PERSPECTIVES: MOLECULAR SPECTROSCOPY

CH_5^+: The Cheshire Cat Smiles

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Protonated methane, CH_5^+, is one of the Holy Grails of rotational-vibrational molecular spectroscopy. The reasons are manifold. First, adding a proton to the simple methane molecule, CH_4, generates the floppy or fluxional molecule CH_5^+, to which the traditional concepts of vibrational spectroscopy no longer apply (*1*). As a result, bare CH_5^+ has resisted characterization by infrared spectroscopy ever since its discovery by mass spectroscopy in the early 1950s (*2*)—until now when Takeshi Oka and his group at the University of Chicago have finally managed to record its spectrum, as reported on page 135 of this issue (*3*). Second, the chemical bonding in CH_5^+ cannot be described by single Lewis structures as taught in freshman chemistry, where a line between two atoms denotes a chemical bond formed by two electrons. Rather, in CH_5^+, three atoms are connected by two electrons. Such three-center–two-electron (3c-2e) bonds (see Fig. 1A) characterize hypercoordinated carbocations for which CH_5^+ is the prototype. These carbonium ions or nonclassical carbocations, as they are also called, are crucial as extremely reactive intermediates in hydrocarbon reactions catalyzed by very strong so-called magic acids and are at the heart of the electrophilic substitution chemistry of aliphates developed by George Olah and his school (*4*). Finally, there is substantial astrochemical interest in CH_5^+, which is implicated in reactions that form part of the intricate synthesis of polyatomic species in cold interstellar clouds (*5*).

The first detailed insights into CH_5^+ were of theoretical origin, because its small size made it amenable to calculations at an early stage. Its global minimum has C_s point group symmetry (*6*) and is best pictured as a "CH_3 tripod" with an "H_2 moiety" attached to the carbon, thereby forming the famous 3c-2e bond (see Fig. 1A). The next higher lying stationary point is a C_{2v} saddle point (*7*), where the H_2 moiety is broken apart and a four-center–four-electron (4c-4e) bond involving three coplanar protons and the carbon is formed (*8*) (see Fig. 1B).

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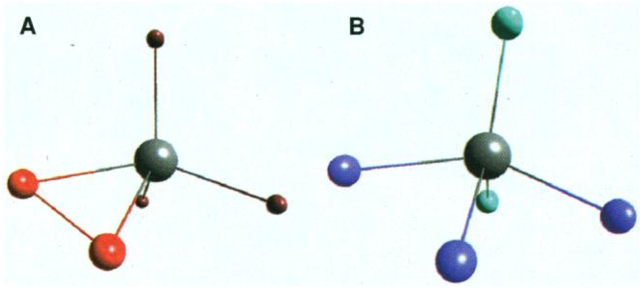

Fig. 1. Sketches of the most important static structures of CH_5^+. In the global minimum C_s structure (**A**), the two protons forming the H_2 moiety and thus the 3c-2e bond with the carbon (gray) are marked in bright red, with the residual protons in the CH_3 tripod in dark red. In the transition state C_{2v} structure (**B**), the three protons forming the 4c-4e bond with the carbon are marked in purple, with the residual protons in green.

Calculations of CH_5^+, however, proved to be harder than anticipated. Werner Kutzelnigg and collaborators were the first to point out that the Hartree-Fock approximation, which at the time was the workhorse of quantum chemistry, was not adequate for CH_5^+ because it neglects electron correlation (*7*). When this intricate many-body effect is included, the potential energy surface for CH_5^+ becomes extremely flat, and the energy difference between the minimum and saddle point structures described above becomes negligible (*7*). Already in 1974, Dyczmons and Kutzelnigg had concluded that "at room temperature all the protons are dynamically equivalent" (*7*, p. 247). The quantification of "negligible" had to wait more than 20 years for an essentially converged ab initio calculation by Kutzelnigg and co-workers (*9*). The transition state was determined to be 0.8 kcal/mol (corresponding to about 300 cm^{-1} or 0.03 eV) above the minimum, with a barrier to internal rotation of the H_2 moiety of only 0.1 kcal/mol in the ground state (*9*).

A team headed by Schaefer and Schleyer went a step further and took into account nuclear quantum effects in the form of zero-point vibrations in the harmonic approximation (*10*). They concluded that "the usual representation of CH_5^+, C_s, with three-center–two-electron bonding is misleading" and that "CH_5^+ is a highly fluxional molecule without a definite structure" (*10*, p. 3720). This is a far-reaching statement, as the 3c-2e bonding concept, which is at the heart of hypercoordinated carbocation chemistry, is called into question for the parent molecule (or prototype) CH_5^+. Moreover, the very concept of molecular structure was questioned for CH_5^+. Thus, a subtle interplay of electron correlation and nuclear quantum effects is at the very core of the puzzle that is CH_5^+.

More recently, CH_5^+ has been the subject of ab initio path integral calculations (*11*), which include nuclear quantum effects such as zero-point motion and tunneling in full dimensionality and go beyond the harmonic approximation (*12*). The results indicate that the situation may not be as extreme as previously conjectured (*10*). The protons do indeed undergo large-amplitude pseudorotational motion and thereby become scrambled and thus statistically equivalent, as previously predicted (*7, 10*), but this motion is found to be concerted to some extent (*11*). Situations with the vibrating nuclear skeleton possessing an H_2 moiety attached to a CH_3 tripod turn out to contribute most to the overall appearance of CH_5^+ (see Fig. 2A). In these

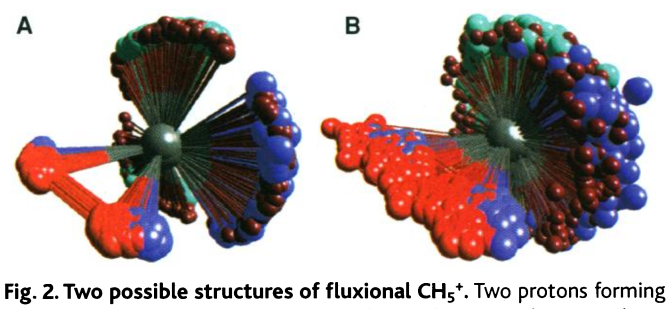

Fig. 2. Two possible structures of fluxional CH_5^+. Two protons forming an H_2 moiety attached to a CH_3 tripod may dominate the general appearance of the molecule in the ground state (**A**) [from (*11*)]. Alternatively, overwhelming fluctuations may destroy the notion of an H_2 moiety attached to a CH_3 tripod at very high temperatures (**B**) [from (*13*)]. The pseudorotational motion was removed for the purpose of presentation by projecting the superimposed instantaneous snapshot configurations on the plane defined by the carbon and the two closest protons for every configuration. Orientation, perspective, and color code are the same as used to depict the static structures. A cutoff H–H bond length of 1.15 Å defines the H_2 moiety (colored in bright red) and thus C_s-like structures.

calculations, the notion of an H_2 moiety attached to a CH_3 tripod is only lost before dissociation if the temperature is very high (Fig. 2B) (*13*).

If the theoreticians are right in thinking that CH_5^+ is a highly fluxional molecule, it should come as no surprise that CH_5^+ is quite resistant to direct experimental characterization. Kenzo Hiraoka and co-workers found their mass spectrometric data to be compatible with a 3c-2e bonded structure of C_s symmetry (*14*). However, this conclusion was arrived at by attaching methane molecules as thermochemical sensors to a CH_5^+ core. Using less perturbing H_2 molecules instead of CH_4 yielded somewhat less clear evidence in favor of 3c-2e bonding (*14*). Mass spectrometric evidence for the C_s structure was also found by contrasting the reactivity of CH_4D^+ and CD_4H^+(*15*). Stabilizing CH_5^+ by attaching H_2 molecules led to the first infrared spectra of the C–H stretching bands of CH_5^+ cores in trapped $CH_5^+ \cdot (H_2)_n$ complexes ($n > 1$) (*16*). As expected, solvation clearly affected hydrogen scrambling in the CH_5^+ core, which became frozen when at least three H_2 molecules were attached. However, none of these studies can claim to have resolved the puzzle of unperturbed CH_5^+. Takeshi Oka started his quest for free CH_5^+ in the spring of 1983 (*17*), the fruits of which he presents now (*3*). The resulting determination of the high-resolution infrared spectrum of the C–H stretching band of CH_5^+ is a major achievement. However, we will not know the real structure of CH_5^+ until the jungle of 1000 lines resolved by Oka's group in a very narrow spectral range is assigned.

To arrive at a comprehensive understanding of CH_5^+, cutting-edge experimental and theoretical studies will be needed. Embedding molecules in nanofridges, that is, small superfluid helium droplets, may allow high-resolution rotational-vibrational spectra to be obtained at a temperature of only 0.4 K, with minimal interaction between the molecule and the cooling agent (*18*). At this extremely low and controlled temperature, the CH_5^+ spectrum will hopefully become somewhat simpler. Another exciting perspective is the use of Coulomb explosion imaging (*19*), which allows direct measurement of the many-body nuclear probability density, reconstructed from many independent "snapshots" of the vibrating nuclear skeleton. In this way, a representation like that depicted in the figures could be inferred directly from experiment. Theoretical studies must seek a solution to the time-dependent quantum motion of CH_5^+ on a potential energy surface of the quality provided in (*9*, *10*), while simultaneously taking into account all degrees of freedom—a highly complex endeavor. CH_5^+ will certainly continue to challenge many groups in various fields of expertise for some time to come.

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NOTA BENE: MEDICINE

Fear of Flying!

The meager peanut snacks offered on airplanes may be a source of irritation for most passengers, but for those unfortunate enough to be allergic to peanuts they pose a serious health hazard. In the United States, about 100 individuals allergic to different foods (primarily peanuts) die each year from anaphylactic shock after accidental exposure to the culinary culprit. Peanut allergy appears to be on the increase particularly among young children, so much so, that U.S. lawmakers may mandate peanut-free zones in schools and on airplanes.

Anaphylaxis is an immune reaction initiated by an allergen such as peanut protein that crosses the mucosa and binds to immunoglobulin E (IgE) on the surface of mast cells. Cross-linking of IgE triggers mast cells to release histamine and other mediators that cause a systemic anaphylactic reaction, which includes the contraction of smooth muscle in the tissues lining the airways. Unless epinephrine is administered quickly, anaphylaxis can be fatal.

The approach outlined in a paper in this month's *Nature Medicine* (*1*) may provide a solution for individuals suffering from food allergies or other types of IgE-mediated (atopic) diseases, such as hay fever and asthma. Roy and his colleagues at the Johns Hopkins University in Baltimore used an oral DNA vaccine to induce tolerance to peanut allergen in mice. Animals were fed nanoparticles composed of DNA encoding Arah2 (the principal allergen in peanuts) and chitosan, a biodegradable component of crustacean shells that protects the DNA and delivers it to the epithelial cells lining the intestine. In nanoparticle-fed mice, mucosal IgA levels increased as did the T helper cell type I immune response, with a concomitant decrease in peanut allergen–specific IgE antibody. When orally immunized animals were sensitized to peanuts and then challenged with Arah2, they showed a delayed and much milder anaphylactic reaction than nonimmunized mice or mice that received control DNA instead of peanut allergen DNA.

The authors note that this is a preventive vaccine model in which mice are orally immunized before sensitization to peanut protein. Closer to the human situation, but less likely to succeed, is a therapeutic vaccine model in which the peanut allergen DNA is administered to animals that are already sensitized, with the goal of rerouting an immune response that is already under way. If Roy *et al.* can reproduce their findings in sensitized mice, then an oral vaccine to induce tolerance in humans with peanut allergy may be on the horizon. And passengers allergic to peanuts need fear flying no more.

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