Halogen Bonding

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Halogen Bond Anion Templated Assembly of an Imidazolium Pseudorotaxane**

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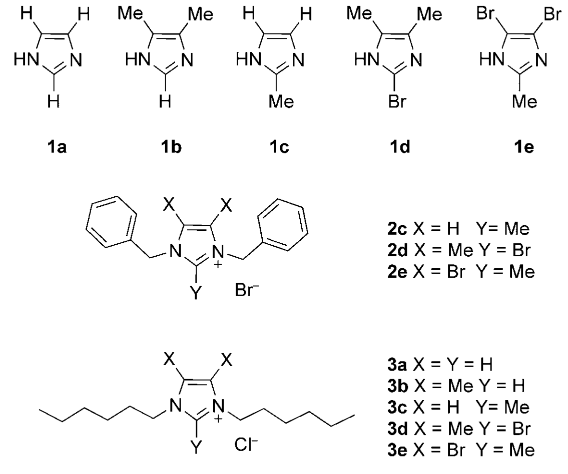
Halogen bonding is the noncovalent bonding interaction between halogen atoms that function as electrophilic centers (Lewis acids) and neutral or anionic Lewis bases.[1] Of the many noncovalent interactions that are commonly utilized in solid-state and solution supramolecular assemblies, halogen bonding is arguably the least exploited, which is surprising given its potentially powerful analogy to ubiquitous hydrogen bonding.[2,3] In fact, the use of halogen bonding as an alternative or complement to hydrogen bonding in the assembly of functional supramolecular materials is underexplored, having been largely restricted to the field of crystal engineering.[4] In particular, halocarbons, for example iodo- and bromoperfluorocarbons, have proved to be versatile building blocks in the assembly of a diverse range of solid-state magnetic and conducting materials, and liquid crystals.[5–10] In addition, organic–inorganic networks that are based on interactions between organic halogens (C−X) and inorganic metal halides and cyanides have been constructed.[11] Importantly, evidence of halogen bonding in the solution phase is extremely rare.[12–14]

Stimulated by the fundamental roles that negatively charged species play in a range of chemical, biological, medical, and environmental processes, the field of anion supramolecular chemistry has expanded enormously during the past few decades. Numerous synthetic anion receptors, which function by complementary electrostatic, hydrogen bonding, Lewis acid–base, and anion–π noncovalent interactions, have been reported to date.[15–18] However, the recognition of anions in solution by halogen bonding is only just beginning to be realized.[19–20] Inspired by nature's sophisticated highly selective sulfate- and phosphate-binding proteins, we have used anion templation to construct elaborate interlocked host molecules. These unique three-dimensional topological cavities are designed to emulate nature's oxoanion binding site protein network of hydrogen bonds. Halogen bonds are considered to be of comparable strength to hydrogen bonds but have a more strictly linear geometry[21] and different steric requirements. These properties make halogen bonds an attractive supramolecular interaction to integrate into and, importantly, potentially tune the selectivity of interlocked binding pockets.

In a significant step towards incorporating halogen bonds into interlocked host systems, we report herein the first example of halogen bonding being exploited to facilitate interpenetrative assembly by anion-templated pseudorotaxane formation. A halogen-functionalized imidazolium threading component is shown to interpenetrate an isophthalamide macrocycle by chloride ion templation. Furthermore we demonstrate that the stability of the interpenetrated assembly is enhanced for the halogen-bonded pseudorotaxane as compared to hydrogen-bonded pseudorotaxane analogues. In addition, we also report a new hydrogen-bonding mode for imidazolium pseudorotaxane assemblies.

In order to elucidate the halogen- and hydrogen-bonding effects of anion-templated interpenetrative assemblies, a series of potential threading bromo- and methyl-functionalized imidazolium derivatives were prepared (Scheme 1 and Schemes S1, S2 in the Supporting Information). In particular, varying the substitution pattern of the bromo and methyl groups around the imidazolium motif would help delineate



Scheme 1. Imidazole starting materials and imidazolium salts.

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and establish the halogen bonding contribution to the overall anion-templated pseudorotaxane assembly process.

4,5-Dimethylimidazole (**1b**) was synthesized in a stepwise procedure from 4-methyl-5-imidazolemethanol hydrochloride.[22] Bromination of **1b** and **1c** was achieved by reaction with elemental bromine in the presence of potassium carbonate, to give **1d** and **1e**.[23]

X-ray structural analysis of the bis(benzyl)imidazolium bromide salts **2d** and **2e** confirmed anion coordination by halogen bonding in the solid state (Figure 1). In both **2d** and **2e**, strong interactions are observed between the terminus of the respective C–Br bond and the bromide anion ($R_{\mathrm{Br-Br}}$ = 0.86–0.89.[24] These interactions are essentially linear, with a mean angle of 174°, which is consistent with a halogen-bonded anion coordination system.[25,26] Comparison of these structures with those obtained for **2c** and the bis(hexyl) chloride salt **3b** highlight the increased linearity of the halogen bond, since the hydrogen-bonded systems have a mean angle of 153° at the protic hydrogen atom.

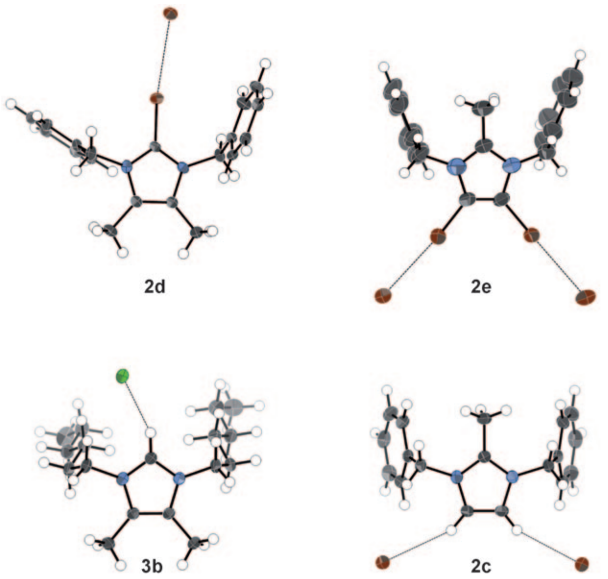


Figure 1. X-ray crystal structures of **2c**, **2d**, **2e**, and **3b**. Thermal ellipsoids set at 50% probability. Br brown, C gray, Cl green, H white, N blue.

We have previously demonstrated that the chloride ion is capable of templating the formation of pseudorotaxanes between isophthalamide macrocycles and pyridinium, imidazolium, guanidinium, and triazolium threading components.[27,28] We therefore chose the chloride ion as a potential template for halogen-bonded interpenetrative assembly investigations.

Solubility problems with the various bis(benzyl)imidazolium derivatives necessitated use of the corresponding bis(hexyl)imidazolium chloride salt analogues **3a**–**3e** in ^{1}H NMR pseudorotaxane titration experiments, which were conducted in $CDCl_3$ with the isophthalamide–hydroquinone macrocycle **4**. Aliquots of imidazolium chloride salts **3a**–**3e**, were added to a solution of **4**. Typically, in the case of **3a**–**3d**, downfield progressions of the amide proton (labeled d) and the interior isophthalamide proton (labeled c) resonances of the macrocycle occurred, which are indicative of anion binding (Figure 2). Upfield movement of the hydroquinone protons (labeled g and h) with concomitant splitting caused by the proximal imidazolium ring current was also observed, and is diagnostic of threading as opposed to solely anion-binding (Figures S7–S12 in the Supporting Information). The addition of chloride ions in the noncoordinating tetrabutylammonium salt to **4** causes a downfield progression of the hydroquinone protons (Figure S14 in the Supporting Information). Pseudorotaxane assembly association constants were calculated from the respective titration data using WinEQNMR[29] (Table 1). There was good agreement between values determined from titration data obtained by monitoring the different protons of the macrocycle (see the Supporting Information), thus indicating strong ion pairing and interpenetration rather than anion binding.[27,30]

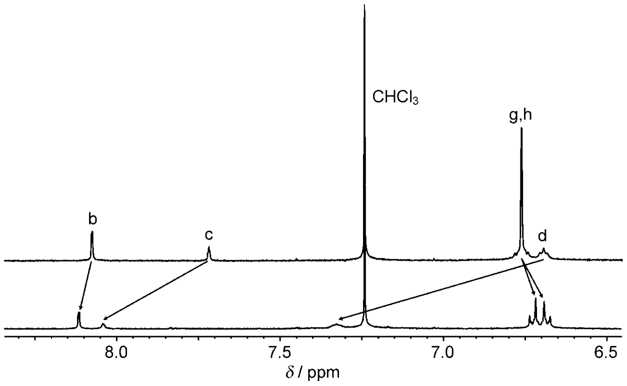
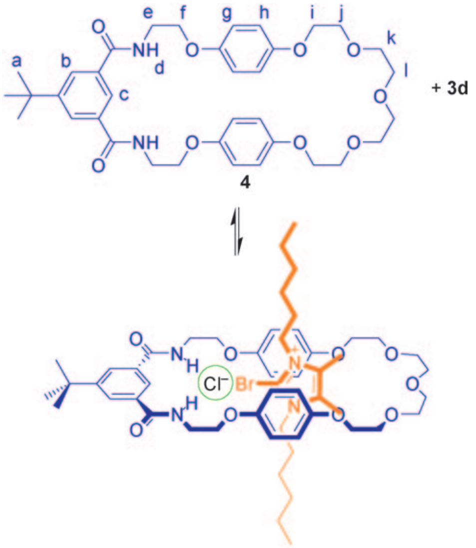


Figure 2. ^{1}H NMR spectra of **4** (top) and **4** with 1.2 equivalents of **3d** (bottom) in $CDCl_3$. Proton assignments are given in Scheme 2.



Scheme 2. Halogen-bond-mediated anion-templated penetration of **3d** through macrocycle **4**.

Table 1: Association constants for **4** and **3a–e**.[a]

Thread	K_a [M^{-1}]
3a (imidazolium)	92 (3)
3b (4,5-dimethyl)	97 (3)
3c (2-methyl)	245 (5)
3d (2-bromo)	254 (6)
3e (4,5-dibromo)	negligible
3d.PF$_6$ (2-bromo)	negligible

[a] Values determined from amide proton titration data in CDCl$_3$ and at 293 K. Errors are given in brackets.

The strongest pseudorotaxane assembly association was observed when halogen bonding was employed with 2-bromo-imidazolium chloride thread **3d** (Scheme 2); remarkably, more than double the value of the hydrogen-bonded equivalent **3b** was obtained (Table 1). The occurrence of a halogen-bonded anion template mechanism rather than improved π–π stacking was confirmed by comparison with the analogous hexafluorophosphate salt **3d**-PF$_6$, which showed no interaction with the macrocycle.

Importantly, the pseudorotaxane formation behavior of the other potential imidazolium chloride threading components serves to further highlight the differences between hydrogen and halogen bonding. The behavior of **3b** was almost identical to that of **3a**, and is consistent with chloride ion hydrogen bonding in unsubstituted imidazolium systems occurring primarily through the acidic 2-position. However, the 2-methyl-imidazolium thread **3c** formed a much more stable pseudorotaxane assembly (Table 1). This result indicates that the comparative directional flexibility of hydrogen bonds allows a cooperative chelating hydrogen-bonding mode to the chloride anion through the 4 and 5 positions, which is beneficial for threading. The change in orientation is further corroborated by a clear diagnostic change in the pattern of hydroquinone shifts during the titration, characteristic of a qualitative difference in the π–π stacking motif (Figure 3 and Figures S9, S10 in the Supporting Information). Different shifting effects were also observed for the imidazolium methyl protons, thus suggesting that improved C–H···O hydrogen bonding to the polyether macrocycle of **4** may also assist the formation of **4·3c** (Figure S15 in the Supporting Information).

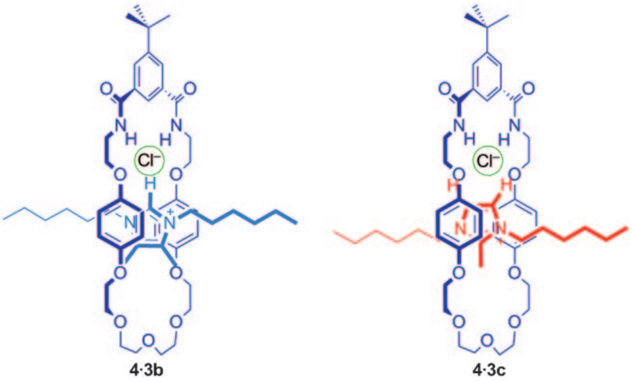


Figure 3. Pseudorotaxanes **4·3b** and **4·3c**.

It is noteworthy that this hydrogen-bonding directional elasticity was not seen with the halogen-bonded analogue **3e**, which displayed no affinity for the macrocycle. The dramatic impact of the requirement of linearity in halogen bonding does not allow for a chelation effect with divergent C–Br bonds; this observation is also consistent with crystallographic and theoretical calculations.[21] Thus the pseudorotaxane assembly is not formed with **3e**.

Further evidence for halogen-bond mediated anion-templated interpenetration to form **4·3d** in the solution phase was obtained by ^{1}H ROESY NMR spectroscopy (Figures S16–S19 in the Supporting Information). This experiment showed that a number of through-space interactions occur between **3d** and the macrocycle, thus confirming both pseudorotaxane formation and orientation of the thread within the macrocycle cavity, which is consistent with the halogen-bonding model.

The anion-templated assembly of pseudorotaxane **4·3d** mediated by halogen bonding was further investigated by means of combined molecular dynamics and density functional theory calculations (see the Supporting Information for full details). The DFT-optimized structure of **3d** (Figure S20 in the Supporting Information) shows a C–Br···Cl$^-$ interaction with an equilibrium distance of 2.62 Å ($R_{\mathrm{Br-Cl}} = 0.73$) and an angle of 179°, which is consistent with the X-ray structures of **2d** and **2e** and the expected directional linearity of the halogen bond.[21] Furthermore, the C–Br distance in **3d** is slightly longer (1.99 Å) than that found in the imidazolium thread without the chloride ion (**3d***; 1.86 Å). The nature of this type of halogen bonding was elucidated by Clark et al.,[31] who introduced the term "σ-hole" to describe the positive surface region of the halogen atom capable of establishing interactions with electron-rich sites. This concept is precisely illustrated with the calculated molecular electrostatic potential surfaces of **3d** and **3d*** (Figure 4). In **3d** the chloride ion is clearly negative (Figure 4a; shown in red), the intermolecular region is shown in yellow and the Br atom is slightly positive (Figure 4b; shown in green). However, in the "chloride-free" imidazolium derivative **3d***, the negative charge density is more concentrated on the two hexyl alkane tails and the bromine atom is slightly positive, with a more positive area at the tip (colored blue). This positive charge enables the interaction with the chloride ion.

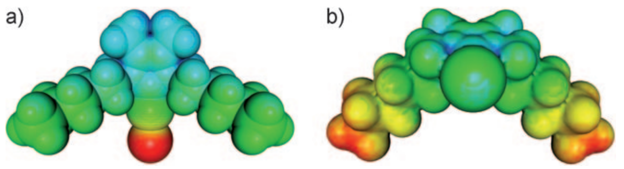


Figure 4. Molecular electrostatic potential surfaces for a) **3d** and b) **3d*** (right). The color ranges are from red (more negative sites) < yellow < green < blue (more positive sites), scales normalized.

Having established that there is a stable C–Br···Cl$^-$ halogen bond in **3d**, we then focused on the study of the anion-templated interpenetrated structure **4·3d**. As this pseudorotaxane has a large conformational freedom, we performed a conformational analysis with quenched molecular dynamics, which uses a combined molecular dynamics/molecular mechanics (MD/MM) approach. The lowest energy coconformation obtained by MD/MM (**4·3d-A**) was then DFT-optimized (Figure 5). The $C{-}Br\cdots Cl^-$ halogen-bond interaction is present with a distance of 2.92 Å ($R_{Br-Cl} = 0.81$) and a bond angle of 174.8°. As observed for other related pseudorotaxane systems,[27] the imidazolium derivative also partakes in charge-assisted π-stacking interactions with the hydroquinone units of macrocycle **4**. The chloride anion establishes hydrogen bonds with the amide protons of the isophthalamide with $H\cdots Cl^-$ distances 2.50 Å and 2.49 Å.

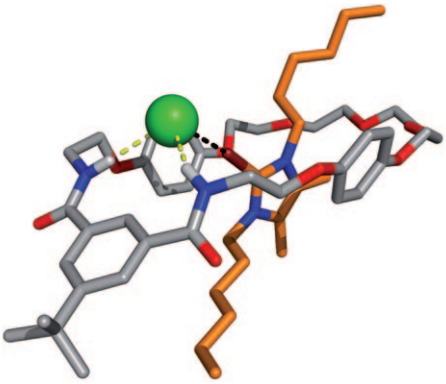


Figure 5. DFT-optimized structure of **4·3d** (co-conformation **4·3d-A**) showing the linear $C{-}Br\cdots Cl^-$ halogen bond (black dashed line) and the $N{-}H\cdots Cl^-$ hydrogen bonds (yellow dashed lines). Br brown, C gray, N blue, O red. Imidazolium alkyl chains are shown in orange, and the chloride ion is shown as a green sphere.

The strength of the $C{-}Br\cdots Cl^-$ interaction in **3d** and **4·3d-A** was evaluated through a natural bond order (NBO) population analysis carried out for these two molecules and **3d*** (Table S1 in the Supporting Information).[32] These studies demonstrate that the magnitude of the "σ-hole" in **3d***, **3d**, and **4·3d** is greater than that in CF_3Br. The natural charges calculated for these compounds (Table S1 in the Supporting Information) follow the same trend. Wiberg bond indices (WI)[33] were also calculated (Table S2 in the Supporting Information). The C−Br distance in **3d** is longer and the respective WI is smaller than in **3d***, thus implying that this bond is weakened by the $C{-}Br\cdots Cl^-$ interaction whose WI is rather large (0.3401), almost half of the respective C−Br value (0.8477). Although halogen bonds are normally considered to be noncovalent interactions, the relatively large WI indicates that the $C{-}Br\cdots Cl^-$ interaction is strong, with relevant covalent character. The covalent contribution for strong halogen bonds was previously identified, based on ab initio and quantum theory of atoms in molecules (QTAIM) analysis, by Zou and co-workers.[34] On forming the pseudorotaxane **4·3d-A**, the C−Br bond becomes stronger (WI = 1.0248), whereas the $C{-}Br\cdots Cl^-$ halogen bonding is weakened (WI = 0.1335) because of the new $N{-}H\cdots Cl^-$ interaction. Nonetheless, the $C{-}Br\cdots Cl^-$ interaction is still strong enough to maintain the pseudorotaxane arrangement, which is consistent with the experimental data. In summary, all calculations support the formation of the pseudorotaxane **4·3d** assembly assisted by a combination of $C{-}Br\cdots Cl^-$ and $N{-}H\cdots Cl^-$ bonds with charge-assisted π-stacking interactions.

In conclusion, halogen bonding has been exploited for the first time in the assembly of an interpenetrated molecular system. Halogen bonding has been demonstrated to effect and enhance the strength of chloride ion templated pseudorotaxane formation between a 2-bromo-functionalized imidazolium threading component and an isophthalamide macrocycle, as compared to hydrogen-bonded pseudorotaxane analogues. In addition, whereas a cooperative 4,5-imidazolium hydrogen-bonding chloride ion chelation effect facilitates the formation of pseudorotaxane **4·3c**, the strongly linear nature of halogen bonding negates such a cooperative effect taking place with 4,5-dibromoimidazolium chloride derivative **3e**, and, as a consequence, interpenetration does not occur. Work toward the construction of interlocked halogen-bonded host systems for anion recognition applications is currently underway.

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Keywords: anions · halogen bonding · pseudorotaxanes · supramolecular chemistry · template synthesis

[1] P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Terraneo, *Angew. Chem.* **2008**, *120*, 6206; *Angew. Chem. Int. Ed.* **2008**, *47*, 6114.

[2] P. Metrangolo, G. Resnati, *Science* **2008**, *321*, 918.

[3] C. B. Aakeröy, M. Fasulo, N. Schultheiss, J. Desper, C. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 13772.

[4] K. Rissanen, *CrystEngComm* **2008**, *10*, 1107.

[5] M. Fourmigué, P. Batail, *Chem. Rev.* **2004**, *104*, 5379.

[6] R. Liantonio, P. Metrangolo, F. Meyer, T. Pilati, W. Navarrini, G. Resnati, *Chem. Commun.* **2006**, 1819.

[7] R. H. Graeme, J. Paul, M. John, R. Llew, S. M. Aaron, *Chem. Eur. J.* **2009**, *15*, 4156.

[8] C. Präsang, H. L. Nguyen, P. N. Horton, A. C. Whitwood, D. W. Bruce, *Chem. Commun.* **2008**, 6164.

[9] D. W. Bruce in *Halogen Bonding: Fundamentals and Applications*, *Vol. 126* (Eds.: P. Metrangolo, G. Resnati), Springer, Berlin, **2008**, p. 161.

[10] M. Fourmigue in *Halogen Bonding: Fundamentals and Applications*, *Vol. 126* (Eds.: P. Metrangolo, G. Resnati), Springer, Berlin, **2008**, p. 181.

[11] S. Derossi, L. Brammer, C. A. Hunter, M. D. Ward, *Inorg. Chem.* **2009**, *48*, 1666.

[12] B. José Fernández, R. Mario, *Org. Magn. Reson.* **1979**, *12*, 92.

[13] M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras, M. S. Taylor, *J. Am. Chem. Soc.* **2010**, *132*, 1646.

[14] S. Libri, N. A. Jasim, R. N. Perutz, L. Brammer, *J. Am. Chem. Soc.* **2008**, *130*, 7842.

[15] C. R. Bondy, S. J. Loeb, *Coord. Chem. Rev.* **2003**, *240*, 77.

[16] C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520.

[17] O. B. Berryman, D. W. Johnson, *Chem. Commun.* **2009**, 3143.

[18] J. L. Sessler, P. A. Gale, W.-S. Cho, *Anion Receptor Chemistry*, Royal Society of Chemistry, Cambridge, **2006**.

[19] A. Mele, P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *J. Am. Chem. Soc.* **2005**, *127*, 14972.

[20] M. G. Sarwar, B. Dragisic, S. Sagoo, M. S. Taylor, *Angew. Chem.* **2010**, *122*, 1718; *Angew. Chem. Int. Ed.* **2010**, *49*, 1674.

[21] A. C. Legon in *Halogen Bonding: Fundamentals and Applications*, *Vol. 126* (Eds.: P. Metrangolo, G. Resnati), Springer, Berlin, **2008**, pp. 17.

[22] A. D'Sa, L. A. Cohen, *J. Heterocycl. Chem.* **1991**, *28*, 1819.

[23] M. Bahnous, C. Mouats, Y. Fort, P. C. Gros, *Tetrahedron Lett.* **2006**, *47*, 1949.

[24] Normalized distances $R_{XY} = d(XY)/(r_X + r_Y)$ where r_X and r_Y refer to van der Waals radii.

[25] T. Mukai, K. Nishikawa, *Chem. Lett.* **2009**, *38*, 402.

[26] N. Kuhn, A. Abu-Rayyan, K. Eichele, S. Schwarz, M. Steimann, *Inorg. Chim. Acta* **2004**, *357*, 1799.

[27] M. R. Sambrook, P. D. Beer, J. A. Wisner, R. L. Paul, A. R. Cowley, F. Szemes, M. G. B. Drew, *J. Am. Chem. Soc.* **2005**, *127*, 2292.

[28] K. M. Mullen, J. Mercurio, C. J. Serpell, P. D. Beer, *Angew. Chem.* **2009**, *121*, 4875; *Angew. Chem. Int. Ed.* **2009**, *48*, 4781.

[29] M. J. Hynes, *J. Chem. Soc. Dalton Trans.* **1993**, 311.

[30] The smallest error was correlated to the greatest change in chemical shift, and so the values derived from the amide protons (Table 1) are regarded as the most accurate.

[31] T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291.

[32] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899.

[33] K. B. Wiberg, *Tetrahedron* **1968**, *24*, 1083.

[34] Y.-X. Lu, J.-W. Zou, Y.-H. Wang, Y.-J. Jiang, Q.-S. Yu, *J. Phys. Chem. A* **2007**, *111*, 10781.