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Inside-Protonated 1-Azaadamantane. Computational Studies on the Structure, Stability and Generation

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Abstract: Post Hartree-Fock and density functional theory methods have been employed to study inside-protonated 1-azaadamantane **7** and its complexes with the fluoride counterion (contact ion pairs) **10**, **11**. The study also involved 1-azaadamantane **4**, its outside-protonated form **8**, and 1-azaadamantane radical cation **17**. Inside-protonated 1-azaadamantane **7** is more than 82 kcal mol⁻¹ less stable than *out*-isomer **8**. The repulsive interaction between the internal N⁺-H group and the azaadamantane cage, and a substantial deformation of this cage, greatly weaken the C-N and C-C bonds and, consequently, lead to a low kinetic stability of *in*-ion **7** in the studied unimolecular and bimolecular reactions involving the removal of the encapsulated proton from the cage. Among these reactions, a **7** → **8** rearrangement through a reversible cage opening at the C-N bond was found to be the main transformation channel ($\Delta G^\ddagger_{298} < 16$ kcal mol⁻¹) for *in*-ion **7**. This rearrangement can be catalyzed by an external base, e. g., the fluoride anion. A 1,4-hydrogen migration in 1-azaadamantane radical cation **17** as a possible pathway to the inside-protonated 1-azaadamantane **7** was explored. It was found that this process has a prohibitively high activation barrier, $\Delta G^\ddagger_{298} > 104$ kcal mol⁻¹, and is not able to compete with the α -C-C cleavage of the azaadamantane cage ($\Delta G^\ddagger_{298} < 26$ kcal mol⁻¹).

Key words: 1-azaadamantane, 1-azaadamantane radical cation, inside-protonated cage molecules, theoretical model study

Introduction

Complexes consisting of a hydrocarbon cage molecule (host) and a cation (guest) have been objects of theoretical studies¹⁻⁵ for several decades. Larger host molecules such as dodecahedrane¹ and fullerenes³ have attracted the most attention. Relatively small cage complexes were studied by Schleyer and co-workers² from which was found that adamantane (**1**), C₁₀H₁₆, was the smallest host molecule capable of forming stable and metastable endohedral complexes. These complexes, referred to as X@C₁₀H₁₆, have been utilizing a wide variety of atoms (X = H, He, Ne, Li, Na, Be) and cations (X = Li⁺, Na⁺, Be⁺, ²⁺, Mg²⁺). Since Schleyer's work, adamantane has become a popular host molecule. In-depth studies^{4, 5a} of the nature of "host-guest" interaction were carried out for the He@C₁₀H₁₆ complex and concepts of chemical bonding were discussed based upon the obtained results. Along the same line, endohedral complexes of adamantane with charged species such as Li⁺, Be²⁺ and B⁺³ were also investigated.^{5a} Alkorta and co-workers^{5b} used the Li⁺@C₁₀H₁₆ complex containing an external counterion (F⁻, Cl⁻, Br⁻) as a model compound for a theoretical study on the ionic permeability of diamondoids as potential charge insulators.

Quantum chemical studies^{1d,e, 2} of endohedral complexes containing a bare proton demonstrated that, in contrast to the metal cations, H⁺ has a tendency to react with C-C bonds of the host molecule. To maintain the proton's endohedral placement symmetry constraints proved to be necessary. However, such highly symmetrical structures are characterized by several imaginary Hessian frequencies and are neither local minima on the potential energy surfaces (PES) nor transition states. In particular, for the inside-protonated adamantane (**2**), the *T_d* and *C_{3v}* structures were found² to be third- and second-order saddle points, respectively. The geometry optimization

of **2** with the C_s symmetry led to an opening of the adamantane cage via the C-C bond cleavage and formation of carbonium ion **3**.

INSERT Formulae 1-9 HERE

It was of interest for us to investigate how the internal protonation of the adamantane cage will change if an atom bearing a lone pair, i. e. a nitrogen atom, replaces a bridgehead carbon. One can suggest that interaction of the encapsulated proton with the nitrogen lone pair in 1-azaadamantane (**4**), rather than a C-C bonding pair, will help preserve the cage structure.

Earlier in-cage protonation of oligocyclic bridgehead amines has been studied⁶ for molecules with a relatively large cavity and flexible skeleton, such as 1,6-diazabicyclo[4.4.4]tetradecane (**5**). In this molecule, the bridgehead nitrogen is pyramidalized inward the molecular cage and forms a normal tetrahedral ammonium ion **6** after protonation. Unlike the large-size oligocyclic structures, the adamantane skeleton has a smaller cage volume² for accommodation of an internal N^+H group and an apparent rigidity of this skeleton should resist the inward pyramidalization of the bridgehead nitrogen in ion **7**. Both these circumstances must lead to a substantial destabilization of **7** with respect to the outside-protonated isomer **8**. A similar situation has been described by Irikura⁷ for adamantane **9** containing an inverted bridgehead carbon. This compound can be considered an isoelectronic analog of *in*-ion **7**. Irikura's calculations performed at the CCSD(T)/6-31G*//MP2/6-31G* theoretical level give a 116 kcal mol⁻¹ difference in energies between adamantane isomers **1** and **9**.

Highly strained oligocyclic hydrocarbons are widely used⁸ as efficient fuels and explosives. The caged compounds also benefit from a decrease in molecular motion which often leads to higher density and a corresponding increase in the heat of combustion or explosive performance. Salts

containing the high-strained cation **7** in combination with such energetic anions as dicyanamide, nitrocyanamide, nitrate, dicyanoborate and others^{8c} might be of interest as potential hypergolic materials. However, for this it is necessary that (i) cation **7** possess a sufficient kinetic stability and that (ii) there is a possibility of its generation (synthesis).

At the beginning of our study we had to answer the question whether the inside-protonated 1-azaadamantane **7** is a local minimum on the $C_9H_{16}N^+$ PES. Having obtained a positive answer, we calculated the thermodynamic stability of *in*-ion **7** with respect to *out*-isomer **8** as well as proton affinity at the inside and outside protonation of 1-azaadamantane **4**. The kinetic stability of *in*-ion **7** was estimated from the activation energies of unimolecular and bimolecular reactions through which the encapsulated proton escaped the azaadamantane shell. Finally, the possibility of generating *in*-ion **7** through an intramolecular 1,4-hydrogen shift in the 1-azadamantane radical cation was explored.

Computational Details

All quantum chemical calculations presented here were performed with the Gaussian 16 system⁹ of programs. The geometry optimizations and frequency calculations were carried out at the (U)M062X/6-311++G(d,p) and (U)MP2/6-311++G(d,p) theoretical levels using procedures implemented in the Gaussian molecular orbital package. In the case of the MP2 calculations, the frozen core approximation was used. Applicability of the M06-2X and other density functionals in chemistry has been discussed elsewhere.^{10a,b} Both M06-2X and MP2 methods produce qualitatively similar geometrical and electronic molecular parameters.

The inside-protonated molecules where the molecular skeleton was substantially distorted were checked for wave function instabilities, however, none were found. For the open-shell species

considered here, the spin contamination was negligible as attested by the calculated $\langle S^2 \rangle$ values, which were very close to 0.75 after spin annihilation. The harmonic frequency analysis verified the nature of the stationary points as minima (all real frequencies) or as transition structures (one imaginary frequency). The relative enthalpies (ΔH_{298}) and Gibbs free energies (ΔG_{298}) were computed using unscaled harmonic frequencies. Unimolecular half-lives were derived from the $\Delta G^\ddagger_{298}$ values using transition-state theory. Connections between the reactants, transition structures and products were confirmed by intrinsic reaction coordinate calculations.¹¹

The proton affinities^{12a,b} (PA) for the inside and outside protonation of 1-azaadamantane **4** were calculated as the negative of the enthalpy change for the reaction **4** + H⁺ $\rightarrow$ *in-ion* **7** or *out-ion* **8** (PA = $-\Delta H_{298}$).

Effect of solvation (with acetonitrile as solvent) on the structure and energy was simulated employing the self-consistent reaction field (SCRF) theory incorporating the polarizable continuum model¹³ (PCM).

The natural bond orbital (NBO) analysis^{14a} was performed using NBO 3.1 module^{14b} as implemented in Gaussian 16.

The bonding analysis was done in the framework of quantum theory of atoms in molecules^{15a} (AIM) using AIMAll software.^{15b}

Results and Discussion

Structural and Electronic Features and Thermodynamic Stability of Inside-Protonated 1-Azaadamantane. The geometry optimization of inside-protonated 1-azaadamantane **7** with the C_{3v} symmetry leads to a stationary structure (Figure 1, Table 1) with all real frequencies. Upon

lowering the molecular symmetry from C_{3v} to C_s and then to C_1 , *in-ion* **7** remains a local minimum on the $C_9H_{16}N^+$ PES with its total energy and geometry unchanged.

INSERT Figure 1 HERE

The quaternary ammonium fragment in *in-ion* **7** is reminiscent – geometrically – of a distorted trigonal pyramid with the *in*-hydrogen at an inverted peak, and quaternary nitrogen bulging slightly from the center of the base. The nitrogen bulge of this trigonal pyramidal shape is directed outside the azaadamantane cage and all four nitrogen covalent bonds lie within one hemisphere (Figure 1). The geometry at the protonated nitrogen atom is reflected by the sum, $\Sigma\theta$, of the three CNC angles, θ , and by the distance, h , of this atom from the plane of its bonded C neighbors. Planarity implies $\Sigma\theta = 360^\circ$ and $h = 0$, while a decrease in the former and an increase in the latter indicate a progressive pyramidalization. As can be seen from Table 1, the value of $\Sigma\theta$ for *in-ion* **7** is close to 360° and the height of the nitrogen pyramid, h , in this compound is about two times lower than that of the *out*-isomer **8**. The outward orientation of the nitrogen pyramid in **7** is confirmed by the value of the C-N-H valence angle that is less than 90° (Table 1).

INSERT Table 1 ABOUT HERE

The 1-azaadamantane cage may be described as consisting of three fused piperidine rings and one cyclohexane ring. Comparative topological analysis of ions **7** and **8** show that moving the proton inside the cage leads to the disappearance of the (3, +1) critical point (CP) for the cyclohexane ring and the (3, +3) CP for the cage.¹⁶ Three remaining (3, +1) CP in *in-ion* **7** belong to the piperidine rings. For the encapsulated proton, only one (3, -1) bond CP was found. This CP lies on the line of atomic interaction with the nitrogen. There are no electron-density

bridges of the encapsulated proton with the other nuclei of the cage, although the distances between the proton and C1, C2, C3 atoms (Table 1) are less than the sum of van der Waals radii of H and C (2.9 Å). The electron densities $\rho(r_{cp})$ in the N-H bond critical points for both isomers **7** and **8**, as well as large, negative values of the Laplacean of the density, $\nabla^2 \rho(r_{cp})$ (Table 2), are as expected for covalent, electron-sharing bonds.^{15a}

INSERT Table 2 ABOUT HERE

The flattening of the nitrogen pyramid should result in an increase in the s-character of the C-N bonds and, correspondingly, an increasing p-character for the N-H bond in **7**. This is confirmed by our NBO analysis of these bonds in isomers **7** and **8** (Table 2). Normally, for unstrained molecules, such a change in hybridization is accompanied by a shortening of bonds undergoing an increase in s-character and a lengthening of bonds upon an increase in p-character. However, repulsive interactions involving the internal N⁺-H group with the cage elicits the opposite structural effect: the N-H bond is ~0.03 Å shorter and the C-N bonds are 0.02 Å longer in **7** than the corresponding bonds in **8** (Table 1). A noticeable decrease in the N-C-C valence angles and elongation of all C-C bonds (Table 1) also indicate a significant deformation of the adamantane cage in endohedral ion **7**.

The cage deformation and the in-cage repulsive interactions create molecular strain that is expressed as a considerable thermodynamic destabilization (>82 kcal mol⁻¹) of *in*-ion **7** with respect to *out*-isomer **8** (Table 1). The cage deformation energy (ΔE_{def}) can be estimated as the difference in single-point energies between a model 1-azaadamantane (**4**[†]) frozen in the structure optimized for *out*-ion **8** and another model 1-azaadamantane (**4**^{*}) frozen in the structure optimized for *in*-ion **7** (Equation 1). Another approach is to calculate the difference in energies ($\Delta E'_{def}$)

between the fully optimized *out*-ion **8** and a partially optimized *out*-ion **8**^{*} (Equation 2). The latter was frozen in the structure optimized for *in*-ion **7** and only the outer N-H bond was optimized.

$$\Delta E_{def} = E(\mathbf{4}^*) - E(\mathbf{4}^\dagger) \quad (1)$$

$$\Delta E'_{def} = E(\mathbf{8}^*) - E(\mathbf{8}) \quad (2)$$

These two equations give similar results at both M06-2X and MP2 levels of theory (Table 1). Hence, the deformation energy of the adamantane skeleton is about 33% of the destabilization energy (ΔE_T) of the endohedral ion **7**. The major part, about 67%, of the relative destabilization of *in*-ion **7** is thus due to repulsive interaction between the inner N⁺-H group and the adamantane cage.

Values of proton affinity (PA), 233.9 (M06-2X) and 234.3 kcal mol⁻¹ (MP2), predicted for the external protonation of 1-azaadamantane **4** fit quite perfectly into the range of experimental and theoretical PAs for aliphatic trialkylamines,^{12c,d,e} 230 – 235 kcal mol⁻¹. In the case of the inside protonation of **4**, calculated PA values, 148.3 (M06-2X) and 151.8 kcal mol⁻¹ (MP2), are so low that they are more reminiscent of PAs for fluorosubstituted methanes^{12e} than PAs for any amines.

Kinetic Stability of Inside-Protonated 1-Azaadamantane. Based upon the structure of the inside-protonated 1-azaadamantane **7**, one can assume two pathways for transformation of this cation in which removal of the encapsulated proton takes place. The first pathway is a proton exit along the *C*_{3v} symmetry axis through the cyclohexane ring (Chart 1a) and the second one is an exit through the piperidine ring in the *C*_s symmetry plane (Chart 1b).

INSERT Chart 1 HERE

In order to evaluate the kinetic stability of *in*-ion **7**, unimolecular and bimolecular versions of both deprotonation pathways were studied. For the bimolecular mechanism, deprotonation under the action of a fluoride counterion in complexes **10**, **11**¹⁷ was chosen. In each of these complexes, the counterion was placed on the exit path of the encapsulated proton from the cage (Chart 1c,d).

Unimolecular reactions. Simulations of the proton exits along the C_{3v} symmetry axis and in the C_s symmetry plane led to saddle points – a third-order point **SP₃(7)** and a second-order point **SP₂(7)**, respectively. True transition states **TS(7/12)** and **TS(7/8)** (Figure 2, Figure S1) were located under the removal of the symmetry constraints.

In the first reaction, the N-H bond cleavage and insertion of the proton into the C2-C3 bond takes place to form an exohedral 3-center-2-electron complex **12** (Figure 2).

INSERT Figure 2 HERE

The second unimolecular reaction proceeds through transition state **TS(7/8)** by a pathway of a reversible cage opening at the C-N bond with a simultaneous inversion of the C-N(H)-C fragment (Figures 2). In this case, the N-H bond remains unaffected. A calculated barrier ($\Delta G^\ddagger_{298}$) of this transformation is ~ 3 kcal mol⁻¹ below the barrier of the first reaction and corresponds to a half-life from 0.4 (M06-2X) to 72 msec (MP2) at 298K. A similar *in-out* rearrangement has been found⁷ for *in*-adamantane **9**. A predicted activation enthalpy (17 kcal mol⁻¹) of this rearrangement is close to the MP2 value of 17.3 kcal mol⁻¹ calculated here for *in*-ion **7**.

Bimolecular reactions. In complex **10**, movement of the proton along the C_{3v} symmetry axis toward the fluoride counterion leads to a third-order saddle point **SP₃(10)**¹⁸ (Figure 3) as in the case of the described above unimolecular C_{3v} proton removal.

At lowering the symmetry to the C_s , was located transition state **TS(10/13)** (Figure 3, Figure S1) that is formed upon the attack of the fluoride counterion on the proximal proton of a methylene group of the cyclohexane ring. The pulling of the methylene proton by the fluoride anion promotes 1,4 (N→C) migration of the endohedral proton. In general terms, this reaction can be described as a S_E2 push-pull electrophilic substitution promoted by a base.^{19a,b}

INSERT Figure 3 HERE

Earlier, Alder and co-workers^{6b,c, 20} suggested a similar mechanism involving a methylene group for in-cage protonation of **5** and other large-sized bicyclic bridgehead amines.

For the removal of the encapsulated proton in complex **11**, two transition states were found (Figure 4, Figure S1). The first transition state, **TS(11/14)**, has C_s symmetry, and the second one, **TS'(11/14)**, has no symmetry. Complex **14** was the reaction product in the both cases.

INSERT Figure 4 ABOUT HERE

Process involving the C_s symmetrical **TS(11/14)** is the least favorable kinetically among the bimolecular reactions considered here and this process is the only one, in which the encapsulated proton really leaves the adamantane cage. The proximal C-N bonds are synchronously stretched to 1.644 (M06-2X) and 1.656 Å (MP2) in the transition state and, as the proton leaves the cage, the lengths of these bonds are restored to their normal values of 1.477 (M06-2X) and 1.479 Å (MP2).

An interesting feature of the reaction involving the non-symmetrical **TS'(11/14)** is that it begins with the attack of fluoride counterion on the nearest proton of CH₂ group like the *S_E2* substitution in complex **10** but develops further like the *in-out* rearrangement of **7**. In other words, the pulling of the proton from the α-CH₂ group by the fluoride ion is accompanied by elongation of the C-N bond and the inversion of the C-N(H)-C fragment takes place through the formed gap. Then, the proton is transferred from HF back to the α-carbon atom and the cage is closed at the C-N bond. Thus, the fluoride counterion acts as a catalyst for the *in-out* rearrangement of the inside protonated 1-azaadamantane **7**.

Calculated activation barriers of both bimolecular reactions involving the methylene groups in the ion pairs **10**, **11** are extremely low ($\Delta G^\ddagger_{298} < 2.0 \text{ kcal mol}^{-1}$) that can be explained based on the substantial destabilization of these pairs in the gas phase due to a strong charge separation. The PCM SCRF calculations predict an increase in the Gibbs free energies of activation (Figures 3, 4) when the highly polar complexes **10**, **11** and the less polar transition structures **TS(10/13)**, **TS'(11/14)** were placed in a fitted cavity with the dielectric constant of acetonitrile. The activation barrier for the catalytic *in-out* rearrangement in complex **11** in acetonitrile was found to be ~2 kcal mol⁻¹ lower than the barrier for the *S_E2* substitution in **10**.

We were unable to evaluate the implicit influence of acetonitrile on the relative energy of the *C_s* symmetrical **TS(11/14)** because an optimization of this structure within the PCM model led to a second-order saddle point **SP₂(11)** (Figure 4) at both M06-2X and MP2 levels of theory (Figure 4).

Obviously the reactions studied here do not encompass the whole chemistry of the inside-protonated 1-azaadamantane **7**. However, the obtained data sufficiently indicate a low kinetic stability of this ion.

On the Possibility of Generation of Inside-Protonated 1-Azaadamantane. The calculated data on the thermodynamics of interconversion of the inside- and outside-protonated ions **7**, **8** (Figure 2) and the corresponding complexes **10**, **13** and **11**, **14** (Figures 3, 4) exclude a possibility of the internal protonation of 1-azaadamantane **4** by a simple reaction with acids. In fact, the *out*-isomers are 82-126 kcal mol⁻¹ more stable than the *in*-isomers and the activation barriers of the rearrangements of the former into the latter ones are exceptionally high, 98-133 kcal mol⁻¹.

It should be noted that the conventional inside protonation is substantially hindered kinetically even in the case of large-sized bicyclic amines, for which the *in*-protonated forms are more thermodynamically favorable than the *out*-protonated ones.^{6b,c, 20a} Alder and co-workers^{6b,c, 20b} discovered that the inside-protonation of caged diamine **5** is strongly promoted by one-electron oxidants. The authors suggested that the reaction proceeds via formation of radical cation **15**, in which a facile 1,5-hydrogen migration takes place, leading to a distonic radical dication **16** (Scheme 1a).

INSERT Scheme 1 HERE

The ease of the 1,5-hydrogen shift is also confirmed by quantum chemical calculations,^{21a-d} according to which activation energies for this reaction lie in the range of 2-12 kcal mol⁻¹, although these calculations were performed for the radical cations of acyclic amines and at different theoretical levels.

For the 1-azaadamantane radical cation **17**^{22, 23} of interest to us, a possible pathway for the methylene hydrogen transfer into the cage is the 1,4-migration (Scheme 1b). Theoretical activation barriers for this type of reaction in acyclic amine radical cations are 10-12 kcal mol⁻¹ higher than the barriers calculated for the 1,5-hydrogen shift in the same species.^{21a-d} The piperidine radical cation **19** (Scheme 1c) is closest in structure to **17**. In this case, a Gibbs free energy of activation for the 1,4-migration was 29.8 kcal mol⁻¹ at the G3B3 theoretical level.²⁴

We located a transition state, **TS(17/18)**, for the 1,4-hydrogen migration in radical cation **17** (Figure 5, Figure S1) and found that an activation barrier of this reaction is ~3.5 times as high as the barrier observed for this rearrangement in piperidine radical cation **19**.

INSERT Figure 5 HERE

Such a big difference between these barriers is, apparently, caused by two circumstances. Firstly, stereoelectronic situation for the 1,4-hydrogen shift in **17** is substantially less favorable in comparison with **19**. The latter is able to adopt a boat conformation, in which the hydrogen atom involved in the rearrangement is spatially close to the spin-bearing nitrogen p-orbital²⁴ (Chart 2a). Such an arrangement is impossible in the case of the rigid chair conformation of the piperidine ring in **17** (Chart 2b). Secondly, it is important that the migrating hydrogen atom in **TS(17/18)** enters the inner space of the adamantane cage and begins to experience strong destabilizing interactions, characteristic for the in-cage position of the N⁺-H group.

INSERT Chart 2 HERE

In addition to the 1,4-migration, we considered a 1,2-hydrogen shift^{21a-d, 24} and α -C-C bond cleavage^{21c, 25a,b} in radical cation **17** in order to have a more complete picture of unimolecular transformations for this compound.

According to the published theoretical data, the 1,2 migration is characterized by the highest activation energy (40-44 kcal mol⁻¹) in the series of 1,n migrations (n = 2, 3, 4, 5) in the acyclic amine radical cations^{21a-d} and piperidine radical cation **19**²⁴ due to significant ring strain in the 3-membered-ring transition structure. In the case of **17**, this situation is aggravated in that the nitrogen is in the bridgehead position and its spin-bearing p-orbital is orthogonal to the π -orbital of the α -methylene group (Chart 2c). As a result, the activation barrier of the 1,2-hydrogen shift in **17** is ~20 kcal mol⁻¹ higher (Figure 5) than those in the non-bridgehead radical cations.^{21a-d, 24} Nevertheless, this barrier is already substantially below the barrier calculated for the 1,4-migration in **17** (Figure 5).

An even lower activation barrier is predicted for the cage opening at the α -C-C bond in **17** (Figure 5). The obtained values of Gibbs free energy of activation fall within the range of activation energies, 17-30 kcal mol⁻¹, for the acyclic amine radical cations.^{21c, 25a,b} This reaction is facilitated by a favorable spatial arrangement of the spin-bearing nitrogen orbital and σ -orbital of the α -C-C bond (Chart 2d). However, the distonic radical cation **22** formed in this case is less favorable thermodynamically than **21** – product of the 1,2-hydrogen migration (Figure 5).

Among the transformations of **17** studied here, the 1,4-migration that could be considered a potential pathway for generation of *in*-ion **7** is the least energetically favorable process both from the kinetic and thermodynamic points of view. Wigner^{26a} and Bell-Truhlar^{26b,c,d} tunneling corrections provide only a small decrease in the Gibbs free activation energy for this rearrangement by 0.6 and 2.4 kcal mol⁻¹, respectively, at the both theoretical levels. Although, it has been indicated^{21a,b} that the tunneling effects for the class of reactions described above can be more substantial than what is predicted by the simple corrections.

Conclusions

The inside-protonated 1-azaadamantane (**7**) is a local minimum on the $\text{C}_9\text{H}_{16}\text{N}^+$ potential energy surface. The quaternary nitrogen atom in this high-strained cation has an abnormal propellane-like configuration of a strongly flattened pyramid with all four covalent bonds lying within one hemisphere.

The calculations predict a high destabilization energy, $\Delta H_{298}^0 > 82 \text{ kcal mol}^{-1}$, of *in*-ion **7** with respect to its outside-protonated isomer **8** which has the normal tetrahedral configuration of a quaternary nitrogen. The major part, about 67%, of this energy is due to repulsive interaction between the inner $\text{N}^+\text{-H}$ group and the adamantane cage and the rest, about 33%, is due to cage deformation.

The molecular strain caused by the internal protonation of 1-azaadamantane leads to a significant weakening of the skeleton bonds and, consequently, to a low kinetic stability of the *in*-ion **7**. A rearrangement of the latter into *out*-isomer **8** through the reversible opening of the adamantane cage at the C-N bond was found to be the most energetically favorable transformation channel among the herein studied pathways for the removal of the encapsulated proton from the cage. In the gas phase, this rearrangement is characterized by a low Gibbs free activation energy, from 13.0 (M06-2X) to 16.1 kcal mol^{-1} (MP2), which corresponds to a half-life from 0.4 to 72 msec, respectively, at 298K. In a complex consisting of *in*-cation **7** and fluoride counterion (contact ion pair **11**), the latter catalyzes the *in-out* rearrangement of **7** into **8**, decreasing the activation barrier to negligible values $< 1.9 \text{ kcal mol}^{-1}$. This barrier is increased to 8.5 (M06-2X) and 11.4 kcal mol^{-1} (MP2) in a PCM SCRF simulated polar medium with the dielectric constant of acetonitrile, but remains below the barrier of the gas-phase non-catalytic reaction.

The calculated data on the thermodynamics of the equilibrium between the inside- and outside-protonated forms of 1-azaadamantane indicate that a simple reaction of this base with acids cannot be considered as a method for generation of *in*-ion **7**. An alternative pathway to this ion through 1,4-hydrogen migration in 1-azaadamantane radical cation **17** was also found to be improbable because of an extremely high activation barrier, 103.9 (MP2) and 106.6 kcal mol⁻¹ (M06-2X). The most energetically favored transformation of radical cation **17** is the α -C-C bond cleavage to yield a distonic radical immonium cation **22**.

Supplementary data

Figure S1 showing optimized transition structures. Cartesian coordinates, dipole moments, and energy parameters for all investigated species. Supplementary data are available with the article through the journal Web site at <http://nrcresearchpress.com/doi/suppl/xxxxx>.

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References

1. (a) Dixon, D. A.; Deerfield, D.; Graham, G. D. *Chem. Phys. Lett.* **1981**, *78*, 161-164. doi: 10.1016/0009-2614(81)85576-5. (b) Disch, R. L.; Schulman, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 3297-3300. doi: 10.1021/ja00402a012. (c) Moran, D.; Stahl, F.; Jemmis, E. D.; Schaefer, H. F., III; Schleyer, P. v. R. *J. Phys. Chem. A* **2002**, *106*, 5144-5154. doi: 10.1021/jp014471z. (d) Mascal, M. *J. Org. Chem.* **2002**, *67*, 8644-8647. doi: 10.1021/jo026226x. (e) Chen, Z.; Jiao, H.; Moran, D.; Hirsch, A.; Thiel, W.; Schleyer, P. v. R. *J. Phys. Chem. A* **2003**, *107*, 2075-2079. doi: 10.1021/jp0273631.
2. Moran, D.; Woodcock, H. L.; Chen, Z.; Schaefer, H. F., III; Schleyer, P. v. R. *J. Am. Chem. Soc.* **2003**, *125*, 11442-11451. doi: 10.1021/ja0345470.
3. (a) Maheshwari, S.; Chakraborty, D.; Sathyamurthy, N. *Chem. Phys. Lett.* **1999**, *315*, 181-186. doi: 10.1016/S0009-2614(99)01229-4. (b) Ramachandran, C. N.; Roy, D.; Sathyamurthy, N. *Chem. Phys. Lett.* **2008**, *461*, 87-92. doi: 10.1016/j.cplett.2008.06.073. (c) Starikov, A. G.; Garupenko, O. A.; Buchachenko, A. L.; Levin, A. A.; Breslavskaya, N. N. *Russ. J. Gen. Chem.* **2008**, *78*, 793-810. doi: 10.1134/S1070363208040397. (d) Yang, S.; Wang, C.-R., Eds.; *Endohedral Fullerenes. From Fundamentals to Applications*; World Sci. Publishing Co. Pte. Ltd.; Singapore, 2014.
4. (a) Haaland, A.; Shorokhov, D. J.; Tverdova, N. V. *Chem. Eur. J.* **2004**, *10*, 4416-4421. doi: 10.1002/chem.200400663. (b) Haaland, A.; Strenalyuk, T. *Chem. Eur. J.* **2008**, *14*, 10223-10226. doi: 10.1002/chem.200800715. (c) Wang, S.-G.; Qiu, Y.-X.; Schwartz, W. H. E. *Chem. Eur. J.* **2009**, *15*, 6032-6040. doi: 10.1002/chem200802596. (d) Wang, S.-

- G.; Qiu, Y.-X.; Schwartz, W. H. E. *Chem. Eur. J.* **2010**, *16*, 9107-9116. doi: 10.1002/chem.201000789.
5. (a) Bader, R. F. W.; Fang, D. C. *J. Chem. Theory Comput.* **2005**, *1*, 403-414. doi: 10.1021/ct049839l. (b) Trujillo, C.; Sánchez-Sanz, G.; Alkorta, I. *J. Phys. Chem. A* **2011**, *115*, 13124-13132. doi: 10.1021/jp205300c.
6. (a) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215-1223. doi: 10.1021/cr00095a015. (b) Alder, R. W. *Tetrahedron* **1990**, *46*, 683-713. doi: 10.1016/S0040-4020(01)81354-5. (c) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097-2111. doi: 10.1021/cr940246k. (d) Galasso, V. *Chem. Phys.* **2001**, *270*, 79-91. doi: 10.1016/S0301-0104(01)00383-4. (e) DuPré, D. B. *J. Phys. Chem. A* **2003**, *107*, 10142-10148. doi: 10.1021/jp035476u. (f) Alder, R. W. *J. Am. Chem. Soc.* **2005**, *127*, 7924-7931. doi: 10.1021/ja051049d.
7. Irikura, K. K. *J. Org. Chem.* **2008**, *73*, 7906-7908. doi: 10.1021/jo801806w.
8. (a) Agrawal, J. P.; Hodgson, R. D. *Organic Chemistry of Explosives*; John Wiley & Sons Ltd: Chichester, UK, 2007. (b) Kubota, N. *Propellants and Explosives. Thermochemical Aspects of Combustion*; Third Edition; Wiley-VCH: Weinheim, Germany, 2015. (c) Zhang, X.; Pan, L.; Wang, L.; Zou, J.-J. *Chem. Eng. Sci.* **2018**, *180*, 95-125. doi: 10.1016/j.ces.2017.11.044.
9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.;

- Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16, Revision A. 03* Gaussian, Inc., Wallingford CT, 2016.
10. (a) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157-167. doi: 10.1021/ar700111a.
(b) Mardirossian, N; Head-Gordon, M. *J. Chem. Theory Comput.* **2016**, *12*, 4303-4325. doi: 10.1021/ACS.jctc.6b00637.
11. (a) Hratchian, H. P; Schlegel, H. B *J. Chem. Phys.* **2004**, *120*, 9918-9924. doi: 10.1063/1.1724823. (b) Hratchian, H. P; Schlegel, H. B *J. Chem. Theory Comput.* **2005**, *1*, 61-69. doi: 10.1021/ct0499783.
12. (a) Maksic, Z. B.; Kovacëvic, B.; Vianello, R. *Chem. Rev.* **2012**, *112*, 5240-5270. doi: 10.1021/cr100458v. (b) Raszyńska, E. D.; Gal, J.-F.; Maria, P.-C. *Chem. Rev.* **2016**, *116*, 13454-13511. doi: 10.1021/acs.chemrev.6boo224. (c) Raabe, G.; Wang, Y.; Fleischhauer, J. Z. *Naturforsch.* **2000**, *55a*, 687-694. (d) Moser, A.; Range, K.; York, D. M. . *J. Phys. Chem. B* **2010**, *114*, 13911-13921. doi: 10.1021/jp107450n. (e) Linstrom, P.; Mallard, W., editors. NIST Chemistry WebBook, NIST Standard Reference Database Number 69. Gaithersburg MD: National Institute of Standards and Technology; 2003. <http://webbook.nist.gov>

13. Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999-3093. doi: 10.1021/cr9904009.
14. (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899-926. doi: 10.1021/cr00088a005. (b) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, version 3.1; University of Wisconsin: Madison, 1993.
15. (a) Bader, R. F. W. *Atoms in Molecules – A Quantum Theory*; Clarendon: Oxford, UK, 1990. (b) Keith, T. A. *AIMAll*, version 10.05.04; TK Gristmill Software, Overland Park, KS, 2010.
16. The characteristic set of critical points [$n = 26$, $b = 28$, $r = 3$, $c = 0$] for *in-ion 7* satisfies the Poincaré-Hopf rule, $n - b + r - c = 1$.
17. The less polar complex **10** (dipole moment $\mu = \sim 10.5$ D) is thermodynamically more favorable than **11** ($\mu = \sim 12.4$ D). In the gas phase, a calculated difference in enthalpies (ΔH_{298}^0) was found from 8.9 (M06-2X) to 9.1 kcal mol⁻¹ (MP2). This difference decreases to 3.4 kcal mol⁻¹ in a polar medium (acetonitrile) according to the PCM-SCRF calculations on both levels of theory.]
18. Alkorta and co-workers^{5b} showed that the encapsulated Li⁺ is able to cross the cyclohexane ring quite easily moving along the C_{3v} symmetry axis toward an external fluoride anion in complex Li⁺@C₁₀H₁₆ F⁻ that is topologically similar to complex **10**.
19. (a) Smith, G. G.; Sivakua, T. *J. Org. Chem.* **1983**, *48*, 627-634. doi: 10.1021/jo00153a001. (b) Reist, M.; Carrupt, P. A.; Testa, B.; Lehmann, S.; Hansen, J. J. *Helv. Chim. Acta* **1996**, *79*, 767-778. doi: 10.1002/hlca.19960790319.

20. (a) Alder, R. W.; Moss, R. E.; Sessions, R.B. *J. Chem. Soc., Chem. Commun.* **1983**, 997-998. doi: 10.1039/C39830000997. (b) Alder, R. W.; Moss, R. E.; Sessions, R.B. *J. Am. Chem. Soc.* **1979**, *101*, 3652-3653. doi: 10.1021/ja00507a039.
21. (a) Yates, B.F.; Radom, L. *J. Am. Chem. Soc.* **1987**, *109*, 2910-2915. doi: 10.1021/ja00244a009. (b) Janovský, I.; Knolle, W.; Naumov, S.; Williams, F. *Chem. Eur. J.* **2004**, *10*, 5524-5534. doi: 10.1002/chem.200400401. (c) Hammerum, S.; Nielsen, C. *B. J. Phys. Chem. A* **2005**, *109*, 12046-12053. doi: 10.1021/jp0550614. (d) Richardson, R. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **2008**, *130*, 3169-3180. doi: 10.1021/ja710595u.
22. 1-Azaadamantane radical cation **17** was generated by UV photolysis of **4** in a strongly acidic solution at -50°C: Danen, W. C.; Rickard, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 2303-2304. doi: 10.1021/ja00841a069.
23. The vertical ionization energy of 1-azaadamantane, 7.94 eV, calculated at the UMP2/6-11++G(d,p) level (Figure 5) is in excellent agreement with the experimental value of 7.94 eV: Worrel, C.; Verhoeven, J. W.; Speckamp, W. N. *Tetrahedron*, **1974**, *30*, 3525-3531. doi: 10.1016/S0040-4020(01)97536-2.
24. Vrček, V.; Zipse, H. *J. Org. Chem.* **2009**, *74*, 2947-2957. doi: 10.1021/jo900349e.
25. (a) Hammerum, S.; Henriksen, T.; *Int. J. Mass Spectrom.*, **2000**, *199*, 79-89. doi: 10.1016/S1387-3806(01)00166-4. (b) Hammerum, S.; Norrman, K.; Sølling, T. I.; Andersen, P. E.; Jemsen, L. B.; Vulpius, T. *J. Am. Chem. Soc.* **2005**, *127*, 6466-6475. doi: 10.1021/ja043481l.

26. (a) Wigner, E. P. *Z. Phys. Chem. B* **1932**, *19*, 203-216. doi: 10.1515/zpch-1932-1920. (b) Bell, R. P. *Trans. Faraday Soc.* **1959**, *55*, 1-4. doi: 10.1039/TF9595500001. (c) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall, London, 1980. (d) Skodje, R. T.; Truhlar, D. G. *J. Phys. Chem.* **1981**, *85*, 624-628. doi:10.1021/j150606a003.

Figure captions

Fig. 1. Optimized structures of 1-azaadamantane (**4**) and its protonated forms **7**, **8**. All CH protons are omitted for clarity.

Fig. 2. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the unimolecular reactions of the removal of the encapsulated proton from the cage in *in*-ion **7** at M062X/6-311++G(d,p) and MP2/6-311++G(d,p) (in italics); NImag = number of imaginary frequencies.

Fig. 3. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the removal of the encapsulated proton from the cage in complex **10** at M062X/6-311++G(d,p) and MP2/6-311++G(d,p) (in italics); NImag = number of imaginary frequencies. The migrating proton is labelled bold.

Fig. 4. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the two competing pathways of the removal of the encapsulated proton from the cage in complex **11**

at M062X/6-311++G(d,p) and MP2/6-311++G(d,p) (in italics); NImag = number of imaginary frequencies. The migrating proton is labelled bold.

Fig. 5. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the transformations of radical cation **17** including the vertical (IE_v) and adiabatic (IE_{ad}) ionization energies of its formation at UM062X/6-311++G(d,p) and UMP2/6-311++G(d,p) (in italics). The migrating hydrogen atom is labelled bold.

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Table 1. Selected calculated geometrical parameters (Å and deg) and relative energies (kcal mol⁻¹) of 1-azaadamantane **4**, ions **7**, **8**, non-optimized model compounds **4**[†], **4**^{*} and partially optimized model ion **8**^{*}.

	M06-2X/6-311++G(d,p)						MP2/6-311++G(d,p)					
	4	4 [†]	4 [*]	7	8	8 [*]	4	4 [†]	4 [*]	7	8	8 [*]
N-H	-	-	-	0.994	1.022	1.030	-	-	-	1.000	1.025	1.036
C1-N	1.467	1.512	1.532	1.532	1.512	1.532	1.470	1.512	1.532	1.532	1.512	1.532
C1-C2	1.539	1.528	1.559	1.559	1.528	1.559	1.538	1.527	1.557	1.557	1.527	1.557
C2-C3	1.537	1.537	1.573	1.573	1.537	1.573	1.537	1.537	1.574	1.574	1.537	1.574
H---C1	-	-	-	1.705	-	-	-	-	-	1.719	-	-
H---C2	-	-	-	1.709	-	-	-	-	-	1.700	-	-
H---C3	-	-	-	1.942	-	-	-	-	-	1.923		
H-N-C1	-	-	-	81.9	108.3	98.1	-	-	-	82.6	108.2	97.4
N-C1-C2	111.6	108.6	98.2	98.2	108.6	98.2	111.9	108.6	97.5	97.5	108.6	97.5
Σθ ^a	328.8	331.9	354.1	354.1	331.9	354.1	327.7	332.0	355.1	355.1	332.0	355.1
h ^b	0.486	0.474	0.216	0.216	0.474	0.216	0.496	0.473	0.197	0.197	0.473	0.197
ΔH ₂₉₈	-	-	-	85.6	0	-	-	-	-	82.5	0	-
ΔE _T ^c	-	-	-	87.6	0	-	-	-	-	84.5	0	-
ΔE _{def} ^d	-	0	27.6	-	-	-	-	0	29.8	-	-	-
ΔE' _{def} ^e	-	-	-	-	0	26.9	-	-	-	-	0	29.1

^aSum of the three CNC valence angles. ^bDistance from nitrogen to the plane of its C neighbors. ^cRelative total energy, zero-point energy correction is not included. ^dSee Equation 1. ^eSee Equation 2.

Table 2. Electronic properties of the N-H and C-N bonds in the protonated forms **7**, **8** of 1-azaadamantane **4**.^a

	<i>In</i> -protonated form 7	<i>Out</i> -protonated form 8
AIM analysis ^b		
N-H bond		
$\rho(r_{cp})$	0.368	0.338
$\nabla^2 \rho(r_{cp})$	-2.072	-1.687
C-N bond		
$\rho(r_{cp})$	0.214	0.227
$\nabla^2 \rho(r_{cp})$	-0.423	-0.493
NBO analysis		
σ_{NH}	$0.307(s)_H + 0.952(sp^{5.42})_N$	$0.529(s)_H + 0.849(sp^{4.20})_N$
σ_{CN}	$0.571(sp^{4.51})_C + 0.821(sp^{2.53})_N$	$0.575(sp^{4.17})_C + 0.818(sp^{2.72})_N$

^aBased on the M06-2X/6-311++G(d,p) geometries, electron densities and wave functions.^bValues of $\rho(r_{cp})$ and $\nabla^2 \rho(r_{cp})$ in au.

Formulae 1-9

Chart 1

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Chart 2

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Scheme 1

Fig. 1. Optimized structures of 1-azaadamantane (**4**) and its protonated forms **7**, **8**. All CH protons are omitted for clarity.

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Fig. 4. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the two competing pathways of the removal of the encapsulated proton from the cage in complex **11** at M062X/6-311++G(d,p) and MP2/6-311++G(d,p) (in *italics*); NImag = number of imaginary frequencies. The migrating proton is labelled **bold**.

Fig. 5. Schematic presentation of the relative Gibbs free energies (ΔG_{298} in kcal mol⁻¹) for the transformations of radical cation **17** including the vertical (IE_v) and adiabatic (IE_{ad}) ionization energies of its formation at UM062X/6-311++G(d,p) and UMP2/6-311++G(d,p) (in italics). The migrating hydrogen atom is labelled **bold**.