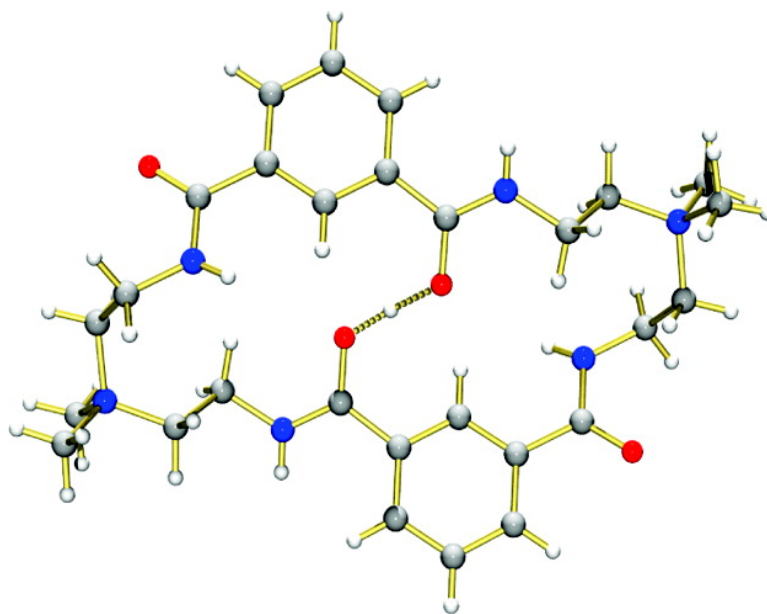


Encircled Proton

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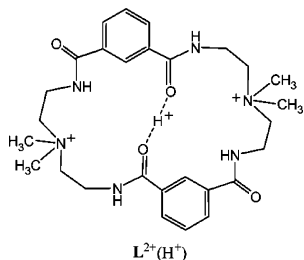
Encircled Proton

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One of the most elegant aspects of supramolecular host–guest chemistry is when the guest is encircled or encapsulated by the host. In most, if not all instances, the guests are neutral, cationic, or anionic species that are of significant atomic mass, such as halides, metal ions, organic ions, or other multiatomic species. There have been a number of reports of inside protonated amine cages, but these are anticipated by virtue of the general basicity of amines.^{1,2} There have also been reports of intermolecular hydrogen bonds involving hemiprotonated amide oxygens^{3–14} and a short intramolecular (carbonyl)O⋯O(hydroxyl) distance observed in benzoylacetone.¹⁵ However, we could only find two reports of similar, but *intermolecular*, amide HNC=O⋯H⁺⋯O=CNH linkages.¹⁶ Thus, it appears to be rare to find a proton held between two chemically and electronically equivalent amide carbonyl oxygen atoms. Herein is reported the strikingly unusual occurrence of an encircled proton in a tetraamido/diamino quaternized macrocycle, **L**²⁺, that is hydrogen bonded to two of the internally oriented carbonyl oxygen atoms to yield **L**²⁺(H⁺). Due to the very short O⋯O distance of 2.45 Å, this interaction can be classified as a low-barrier hydrogen bond (LBHB).¹⁷



LBHBs are very strong hydrogen bonds manifested by donor–acceptor distances shorter than normal hydrogen bonds.¹⁷ It has been postulated that such bonds exist within protein interiors, and although still subject to debate, these symmetrical amide O⋯H⋯O bonds may be an important component of transition-state stabilization in enzymes.^{15,18–20} At normal hydrogen-bonding distances (for O–H⋯O ≥ 2.8 Å), there is an energy barrier that dictates the heteroatom to which the hydrogen is covalently bound, that is, a double-well potential energy situation. However, this barrier decreases with distance, and at about 2.55 Å, a zero-point energy level is reached, and the hydrogen bond is classified as a low-barrier hydrogen bond, LBHB, with the hydrogen being free to move between the two atoms. Shorter distances, down to a limiting 2.29 Å for O⋯O, are attributed to a single-well potential LBHB, or, as coined by Schiøtt, Iversen, Bruice, and co-workers, short-strong hydrogen bonds (SSHBs).¹⁵

The LBHB in **L**²⁺ was synthesized serendipitously by adding a few drops of concentrated H₂SO₄ to an aqueous solution of

L²⁺·2OH[−], prepared as reported previously.^{21,22} The proton complex, [**L**²⁺(H⁺)] [HSO₄[−]]₃·3H₂O, crystallized in the monoclinic space group *P*2₁/*n*²³ with one dicationic host, three bisulfate counteranions, and three water molecules of crystallization. The lone proton within the macrocyclic circumference serves to satisfy the remaining single positive charge requirement. The short intramolecular O⋯O separation between amide oxygens led to the discovery of this encircled hydrogen atom (Figure 1), which was located from a difference Fourier and successfully refined as an independent isotropic atom. The macrocycle lies in a skewed conformation, with the two phenyl rings being offset from each other. The quaternized nitrogens are separated by 12.13 Å. In a related structure of the dichloride salt of **L**²⁺ with no internal hydrogen bonds, the quaternized nitrogen N⁺⋯N⁺ distance is 12.74 Å, with two chlorides also lying outside the cavity.²²

The 2.453(3) Å *intramolecular* O1⋯O3 separation in the present structure is similar to those previously reported for *intermolecular* hydrogen bonds involving hemiprotonated amide oxygens^{3–14} and slightly shorter than the 2.502 Å *intramolecular* O⋯O distance observed in benzoylacetone.¹⁵ The short O⋯O separation, O⋯H⋯O angle of 173(5)°, and O⋯H separations which average 1.23(6) Å are consistent with a symmetrical hydrogen bond, especially given that the two carbonyl oxygen atoms are in identical environments. This LBHB also removes electron density from the donor and acceptor atoms, perturbs the electron density in the amide linkages, and predictably alters their bond lengths. The C=O bond lengths for the two hydrogen-bonded amides [1.272(4) Å] are slightly longer than the C=O bonds [1.240(4) Å] for the two non-hydrogen-bonded amides. Similarly, the C–N bond lengths for the hydrogen-bonded amides average 1.319(5) Å and are slightly shorter than the 1.346(5) Å C–N bonds for the other two amides.

The three bisulfate ions and three water solvate molecules all lie outside of the macrocycle. Two of the bisulfate anions are linked to the macrocycle via hydrogen bonds to the two amide nitrogen atoms that are not associated with the internal proton (Figure 1). A helical packing pattern is observed, with the third bisulfate ion forming hydrogen-bonded anionic channels along the *a*-axis between the macrocyclic chains (Figure 2).

The presence of the lone proton in the positively charged macrocyclic cavity was surprising since it would not be anticipated that a dipositively charged macrocycle would attract another positively charged species, especially considering the presence of surrounding water molecules. That this LBHB is an energetically favorable situation was validated through quantum chemical calculations, using the Gaussian 03 program.²⁴ Full geometry optimizations on the **L**²⁺ macrocycle and the surrounding anions (both with and without a trapped proton) were carried out at the B3-LYP level of theory^{25,26} and 6-31G(d,p) basis sets.²⁷ The final computed geometry for the structure with the proton qualitatively matched the crystal structure with a root mean square deviation of 0.32 Å. The protonated structure was found to be enthalpically

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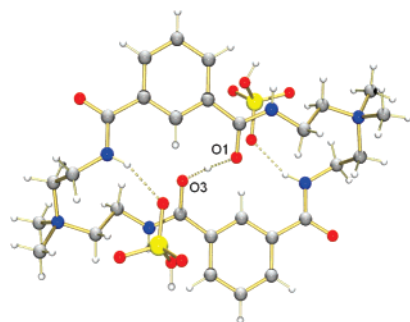


Figure 1. Overhead perspective view of trication $L^{2+}(H^+)$ with the two adjacent hydrogen-bonded bisulfates, $[L^{2+}(H^+)][HSO_4^-]_2^+$.

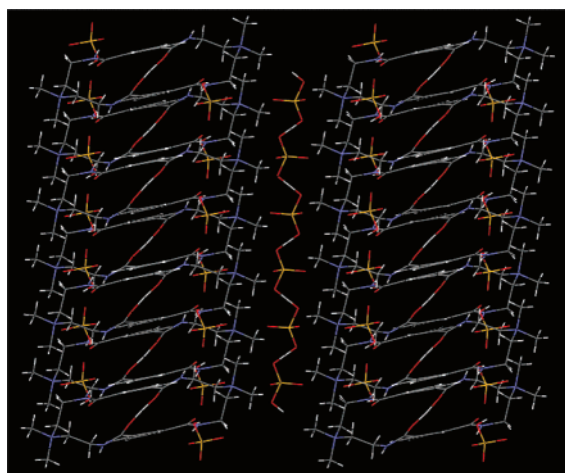


Figure 2. Packing diagram of $[L^{2+}(H^+)][HSO_4^-]_3 \cdot 3H_2O$ viewed down the b -axis, showing the two bisulfates hydrogen bonded directly with L^{2+} and the third bisulfate that forms chains running parallel to the a -axis.

avored over the unprotonated form by 245.1 kcal/mol, in support of the LBHB nature of this unusual hydrogen bond.

NMR spectra showed the presence of a very broad fleeting signal at 12.11 ppm in the 1H NMR. LBHB resonances usually occur downfield at around 15 ppm.² We also observed two signals in the ^{13}C spectrum at 163.0 and 165.7 ppm. These findings might indicate the persistence of the encircled proton in solution; however, there could be other explanations. We are currently working to synthesize similar complexes with other anions in order to understand this unusual phenomenon. Thus, while the generality of this occurrence or the extent of its implications is not known at this time, it could impact other supramolecular interactions, including protein structure and folding, enzyme function, the self-assembly of molecules, and the design of molecular machines and switches.

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Supporting Information Available: Complete author list for ref 24 and one crystallographic file for the structure in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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