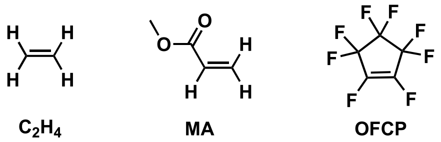
energies of elimination steps being only 1−3.5 kcal/mol. Neutral nucleophiles are much less reactive than anionic nucleophiles. Moreover, even though they are model nucleophiles, the relative reactivities are consistent with the results of Harran's[11] experiments and Mayr's nucleophilic reactivity parameters ($N_{(\text{thiolate})}$:20.97 > $N_{(\text{phenolate})}$:18.86 > $N_{(\text{amide anions})}$:17.52 > $N_{(\text{methylamine})}$:15.19).[19]

3.4. Discussion of the Cascade Reactions. *3.4.1. Model Cascade Reactions Using the Same Nucleophile.* Figure 7 shows the reactions of phenoxide to give four substitutions. The first addition of PhO^- causes a negligible change in the OFCP reactivity. The barrier of secondary attack (11.6 kcal/mol) is essentially identical with the first barrier (11.4 kcal/mol). The activation energy of the third attack is higher (17.1 kcal/mol), presumably due to the endogenic nature of the addition steps and absence of F for hyperconjugation at one α carbon. All of the elimination steps are very fast (Figure 8).

3.4.2. Cascade Reactions That Model Harran's Experiments. The energetics are qualitatively consistent with the experiment except for the third attack to form the six-membered ring. The third substitution is predicted to be very rapid, because we model this reaction starting from the deprotonated amide. Once formed, this reaction is indeed very rapid because the reaction is intramolecular and forms a stable chair six-membered ring product.

To study the regioselectivity, we also calculated the pK_a of phenol (22.1), thiol (18.2), and imidazole (19.0) in DMF; thiol is the most acidic. In this case, the thiolate prefers to attack OFCP first, followed by imidazolate. However, deprotonated amide will be the third nucleophile in Harran's[11] macromolecule formation sequence. That is because a six-membered ring in the chair conformation is formed, and the intramolecular reaction requires little entropy loss for cyclization. The last addition involves the phenolate in a reaction involving much reorganization of the peptide moiety.

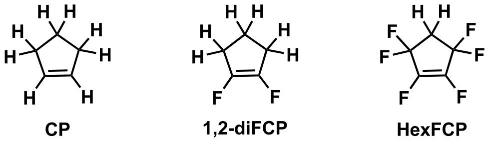
Table 1. Activation Energies for Phenoxide Attack and LUMO Energies of Alkenes



C_2H_4 MA OFCP

	TS energy ΔG (kcal/mol)	INT energy ΔG (kcal/mol)	LUMO energy (eV)
C_2H_4	36.7	36.5	1.1
MA	19.8	14.6	0.3
OFCP	11.4	−2.9	0.0

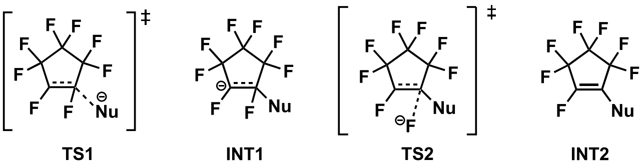
Table 2. Activation Energies, LUMO Energies, and Distortion Energies for the Nucleophilic Addition of PhO⁻ to Various Cyclopentenes



CP 1,2-diFCP HexFCP

	TS ΔG (kcal/mol)	INT ΔG (kcal/mol)	LUMO energy (eV)	distortion energy (kcal/mol)
CP	36.7	36.5	1.59	29.2
1,2-diFCP	34.3	26.6	2.09	25.6
HFCP	17.6	6.6	0.44	15.7
OFCP	11.4	−2.9	0.04	9.5

Table 3. Energy Profiles of Different Nucleophiles



TS1 INT1 TS2 INT2

nucleophiles	TS1 energy ΔG (kcal/mol)	INT1 energy ΔG (kcal/mol)	TS2 energy ΔG (kcal/mol)	INT2 energy ΔG (kcal/mol)
CH_3NH_2	16.0	11.9	15.2	13.6
CH_3CONH^-	11.6	−16.3	−14.9	−26.7
PhO^-	11.4	−2.9	0.2	−10.2
CH_3S^-	8.1	−10.7	−9.6	−25.8
CH_3NH^-	6.8	−49.7	−48.6	−67.7
F^-	6.3	−2.8		

4. CONCLUSIONS

We explored the high electrophilicity of OFCP and found that the hyperconjugative effects of the allylic fluorides are mainly responsible. These are also important in lowering the LUMO energy and increasing the electron affinity of OFCP. Fluoride elimination is very fast after the addition of any of the nucleophiles. In general, the nucleophilic substituent stabilizes the product by resonance from a donor electron lone pair of the nucleophile. This, in combination with the hyperconjugation stabilization by allylic fluorides, provides a "push−pull" stabilized alkene.

By studying the sequence of reactions involved in the Harran group's[11] rapid synthesis of peptide macrocycles, we demonstrate the origin of this effective cascade in reactions of His-Cys-Tyr peptides with OFCP.

5. COMPUTATIONAL METHODS

All calculations were performed with Gaussian 16.[20] Both geometry optimizations and single-point energy calculations were performed with the dispersion-corrected[21] M06-2X functional[22] and the def2-TZVP basis set.[23] Solvation effects were induced by using the SMD implicit solvation model[24] for DMF. Relative Gibbs free energies are reported in kcal/mol. Detailed conformational searches on complex structures were performed using CREST.[25] Only the lowest-energy conformations are discussed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c12690.

> Additional computations referred to in text, correlation of activation energies and LUMO energies, electronic energies, and coordinates of structures computed in this work (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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