ORGANIC LETTERS

2010
Vol. 12, No. 19
4228−4231

C_3-Symmetric Cage-like Receptors: Chiral Discrimination of α-Chiral Amines in a Confined Space

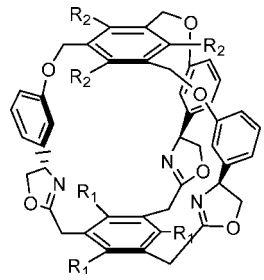
Sunderraman Sambasivan,[†] Sung-Gon Kim,*[,‡] Sun Mi Choi,[†] Young Min Rhee,[†] and Kyo Han Ahn*[,†]

Department of Chemistry and Center for Electro-Photo Behaviours in Advanced Molecular Systems, POSTECH, San 31, Hyoja-Dong, Pohang 790-784, Republic of Korea, and Department of Chemistry, College of Natural Science, Kyonggi University, San 96-4, Iui-Dong, Yeongtong-gu, Suwon 443-760, Republic of Korea

ahn@postech.ac.kr; sgkim123@kgu.ac.kr

Received July 7, 2010

ABSTRACT



(*S,S,S*)-**2a**: $R_1 = R_2 = Me$
(*S,S,S*)-**2b**: $R_1 = R_2 = Et$

Cage-like receptors that have internal binding sites and a C_3-symmetric chiral bias have been synthesized, and their chiral discrimination behavior toward α-chiral amines as their ammonium salts has been compared with that of their open structures.

Cage-like molecules[1] are attractive receptors in the context of supramolecular chemistry, as they exhibit structurally confined cavities that can accommodate guest molecules through molecular interactions. Size- and shape-dependent[2] selectivity can be realized by structurally defined cage receptors. Additionally, cage-like molecules can have a chiral bias by introduction of point chirality.[3,8] This unsurpassable combination of size, shape, and chiral selectivity makes the design and synthesis of cage-like receptors for molecular recognition a matter of enduring interest.[4] Despite such fascinating features, a limited number of chiral cage-like receptors are known because sometimes they require formidable synthetic efforts. Furthermore, a structurally simple cage receptor that provides internal binding sites with a chiral bias remains as a challenging object. Herein, we wish to report a novel type of cage-like molecules with these features.

The tripodal oxazoline receptors **1** developed by us provide unique C_3-symmetric chiral environments toward α-chiral

[†] Pohang University of Science and Technology (POSTECH).
[‡] Kyonggi University.

(1) (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; The Royal Society of Chemistry: Cambridge, U.K., 1994. (b) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, 1995. (c) Anderson, S.; Anderson, H. L.; Sanders, J. K. *Acc. Chem. Res.* **1993**, *26*, 469. (d) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (e) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931. (f) Jeppensen, J. O.; Nielsen, M. B.; Beecher, J. *Chem. Rev.* **2004**, *104*, 5115.

(2) (a) Ebmeyer, F.; Vögtle, F. *Angew. Chem., Int. Ed.* **1989**, *28*, 79. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018.

(3) (a) Pieters, R. J.; Diedrich, F. *Chem. Commun.* **1996**, 2255. (b) Pieters, R. J.; Cuntze, J.; Bonnet, M.; Diedrich, F. *J. Chem. Soc., Chem. Commun.* **1997**, 1891.

(4) (a) Heinz, T.; Rudkevich, D. M.; Rebek, J. *Nature* **1998**, *394*, 764. (b) Tashiro, S.; Tominaga, M.; Kanawo, M.; Therrien, B.; Ozki, T.; Fujita, M. *J. Am. Chem. Soc.* **2005**, *127*, 4546. (c) Kerchoffs, J. M. C. A.; Van Leeuwen, F. W. B.; Spek, A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717. (d) Kurata, H.; Haruki, K.; Oda, M. *Chem. Lett.* **2005**, *34*, 484. (e) Morales-Sanfrutos, J.; Ortega-Muñoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7772.

10.1021/ol1015527
Published on Web 09/02/2010

organoammonium ions.[5] Receptor **1a** (R = Me) provides a "screw-sense" chiral environment toward the α-substituents of α-chiral organoammonium ions (Figure 1). We have

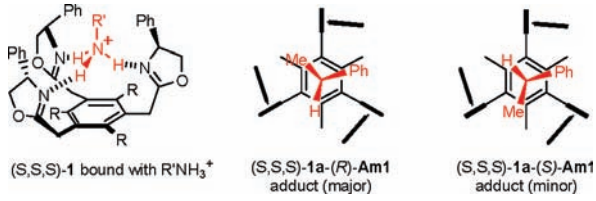


Figure 1. Benzene-based tripodal oxazoline receptors (*S*,*S*,*S*)-**1** complexed with an organoammonium ion and schematic diagrams of top views for the diastereomeric complexes (*S*,*S*,*S*)-**1a**−(*R*)-**Am1** and (*S*,*S*,*S*)-**1a**−(*S*)-**Am1** (**1a**: R = Me; R′NH_3^+ = $PhCH(Me)NH_3^+$ (**Am1**)).

demonstrated that a high level of chiral discrimination of some α-chiral organoammonium ions (∼7:3) can be realized in the C_3-symmetric environment contrary to previous perception.[5a,6] Such a high level of chiral discrimination, however, can be obtained only in the case of α-chiral organoammonium ions that have α-aryl substituents if there is no additional secondary H-bonding interaction.[5b] An emerging question is how such chiral discrimination behavior would change if we confine the recognition motifs as in the cage-like receptors.[7] Compounds **2a** and **2b** seem to be ideal chiral cage-like receptors, as they are structurally simple owing to their symmetry and, more importantly, could provide internal binding sites with screw-sense chirality toward α-chiral organoammonium ions (Figure 2).

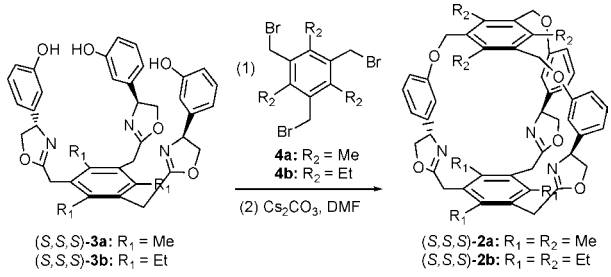


Figure 2. Synthesis of cage-like receptors (*S*,*S*,*S*)-**2a** and (*S*,*S*,*S*)-**2b**.

Receptors **2** should provide more confined chiral environments compared with receptors **1** and thus would exert increased steric interactions toward α-substitutents of the organoammonium ions. Chiral discrimination in such a confined space may be different from that in the "open" environment provided by receptors **1.**

Cage compounds **2a** and **2b** (Figure 2) can be efficiently synthesized in 26% and 29% yields, respectively, from the corresponding 3-hydroxyphenyl-substituted tripodal oxazolines **3**,[8] through a direct coupling with capping molecules **4** under high dilution conditions (Supporting Information). Preorganization of the oxazoline groups seems to be responsible for the good yields in the "double" macrocyclization step.

The ^{1}H NMR spectrum of receptor **2a** obtained at 25 °C shows its C_3-symmetric nature. The protons are readily identified at different resonance frequencies. Whereas the ^{1}H NMR spectrum of receptors **2b** shows a more split pattern owing to the restricted rotation of the ethyl groups. For example, both the benzylic protons of the bottom phenyl ring (H_a, δ 3.7 ppm; H_b, δ 3.0 and 2.7 ppm) in receptor **2b** are split into a AB fashion, respectively (Supporting Information).

The chiral discrimination ability of receptors **2** has been examined toward two typical amines, α-aryl- and α-alkyl-substituted amines: α-phenylethylammonium (**Am1**) and alanine methyl ester (**Am2**). The *R*-, *S*-, or *racemic*-guest as its perchlorate salt (2.0 equiv) was added to a solution of either receptor **2a** or **2b** in $CDCl_3/CD_3CN$ (3:1) and then was analyzed by ^{1}H NMR at various temperatures. The diagnostic peaks are those of the guest methyl groups, which are highly shielded by the receptor and thus resonate upfield relative to those of the unbound guest (Supporting Information). The diagnostic peaks of the inclusion complexes are well resolved at lower temperature, and thus the ratio of their areas directly gives the enantioselectivity of the receptor. The results of chiral discrimination experiments are summarized in Table 1. The ratio of the bound and unbound guest in the presence of an equimolar amount of the receptor is deter-

Table 1. Enantioselective Binding of Receptors **1a**, **2a**, and **2b** toward Organoammonium Ions **Am1** and **Am2**[a]

receptor−guest	temp (°C)	enantioselectivity	binding (%)[b]
1a−(*R*,*S*)-**Am1**	25	71(*R*):29(*S*)[c]	82
2a−(*R*,*S*)-**Am1**	−30	57(*R*):43(*S*)	∼100
	−50	60(*R*):40(*S*)	∼100
2b−(*R*,*S*)-**Am1**	−30		
	−50	61(*R*):39(*S*)	73
1a−(*R*,*S*)-**Am2**	25	47(*R*):53(*S*)[c]	41
2a−(*R*,*S*)-**Am2**	10	61(*R*):39(*S*)	62
	−10	60(*R*):40(*S*)	65
	−30	61(*R*):39(*S*)	67
	−50	64(*R*):36(*S*)	68
2b−(*R*,*S*)-**Am2**	−10	64(*R*):36(*S*)	79
	−30	66(*R*):34(*S*)	83
	−50	72(*R*):28(*S*)	76

[a] **Am1** and **Am2** represent α-phenylethylamine and alanine methyl ester, respectively, which were used as their perchlorate salts. [b] Percentage of receptor−guest adduct with respect to unbound guest, calculated for 1 equiv of receptor. [c] Taken from ref 5a.

(5) (a) Kim, S.-G.; Kim, K.-H.; Jung, J.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2002**, *124*, 591. (b) Kim, S.-G.; Kim, K.-H.; Kim, Y. K.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2003**, *125*, 13819. (c) Kim, S.-G.; Sambasivan, S.; Ahn, K. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 724.

(6) (a) Moberg, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4721. (b) Gibson, S.; Castaldi, M. P. *Chem. Commun.* **2006**, 3045. (c) Hembury, G. A.; Borovkov, V. V.; Inoue, Y. *Chem. Rev.* **2008**, *108*, 1.

(7) For a metal-coordinated cage molecule based on the tripodal oxazoline system, see: Kim, J.; Ryu, D.; Sei, Y.; Yamaguchi, K.; Ahn, K. H. *Chem. Commun.* **2006**, 1136.

(8) Kim, J.; Raman, B.; Ahn, K. H. *J. Org. Chem.* **2006**, *71*, 38.

mined from the relative area of the corresponding diagnostic peaks and gives the percent binding value.

Receptors **2** preferentially bind to the (*R*)-**Am1**, albeit in a lower enantioselectivity compared to the open receptors **1**.[5a] Whereas receptors **2** discriminate the enantiomers of alanine methyl ester with a high enantioselectivity (7:3), the chiral discrimination is not effective with receptors **1**. The sense of chiral discrimination with the cage-like receptors is the same as that observed with the open receptors.

The binding mode of cage compound **2a** toward the (*R*)-α-phenylethylammonium ion was studied by single crystal X-ray diffraction. The X-ray structure[9] of the major adduct **2a**−(*R*)-**Am1** was resolved, which clearly shows that **2a** binds to the ammonium ion through tripodal hydrogen bonds (Figure 3). The N_R-N_G distances (subscript R and G denote

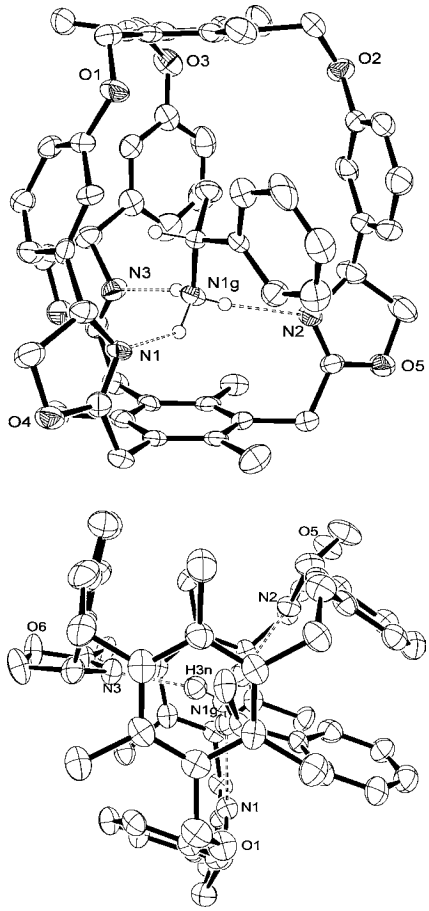


Figure 3. ORTEP representation (side and a top views) of the X-ray crystal structure of the inclusion complex **2a**−(*R*)-PhCH(Me)-$NH_3^+ClO_4^-$. Hydrogen atoms, except for the three NH_3^+ and the chiral hydrogen of the guest, the counter perchlorate anion, and solvent dichloromethane have been removed for clarity.

those of the receptor and guest) range from 2.94 to 3.07 Å, which are close to the average H-bonded N−H···N distance, 2.98 ± 0.16 Å.[10] Values of the $N_R-N_G-N_R$ angles are 105°, 110°, and 133°. The perchlorate counteranion resides outside the inclusion complex with no apparent interaction. A side view of the crystal structure (Figure 3) shows that the three side wall phenyl rings are in a propeller-shaped arrangement, providing a screw-sense chirality. From a top view of the crystal structure, we can recognize that the bottom and top capping phenyl rings are slightly twisted (−11.54°) as the linkages between them, the phenyloxazoline moieties, are curved into the same direction. This helical twist seems to contribute to the chiral discrimination also. Helical chirality in macrobicyclic receptors is known, both in solid[11] and solution phases.[12] Although the phenyl ring of the guest and the side phenyl ring of cage **2a** do not appear to have perfect parallel stacking, the interplanar distances between the benzene carbons are in the range 3.5−4.4 Å, suggesting existence of $\pi-\pi$ interactions[13] between them (Figure 3). However, there is a significant distortion in the bond angle between the phenyl and methyl groups of the guest (114.3°) in the crystal structure, as compared with the major inclusion complex of receptor **1a** (109.4°) (Table 2). This angle distortion suggests that the (*R*)-guest experiences larger steric strain in the cage **2a** than in the open receptor **1a**, which is likely due to a space restriction in the former case. The side wall phenyl rings in **2a**−(*R*)-**Am1** are more contracted compared with those in the open complex **1a**−(*R*)-**Am1**, judging from the shortened distances from the center of bottom phenyl to the center of side wall phenyl groups (6.386−7.242 Å in the cage; 6.528−7.351 Å in the open receptor). Therefore, the guest molecules in the confined space provided by cages **2** experience more steric strain between the α-substituents and the surrounding phenyl walls. The increased steric strain seems to govern the guest selectivity. As a result, the enantioselective recognition of the alanine methyl ester is enabled with the cages, whereas it is a poor guest in the case of the open receptors.

Because we were not able to obtain single crystals from **2a**−(*S*)-**Am1**, we analyzed the molecular structures of both diastereomeric inclusion complexes by quantum chemical calculations. The energy minimized structures of the inclusion complexes obtained at the M06-2X/6-31G(d) level[14] are presented in the Supporting Information. The calculated bond angles of free and bound **Am1** are also listed in the Table 2.

(9) Crystal data for **2a**−(*R*)-PhCH(Me)$NH_3^+ClO_4^-$·3CH_2Cl_2: $C_{62}H_{69}Cl_7N_4O_{10}$, M = 1278.36, triclinic, a = 11.6905(3) Å, b = 12.7459(2) Å, c = 13.0439(2) Å, α = 112.7720(10)°, β = 99.5310(10)°, γ = 113.4180(10)°, V = 1522.81(5) Å^3, T = 223(2) K, space group $P1$, Z = 1, 6349 reflections measured, 5416 independent reflections (R_{int} = 0.0212). The final R_1 values were 0.0734 ($I > 2\sigma(I)$). The final $wR(F2)$ values were 0.1984 ($I > 2\sigma(I)$). The final R_1 values were 0.0795 (all data). The final $wR(F2)$ values were 0.2080 (all data). CCDC 777455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033.

(10) Kuleshova, L. N.; Zorkii, P. M. *Acta Crystallogr., Sect. B: Struct. Sci.* **1981**, *37*, 1363.

(11) (a) Vögtle, F.; Wallon, A.; Müller, W. M.; Werner, U.; Nieger, M. *J. Chem. Soc., Chem. Commun.* **1990**, 158. (b) MacGillivray, L. R.; Atwood, J. L. *J. Org. Chem.* **1995**, *60*, 4972.

(12) (a) Vögtle, F.; Hohner, G. *Angew Chem., Int. Ed.* **1975**, *14*, 497. (b) Nakazaki, M.; Yamamoto, K.; Toya, T. *J. Org. Chem.* **1981**, *46*, 1611. (c) Alajarín, M.; López-Leonardo, C.; Vidal, A.; Berná, J.; Steed, J. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 1205.

(13) Dahl, T. *Acta Chem. Scand.* **1994**, *48*, 95.

Table 2. Selected Bond Angles (deg) of (*R*)- and (*S*)-**Am1** Bound to Receptors **1a** and **2a**

crystal structure		
2a−(*R*)-**Am1**	**1a**−(*R*)-**Am1**[b]	**1a**−(*S*)-**Am1**[b]
N−C−C_{Me} 109.7(7)	N−C−C_{Me} 109.5(7)	N−C−C_{Me} 108.5(4)
N−C−C_{Ph} 111.4(6)	N−C−C_{Ph} 111.7(6)	N−C−C_{Ph} 110.5(4)
C_{Me}−C−C_{Ph} 114.3(6)	C_{Me}−C−C_{Ph} 109.4(7)	C_{Me}−C−C_{Ph} 114.1(4)
calculated values[c]		
2a−(*R*)-**Am1**		**2a**−(*S*)-**Am1**
N−C−C_{Me} 109.24		N−C−C_{Me} 111.56
N−C−C_{Ph} 110.13		N−C−C_{Ph} 108.57
C_{Me}−C−C_{Ph}115.74		C_{Me}−C−C_{Ph}115.07
Am1		**Am1**[d] (crystal structures)
N−C−C_{Me} 107.87−108.2		N−C−C_{Me} 107.7−109.6
N−C−C_{Ph} 106.64−107.11		N−C−C_{Ph} 110.1−112.3
C_{Me}−C−C_{Ph} 116.03−117.21		C_{Me}−C−C_{Ph}111.5−114.4

[a] C_{Me} and C_{Ph} correspond to the carbons of Me and Ph groups in **Am1** ($PhCH(Me)NH_3^+$). [b] Taken from ref 5a. [c] Data from the M06-2X/6-31G(d) calculation using Q-Chem ver 3.2. [d] Taken from crystal structure data of the sulfate and phosphate salts (ref 15).

As we analyzed previously, the less stable complex **1a**−(*S*)-**Am1** manifests an unusual bond angle distortion for the C_{Me}−C−C_{Ph} angle (114.1°).[5a] Both the crystal structure and the calculated one show that there is significant distortion in the bond angle even in the case of the major inclusion complex **2a**−(*R*)-**Am1** (114.3° from the crystal, 115.74° from the calculated structure). The calculation suggests that the minor complex **2a**−(*S*)-**Am1** has a larger bond angle distortion for the C_{Me}−C−C_{Ph} angle (115.07°).

A further analysis of the calculated structures suggests another important structural difference between the inclusion complexes **1a**−**Am1** and **2a**−**Am1**. Because of the steric constraint in the cage, the guest molecule is forced to dislocate from the center of the cavity: the N_G−C bond is tilted from 90° with respect to the bottom receptor phenyl plane. (The angle is expected to be 90° if there is no steric bias between the receptor and guest.) The angle between the phenyl plane and the N_G−C bond is 64.87° in the less stable **2a**−(*S*)-**Am1**, whereas it is 74.95° in the more stable **2a**−(*R*)-**Am1**; the angle is larger in the less strained, open inclusion complexes (70.89° for **1a**−(*S*)-**Am1**, 82.99° for **1a**−(*R*)-**Am1**). These results support that the guest molecule experiences increased steric strain in the cage receptors.

In the calculated structures of **2a**−(*R*)-**Am2** and **2a**−(*S*)-**Am2**, the inclusion complexes of (*R*)- and (*S*)-alanine methyl esters, the ester group behaves as the most sterically demanding group and takes the position of the phenyl group of **Am1** in the inclusion complexes. Structure analysis also gave a similar trend in the bond angle distortion between the major and minor complexes [C_{Me}−C−C_{CO} = 115.40° (major) vs 117.46° (minor)].

We determined the binding affinity of receptor **2a** toward each enantiomeric (*R*)- and (*S*)-**Am1** as their perchlorate salts by ^{1}H NMR titrations. The binding affinities are K_a = 6170 and 2920 M^{-1} for (*R*)-**Am1** and (*S*)-**Am1**, respectively, at 25 °C. At a higher temperature of 50 °C the binding affinities are K_a = 1220 and 850 M^{-1}, respectively. These affinities confirm the higher selectivity of receptor **2a** toward the (*R*)-enantiomer of the guest.

In summary, we have synthesized cage-like chiral receptors based on tripodal oxazolines, which provide internal binding sites for organoammonium ions and a screw-sense chirality toward their α-substituents. The cages show a distinctive chiral discrimination behavior from the corresponding open receptors owing to the confined space available for the guest. Expansion of the inner space of the cage molecules to accommodate other guest molecules is under investigation.

Supporting Information Available: Synthetic route and characterization of receptors **2a** and **2b** and ^{1}H NMR binding studies of receptors **2a** and **2b** with perchlorate salts of α-phenylethylamine and alanine methyl ester. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1015527

(14) Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Voorhis, T. Y.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C.-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172.

(15) Cihelka, J.; Havlíček, D.; Gyepes, R.; Němec, I.; Koleva, Z. *J. Mol. Struct.* **2010**, *980*, 31.