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Rational Computational Design of Systems Exhibiting Strong Halogen Bonding Involving Fluorine in Bicyclic Diamine Derivatives

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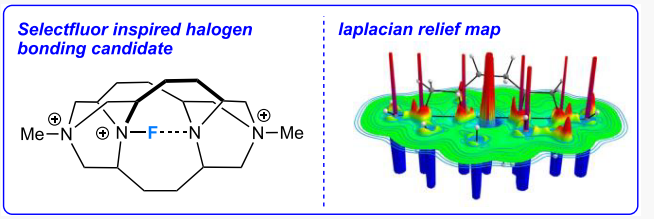
ABSTRACT: Perhaps the most controversial and rare aspect of the halogen bonding interaction is the potential of fluorine in compounds to serve as a halogen bond donor. In this note, we provide clear and convincing examples of hypothetical molecules in which fluorine is strongly halogen bonding in a metastable state. Of particular note is a polycyclic system inspired by Selectfluor, which has been controversially proposed to engage in halogen bonding.



INTRODUCTION

Rational computational design has played a long and honored role in organic chemistry. For example, seminal molecules such as bullvalene,[1] cyclobutadiene,[2] and C–F$^+$–C fluoronium ions[3] were theoretically proposed in the literature first, laying down an effective challenge for their later synthesis. A prime candidate for rational computational design resides in the realm of halogen bonding. Although it constitutes a well-established, weakly attractive interaction for X = Cl, Br, and especially I, it is less known for fluorine. Its occurrence is dependent on the existence of a region of positive electrostatic potential along the axis of an R–X bond and opposite thereto, the so-called "σ-hole", that can interact with an appropriate Lewis base.[4] Moreover, there are other broadened forms and interpretations of halogen bonding that have come to the fore, namely antielectrostatic[5] and charge transfer based complexes.[6] However, fluorine, notorious for its unique if not anomalous behavior, is usually too electronegative to generate a significant σ-hole or other halogen bonding qualities. This result got us thinking, is it possible to design a molecule containing a strong halogen bond containing fluorine, thus providing an analogous thought-provoking challenge? Our group has had a long-standing interest in using fluorine to interact strongly with other functional groups through forced proximity.[7] Using the prototype $H_3N^+F\cdots NH_3$ as a design basis, we imagined suitable metastable candidates arising from the hypothetical *in*-N-fluorination of bridgehead diazabicyclic structures such as 1,5-diazabicyclo[3.3.3]undecane,[8] 1,6-diazabicyclo[4.4.4]-tetradecane (the "Alder" diamine),[9] and 1,7-diazabicyclo[5.5.5]heptadecane,[10] all of which are idealized for intrabridgehead interactions. The present state of synthetic chemistry renders these candidates very difficult to make, although we believe that much can be gleaned from a calculational study.

Metrangelo et al.[11] and others[12] have postulated halogen bonding in fluorine-containing structures (especially in crystals[13]); however, recently, Eskandari and Lessani[14] clarified the differences between classical halogen bonding and examples of fluorine–Lewis base interactions. The authors proposed the term "fluorine bonding" to encompass the electronic, energetic, and spatial differences incumbent upon a much weaker interaction.

Several authors have proposed halogen bonding in R_3N^+–F-based complexes based on the electrophilic nature of fluorine therein.[15] However, experimental and computational studies have shown that nonclassical hydrogen bonding (R_3N^+–C–H···X (X = O, N)) is preferred to halogen bonding in such species.[16] For example, the prototype interaction in the complex $H_3N^+F\cdots NH_3$ is *higher* in energy compared to competing hydrogen bonding forms. Similarly, halogen bonding in Selectfluor (SF) and *N*-fluoropyridinium salts is disfavored as well (Figure 1).

In this article, we address this timely issue through a computational study exploring halogen bonding, e.g., in the proposed structures **1**–**3**, all of which are metastable with respect to isomerization (Figure 2). In this undertaking, factors emblematic of classic halogen bonding (X–F bond elongation, σ-hole existence, short N–F···N distance, significant bond critical point, and Wiberg bond order) are investigated.[17] In each case, competing N^+C–H···N interactions are foreclosed through geometric effects. These proposed structures are compared to the corresponding monoamine fluorides (**4**–**9**, Figure 2), in which the halogen bonding interaction has been greatly attenuated or eliminated. As the reader will see, the strongest case of bonding is shown in structure **10**, in which

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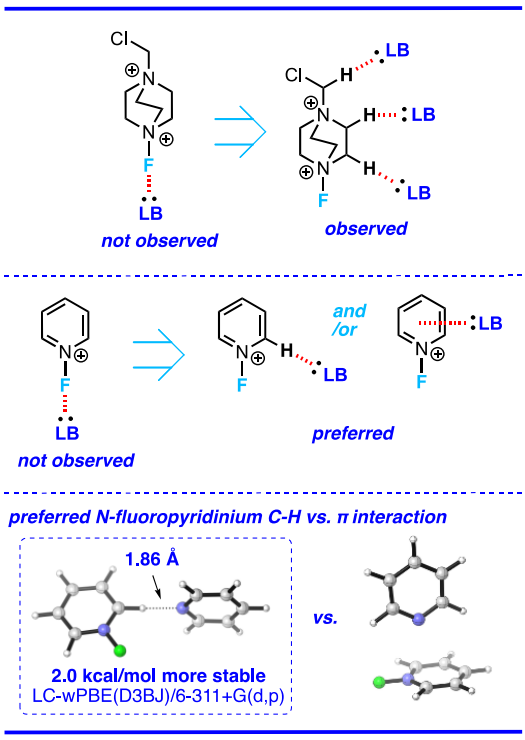

Figure 1. Speculative cases of halogen bonding and comparison of different *N*-fluoropyridinium interactions.

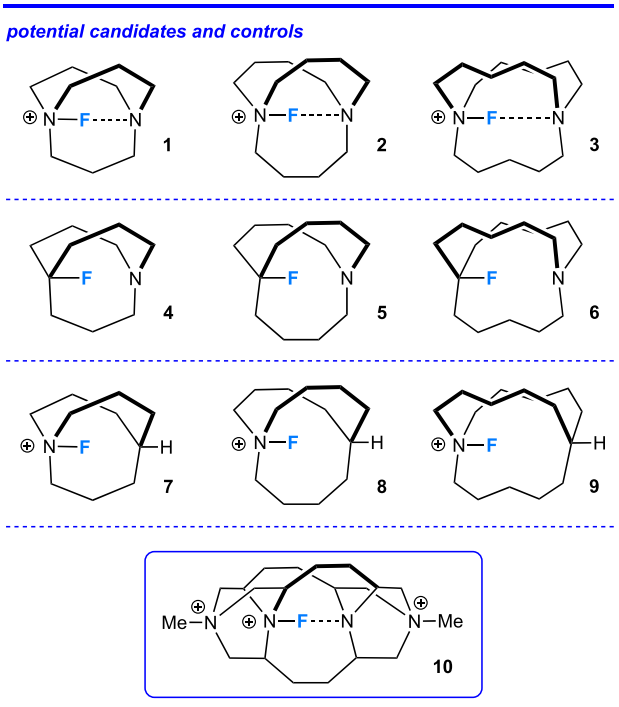

Figure 2. Halogen bonding molecules and controls.

fluorine is truly "trapped". The construction of **10** was inspired in part by the chemistry of Selectfluor, in which halogen bonding has been controversially proposed in the recent literature.[11]

RESULTS AND DISCUSSION

To begin our study, the molecular geometries and electronic wave functions of *in*-(N^+)-fluoronium cation derivatives 1,5-diazabicyclo[3.3.3]undecane, 1,6-diazabicyclo[4.4.4]-tetradecane, and 1,7-diazabicyclo[5.5.5]heptadecane (**1**−**3**) were fully optimized using the software package Gaussian 16, revision C.01.[18] To this end, density functional theory (DFT) model chemistries, including those with empirical dispersion corrections, were employed. This includes the long-range corrected ωPBE functional (LC-ωPBE), composed of a long-range portion of exact exchange that imposes a nonempirically tuned 100% contribution of the asymptotic Hartree−Fock exchange found to be essential for accurately describing long-range interactions, as well as a short-range ωPBE approximation that fulfills the exchange-hole normalization condition for all values of ω.[19]

To account for the importance of long-range dispersion forces in halogen-bonding interactions, Grimme's empirical "D3" dispersion corrections[20] in conjunction with the Becke and Johnson[21] (BJ-damping) approach were invoked. Incidentally, to streamline the discussion, only trends computed at LC-ωPBE-D3(BJ)/6-311+G(d,p) are explicitly covered vide infra, while for reference the findings computed using the long-range-correlated functional wB97XD of Head-Gordon and co-workers,[22] in addition to the hybrid meta-GGA M06-2X functional of Truhlar and Zhao, are provided in the Supporting Information. Overall, we observed consistency between these functionals, and our preferred selection of LC-ωPBE-D3(BJ) derives from its proven robustness for accurately accounting for XB-bonding interactions.[23]

Emerging from these computations was the striking impact of bridging hydrocarbon scaffolding upon interatomic N···F separation, manifesting itself in lengthening from 1.90 to 2.10 Å to 2.40 Å for diazabicyclic structures **1**−**3** (Figures 2 and 4). Accompanying this elongation was an *out*-to-*in* oriented flip of the Lewis basic bridgehead nitrogen lone pairs relative to the bicyclic cage frameworks. This is clearly seen in the computed highest occupied molecular orbitals (HOMO)s, a slight dominance of *out*-*N*-lone pair orbital density in structure **1** vs (p-orbital type) *out*-*in*-*N*-lone pair density in structure **2**, finally giving way to a substantial *in*-*N*-lone pair orbital density in structure **3**.

As a point of reference, the computed molecular electrostatic potential (MESP) surface of a subunit of these bicyclic cages, namely, Me_3N^+−F, displayed the presence of an ostensive F atom centered sigma (σ) hole (V_{max} = 84.9 kcal/mol) interaction (Figure 3). Meanwhile, all these N···F interactions displayed distances well-below the sum of the van der Waals radii of two constituent nuclei, thus fulfilling at least one criterion for XB-bonding: that is, "the interatomic distance between X and the appropriate nucleophilic atom of Y tends to

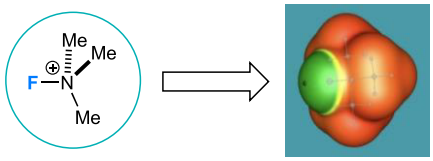

Figure 3. Molecular electrostatic potential (MESP) surface of Me_3N^+−F on the 0.001 au isosurface computed at LC-ωPBE-D3(BJ)/6-311+G(d,p). The color codes refer to red >100, yellow >95, green >10 kcal mol^{-1}.

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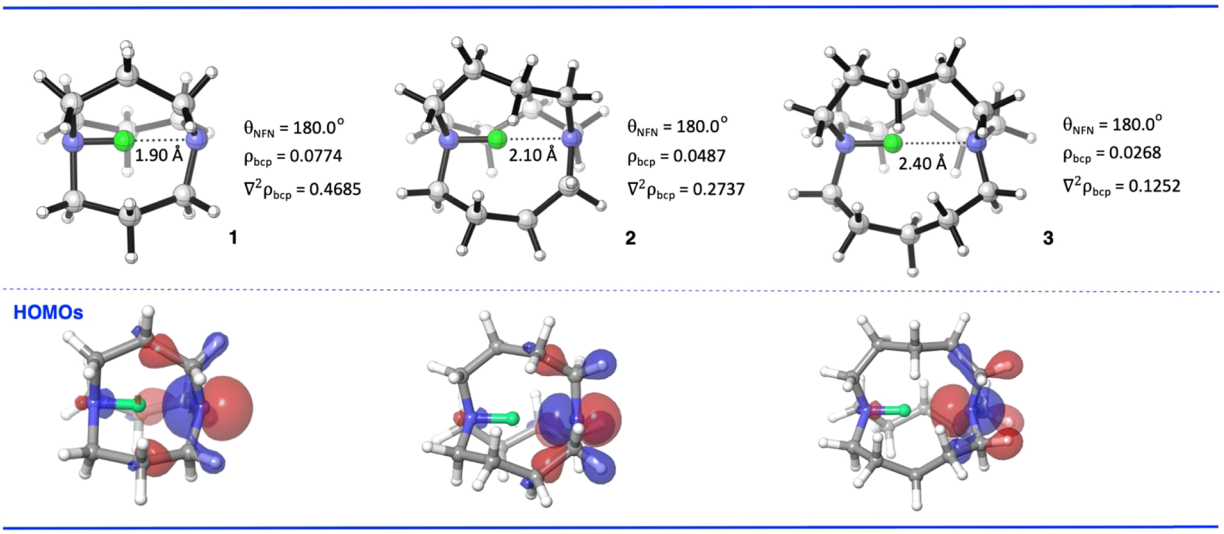

Figure 4. Calculated structures and HOMOs of compounds **1**−**3**.

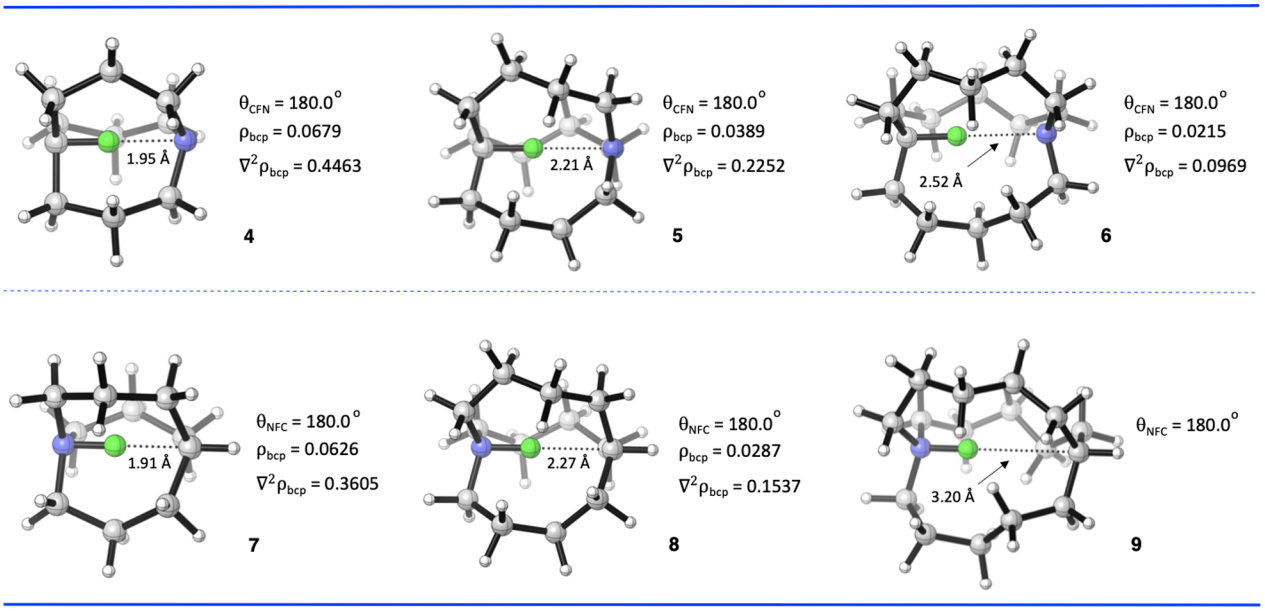

Figure 5. Calculated structures for compounds **4**−**9**.

be less than the sum of the van der Waals radii".[24] What is more, a near-perfect 180° linearity of the N−F···N atoms was found in this trio of derivatives, which is a feature typifying XB-bonding, viz., "the angle R−X···Y tends to be close to 180°, i.e., the halogen bond acceptor Y approaches X along the extension of the R−X bond".

We next turned to quantum theory of atoms in molecules (QTAIM) with a focus upon the computed (3, −1) bond critical points (BCPs) to characterize these N···F interactions.[25] Notably, this approach offers a wealth of chemical information for describing chemical bonding, conveniently allowing atomic interactions to be classified into two main categories: closed-shell interactions and shared interactions. For example, noncovalent interactions, such as halogen bonds, van der Waals interactions, and hydrogen bonds are described as closed-shell, which typically displays a small value of ρ_{bcp} (electron density at the BCP) and a small positive Laplacian $\nabla^2\rho_{bcp}$ value. For instance, ρ_{bcp} in modest hydrogen bonds and van der Waals complexes is about 10^{-2} and 10^{-3} au,[26] while for halogen-bonded complexes, ρ_{bcp} values range from 0.006 au in very weak halogen bonds to 0.05 au in moderate and strong ones.[27] In this regard, the ρ_{bcp} and the Laplacian $\nabla^2\rho_{bcp}$ values at the BCPs of the N···F interactions for diazabicyclic structures **1**−**3** were appreciably large for halogen bonds (ρ_{bcp} = 0.0774, 0.0487, and 0.0268 au and $\nabla^2\rho_{bcp}$ = 0.4685, 0.2737, and 0.1252 au), typifying them as strong noncovalent closed-shell interactions (Figure 4).

Still working in the framework of QTAIM, we turned to the interaction quantum atoms (IQA) method of atomic energy analysis using the Amsterdam Density Functional (ADF) program to shed light on the atomic energies and atomic interactions of the N···F arrays.[28] Specifically, we evaluated the interatomic energy ($V_{inter(total)}$) as well as the exchange (covalent part) and classical Coulomb electrostatic contributions (ionic part) for each of the N···F arrangements (see Supporting Information for covalent and ionic part values). Overall, the evaluated IQA energies show the essential absence of a N···F halogen bonding interaction in structure **1**

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($V_{inter(total)}$ = −0.25 kcal/mol) but *positive* interatomic energy values for structures **2** ($V_{inter(total)}$ = 10.66 kcal/mol) and **3** ($V_{inter(total)}$ = 17.05 kcal/mol), indicating the dominance of repulsive interactions incumbent within forced frameworks.

To gauge the impact of imbedded (N^+)-fluorine cation formal charge upon interatomic N···F interactions, we also considered neutral structures **4**−**6** (Figure 5). This isolobal subset of diazabicyclic analogies, akin to structures **1**−**3**, albeit with a net isoelectric perturbation of charge, was projected to display attenuated N···F interactions, viz., reduced nitrogen lone pair donation to the nearby fluoride "σ-hole". Corroborating this speculation were elongated N···F distances, Wiberg bond index values hovering around zero, reduced electron densities (ρ_{bcp} = 0.0679, 0.03890, 0.0215), and Laplacian values ($\nabla^2\rho_{bcp}$ = 0.4463, 0.2252, 0.0969) at the (3, −1) bond critical points. Clear from this subset of charge-neutral, diazabicyclic structural counterparts is the importance of formal *N*-fluoroammonium cation character that facilitates fluoride σ-hole features conducive for halogen bonding and N···F interactions.

Next, to measure nitrogen lone pair participation, we investigated diazabicyclic structures **7**−**9** (Figure 5), wherein one bridgehead nitrogen of structures **1**−**3** was swapped for a methine carbon with an exocyclic hydrogen atom, thereby removing any chance of XB-bonding. Indeed, we observe elongated N···F distances and Wiberg bond indices near zero (slightly negative), in addition to computed electron densities (ρ_{bcp} = 0.0626, 0.0287) and Laplacian ($\nabla^2\rho_{bcp}$ = 0.3605 and 0.1537) values at the (3, −1) BCPs localized between the bridgehead carbon and fluorine atoms, while in compound **9** a BCP was not present (Figure 5). It is evident that preliminary candidates **1**−**3** demonstrate attributes of fluorine halogen bonding in certain cases, along with a number of counter-indications, making the situation rather hazy.

In any event, having extracted defining elements of these interatomic N···F interactions, we sought to secure by (in silico) design a decidedly *clear-cut example* displaying intra-bridgehead fluorine halogen bonding. Aside from the analogy to Selectfluor, we drew upon the potential of (onium)-point charge subarrays, structural rigidity, and electronic field effects (EFE) to arrive at the tricationic manifold **10** as a superior molecular scaffold for rendering fluorine-based halogen XB-bonding.

Calculated within this designer analog is a short N···F distance of 1.80 Å - well-below the sum of the van der Waals radii of two constituent nuclei by ∼1.25 Å, linked to a Wiberg bond index of 0.0255 and a linear N−F···N alignment of ∼180°. Confirming fluorine (XB-halogen) bonding as well was a positive electronic density (ρ_{bcp} = 0.1031) and Laplacian value ($\nabla^2\rho_{bcp}$ = 0.5383) at the F(X)−N localized (3, −1) bond critical point of **10** (Figure 6). These values are notably *very large* in magnitude relative to most noncovalent interactions.

Likewise, we found a bonding situation under the lens of IQA with a total interaction energy of −21.58 kcal/mol, deriving from a favorable covalent part (E = −59.29 kcal/mol) counterbalanced by an unfavorable ionic part (E = 37.71 kcal/mol). Further, natural bond order (NBO) analysis revealed nitrogen-to-fluorine (donor−acceptor) (e.g., $n_N \rightarrow \sigma^*_{C-F}$ = 38.85 kcal/mol) interactions summing to ∼55.38 kcal/mol (see Supporting Information). In shedding additional light on this N−F···N interaction, we generated relief map surfaces of ρ_{bcp} and the Laplacian ($\nabla^2\rho_{bcp}$) of **10** (Figure 7a). The contour map of the $\nabla^2\rho_{bcp}$ reveals localized regions of valence charge-concentration and charge-depletion contributing to the noncovalent N−F···N interaction. The presence of a large "hole" surrounding the fluorine atom is indicative of a region with electron depletion, while concentration of electron density is denoted by the "lumps" seen on surrounding atoms. Corroborating these trends was the relief map ρ_{bcp} (Figure 7b).

Furthermore, for safe measure, we have computed the interaction energies in both the solvent and gas phases for structure **10**. From these results, we have found a favorable $E_{(int)}$ value of −104.87 kcal mol^{-1}, thereby supporting the presence of a favorable fluorine-centered halogen bond in caged-system **10**. Lastly, the calculated ^{15}N NMR spectrum of **10** (see Supporting Information) provides unique chemical shifts and offers experimentalists data for confirmation of such species.

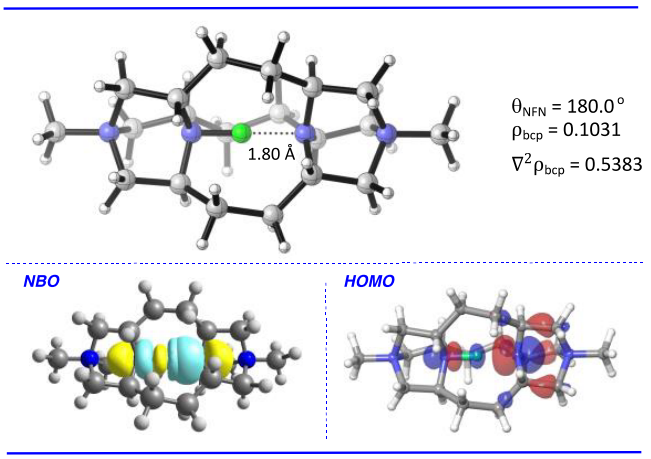

Figure 6. Computed structures of **10**.

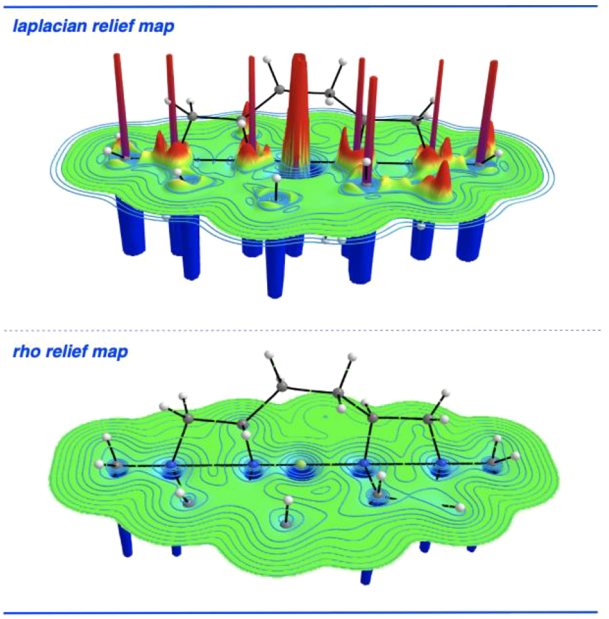

Figure 7. (a) Laplacian of the charge density of **10**. Color codes refer to red and yellow as the most and least negative values of $\nabla^2\rho_{bcp}$, respectively, whereas those to green, cyan, and blue are from the less positive to the most positive values of $\nabla^2\rho_{bcp}$. (b) Contour map of the ρ_{bcp} highlighting regions of charge density in **10**.

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CONCLUSION

Our investigation has identified key design features for realizing N−F···N halogen bonding whereby fluorine serves as a halogen bond donor. Paramount to this understanding was the use of predictive computational tools to provide fundamental clues for achieving fluorine-based halogen bonding. Our design process involved, in turn, the following: (1) identifying a potential prototype fluorine halogen bonding interaction that has been proposed in the literature but that suffers from competitive hydrogen bonding; (2) foreclosing the possibility of hydrogen bonding through rigid cage systems; (3) yielding metastable and reasonable candidates for significant halogen bonding. The ultimate example of clear-cut halogen bonding involving fluorine was found to be the polycycle **10**. Further studies will involve the potential synthesis of fluorine halogen bonders; although extremely challenging at this moment, we believe that it remains feasible.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00497.

Computational information (PDF)

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Notes

The authors declare no competing financial interest.

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