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Perfluorocubane: a tiny electron guzzler

Perfluorination gives cubane the capacity to host an extra electron in its inner structure

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High symmetry arouses a sense of perfection and also of perennity. In “Electron in a cube: synthesis and characterization of perfluorocubane as an electron acceptor”, Sugiyama et al. (1) offer us an aesthetically appealing small molecular gem, a synthetic feat and, most remarkably, a perfect nest for hosting an added electron, with many inciting perspectives.

Eaton and Cole. succeeded in synthesizing cubane in spite of *a priori* improbable bonding angles (2). Yet the strained, thermodynamically unstable molecule proved kinetically inert. In the molecular world, symmetry tends indeed to impede reactivity, as no weak spot, or symmetry-allowed pathway, is available for intrusion. Replacing all the hydrogens of the utterly strained cubane substrate by much larger fluorine atoms was a further momentous challenge. Perfluorination entails indeed a drastic upheaval of the molecule’s structure and electron charge density distribution. Compared to hydrogen, fluorine, with its nine protons and nine electrons, has a much larger size, higher electron density, ionization potential, electron affinity and electronegativity, and lower polarizability. Perfluorocarbons are among the most thermally stable and chemically inert classes of organic molecules ever synthesized. Perfluorination generates new properties or heightens known ones to levels often unattainable otherwise (3). Their outstanding inertness calls, however, for cogent use since their persistence and bioaccumulation characteristics can raise serious environmental issues (4). Regarding perfluorocubane, the predicted perspective of netting an electron in a Platonian carbon polyhedron, thus generating a radical anion (5), offered a tantalizing additional challenge. The Authors selected direct radical fluorination with elemental fluorine, F₂, to achieve their aim. Taming the impulsively explosive element is, however, not obvious. Mainly due to steric hindrance, the homonuclear bond in F₂ is the weakest in its row in the Periodic Table. If not duly controlled, its reaction with organic material is highly exothermal, provoking profuse C—C bond breaking. Direct fluorination had been pioneered by diluting F₂ in an inert gas at low temperature (LaMar process), improved by using a chlorofluorocarbon solvent (Lagow-Exfluor process) (6), and perfected by grafting a heavily fluorinated ester ligand to the substrate to reduce vaporization and enhance solubility in a relatively heavy chlorofluoroether solvent (the “PERFECT” method) (7). Heptafluorocubane was thus produced and the remaining hydrogen was replaced using standard monofluorination reactions. The precious hexa- and hepta-fluorinated cubanes were also isolated.

Notably, X-ray diffraction showed essentially no C—C bond length change upon perfluorination, likely meaning that the C—C bond-shortening expected from highly electronegative fluorine substitution is counterweighted by the fluorines’ increased spatial needs. X-rays also revealed a rare case of directional non-covalent C-bonding in the solid state between a fluorine atom and the center of the face of the nearest cube.

Most importantly, Irikura’s prediction that in perfluorocubane the overlap of all eight antibonding orbitals of the C—F bonds (**Fig. 1A**) would result in the formation of an extended star-shaped low energy antibonding molecular orbital (sigma stellation), and thus in

pronounced electron affinity and the possibility to host an electron inside the 8-carbon cubic frame, hence generating a radical anion (5), certainly added considerable incentive to the challenge.

Reduction potentials measured for perfluorocubane by cyclic voltammetry and differential pulse spectrometry confirmed its predicted electron-accepting capacity and the formation of a radical anion (1). Low-temperature matrix-isolation electron spin resonance spectroscopy, in combination with γ -ray radiolysis, determined a rapidly rotating radical anion. Uniquely, the spin density of the sequestered electron is chiefly located inside the cubane frame and displays octahedral (or cubic) symmetry, in contradistinction with the common π -conjugated polyaromatic electron acceptors that store extra electrons on their surface. The new radical anion could, however, not be isolated.

About evoking “cages” (aka bird-cages) when portraying molecular structures: such pictorial denominations can be delusive (**Fig. 1A**). Cages inevitably suggest possibilities for occupancy and incarceration. But electrons can readily clear out, and it takes the 20-carbon dodecahedrane ($C_{20}H_{20}$) to encage the smallest monoatomic molecule, helium. Besides, the Authors’ calculations (**Fig. 1A**) indicate that part of the caged electron spin distribution is actually located outside the 8-carbon cubic frame, near the fluorine atoms. “Frame” may sound both less engaging and less coercive.

Since its inception almost 60 years ago (2), cubane has inspired an outbreak of investigations, derivatizations, functionalizations, and suggestions for potential uses (8-13). Will perfluorocubane and its derivatives raise similar elation? Perfluorination causes sweeping steric and electronic alterations, entailing profound changes in properties and reactivity, making forecasts hazardous. Only further experimentation and modeling studies can tell.

Future investigations should certainly include the synthesis of additional mono- and 1,4-disubstituted functional fluorinated cubane derivatives, developing means of introducing such building blocks into molecules and polymers, and assessing their “electron chemistry”. Perfluorocubane-derived compounds may offer a unique opportunity to experimentally assess what differentiates an internally netted, σ -star-located electron from an externally located, π -conjugated one. Exploration of the rare global carbon-bonding donor capacity of perfluorocubane (revealed in the solid state by the X-ray diffraction studies) towards cyanide and similarly slim anions is desirable. Use of functional perfluorocubane building blocks as linkers, spacers or appendages in polymer chemistry may also be rewarding.

On the applied side, cubane, which can now be produced in kg-size batches, has triggered intensive investigations in medicinal chemistry. Numerous series of derivatives and building blocks with pharmaceutically significant functionalities were synthesized (8-13). Introducing a cubyl in lieu of a phenyl group in pharmaceuticals was attractive because the two groups are considered bioisosteric (8, 13, 14), that is, have similar space requirements (although one is globular and the other rather flat), while the former appears less toxic and slightly more lipophilic. A further incentive for such substitutions was to help rejuvenate “old” drugs. Cubane derivatives helped probing active centers and mechanisms of biological action. In a study on cubyl-analogs of ten clinically used phenyl-containing molecules (anesthetic, analgesic, antidepressant, anticancer, antiparasitic and neotrophic agents) or pesticides, the cubane analog performed as well or better than the benzene analog in seven instances (13). Use as biologically safe cross-linkers in polymeric prodrugs for controlled release was also suggested.

Yet, to our knowledge, no cubane-containing pharmaceutical has so far entered clinical evaluation.

Anyway, those who would consider investigating perfluorocubane along similar lines must realize that the substantially larger perfluorocubane is no longer isosteric to benzene (**Fig. 1B**) and has significant lipophobic character (in addition to being extremely hydrophobic), forecasting little analogy in behavior. The extra-costs of optimizing and achieving perfluorination may also be prohibitive.

Considering materials science, polymerization of cubane has provided extremely hard, thin and stable nanothreads with exceptional stiffness (15), a feat that, in the case of perfluorocubane, could be hampered by steric hindrance.

But the truly inciting asset of perfluorocubane and its derivatives lies in their distinctive redox activity, electron hosting capacity and, more generally, “electron chemistry”. Further exploration of these features can only be encouraged. New practical means, different from aromatics, of grafting a small, space-filling electron-sequestering building block into molecules, would indeed be valuable. Practical, meaning stable and cost-effective, redox-active, functional electron-carrying and transferring molecular materials and polymers may find various applications, including in electronic devices (organic conducting materials, rechargeable batteries), optoelectronics (light-emitting devices), magnetics (magnetic molecular chains and frameworks, NMR standard), magneto-optics, (dopants in organic semiconductors), therapeutics (photothermal materials), and other fields.

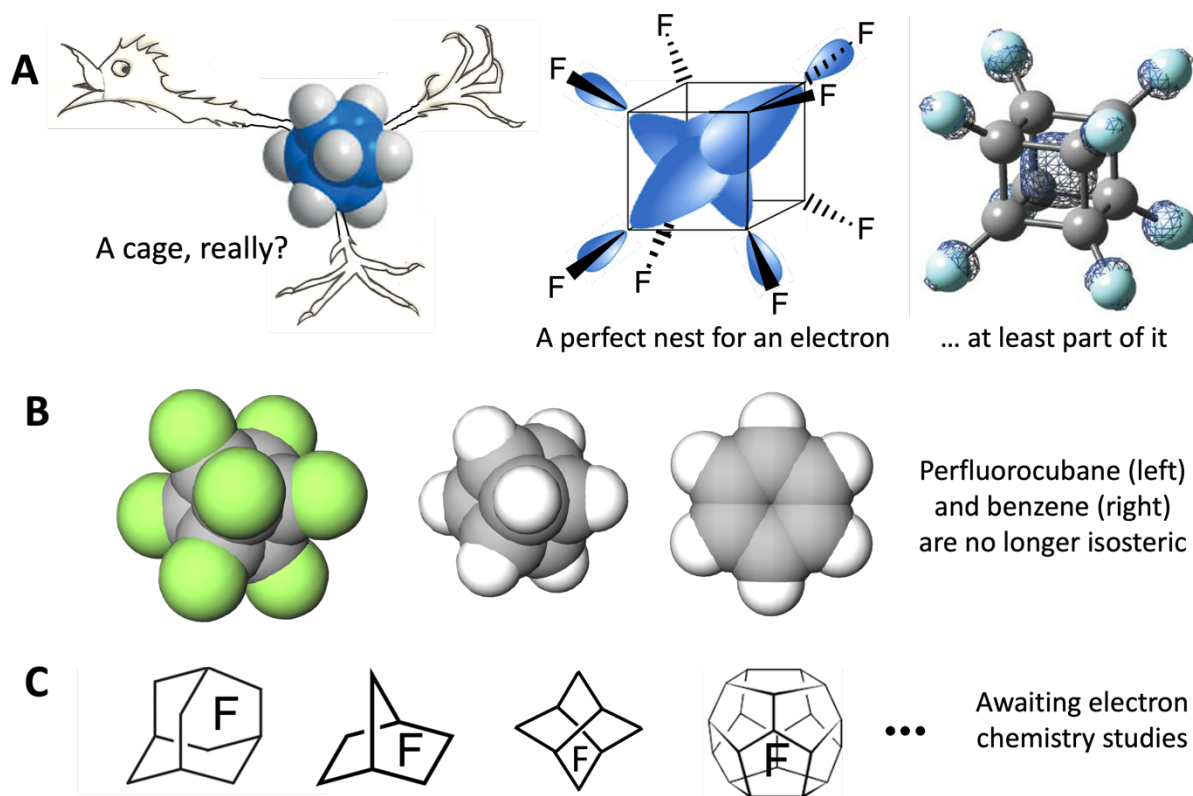
Currently, the availability of functional perfluorocubane-derived reagents on an appropriate scale remains an impediment to extensive use. The $C_8F_8^{\bullet-}$ radical anion is not stable and bottling cubane radical anions is not yet on the agenda. For most uses, it will be hard to compete, in terms of cost and accessibility, with the over a century old and extensively used polyaromatics-based radicals.

The Authors’ findings certainly encourage perfluorination of further polyhedral molecular structures (**Fig. 1C**), especially those susceptible to achieve sigma stellation, and experimental investigation of their electrochemistry. Valuable candidates include perfluoroadamantane, which is commercially available, perfluorododecahedrane ($C_{20}F_{20}$) (16) for which substantial ability to bind an extra electron has been predicted, star-shaped perfluorobisnoradamantane (17) and perfluoronorbornane among a wealth of possibilities. Calculations on the $C_{20}F_{18}(NH)_2C_{20}F_{18}$ double-cage predict electron transfer between cages and applications in non-linear optical materials (18).

Meanwhile, this perfluorocubane study contributes brightly to our understanding of the chemistry and potential of electron-accepting perfluorinated polyhedral constructs, and should inspire plenty new explorations.

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Caption for Figure 1. (A) Small polyhedral molecular frames are hardly friendly cages (cartoon, courtesy J.-M. Dupart; they are extremely exiguous (left) and, where electron spin distribution is concerned (right), only partially inclusive, part of the added electron's spin density lying outside the cubane carbon frame (1). Cubane's electron-acceptor capacity derives from the centered 8-branch star-shaped molecular orbital formed by the overlap of the antibonding sigma orbitals of the C—F bonds (center; for clarity, only half of the orbitals are represented). (B) Perfluorocubane (left) and benzene (right) or cubane (center) are neither isosteric nor isolipophilic. (C) Some perfluorinated molecular polyhedrons waiting for their electron chemistry to be explored experimentally, perfluoro-adamantane, -bisoradamantane, -norbornane, -dodecahedrane (the symbol F inside the molecular frame indicates that all carbons are fully fluorinated); all have been synthesized, some are commercially available.