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ORIGINAL PAPER

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Structures of inclusion complexes of halogenbenzoic acids and α-cyclodextrin based on AM1 calculations

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Abstract Semi-empirical quantum mechanics calculations using AM1 (Austin Method 1) were carried out for various host-guest combinations of α-cyclodextrin and mono-halogen benzoic acids. The energetically favorable inclusion structures were identified. The AM1 results show that α-cyclodextrin complexes with mono-halogen benzoic acid acids (where the halogen is chlorine, bromide, iodine) as guest compounds are more stable in the "head first" position than in the "tail-first" position for *meta* and *para* isomers while *ortho* mono-halogen benzoic acids complexes with α-cyclodextrin are more stable in "tail-first" position. The calculated structures were found to be in good agreement with those obtained from crystalographic databases.

Keywords Molecular modeling · AM1 · Cyclodextrins · Benzoic acids

Introduction

Natural cyclodextrins (α-, β-, and γ-CD) comprise a family of macrocyclic oligosaccharides formed by α-1,4-linked glucopyranose subunits, and shaped as truncated cones [1, 2]. The CD molecules have a hydrophobic cavity and a hydrophilic exterior [3, 4]. The presence of the lipophilic cavity enables many different types of molecules (organic and inorganic, neutral and ionic) to be incorporated into the cavity, both in the solid state and in solution. Inclusion complex formation between guest solutes and the CD cavity depends on the geometry, size, and physicochemical properties of the solutes. However, the hydrophobic interactions inside the cavity can act together with polar or hydrogen-bonding interactions that occur with hydroxyl groups located on the outer edge of the CD cavity.

Cyclodextrins are often used in separation methods to achieve separation of chiral and achiral compounds [5–10]. The mechanisms underlying the separation in the presence of CD as a selector have not yet been fully clarified and at the moment it is not possible to predict the success of achiral or chiral separation using CDs on the basis of the chemical structure of solute. Molecular modeling represents a very promising tool, which is likely to help us in understanding the CD-solute interaction (see review [11]) during the separation of solutes using cyclodextrin stationary or pseudostationary phases [12–15].

In the last decade, quantum chemical computations have become an established method for the prediction of novel structures and properties and are now being used widely to support experimental work. As such, they could provide a powerful tool for the rational design of supramolecular systems and inclusion phenomena [11]. Computations using semi-empirical methods like AM1 and PM3 are currently fast enough to make studies of supramolecular and inclusion systems feasible [11, 16, 17].

Inclusion of the molecules in the cyclodextrin cavity has been attributed to van der Vaals interactions [18], hydrogen bonding [19], hydrophobic interactions [18, 20], release of ring strain in the cyclodextrin molecule [21], and changes in solvent-surface tension [22]. There are no covalent bonds formed or broken during the complex formation process. Various researchers have applied theoretical methods to the study of inclusion complexes of cyclodextrins, such as molecular mechanics [12, 13], molecular dynamics [23], complete neglect of differential overlap (CNDO) with fixed geometries [24], and semi-empirical AM1 methods [25–27].

The aim of this work is to broaden our knowledge of the interaction mechanism of CDs with small organic mole-

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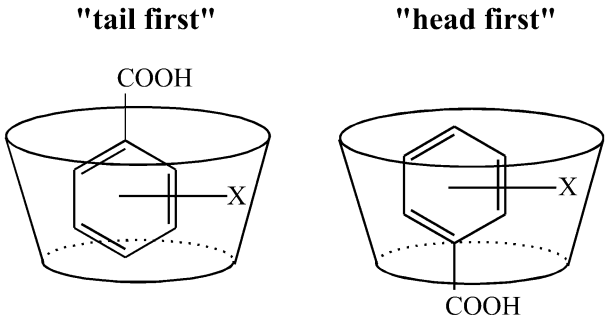

Fig. 1 The two possible penetration pathways for mono-halogenbenzoic acids into α-CD cavity

cules. The interaction energies for α-CD-halogen benzoic acid were calculated for different inclusion-complex orientations using Austin Method 1 (AM1) and are compared to the structures obtained from the crystallographic database.

Experimental

The structures of mono-halogenbenzoic acids were constructed using the InsightII 2000 molecular modeling package (MSI Inc., San Diego, CA, USA). Coordinates of α-cyclodextrin were obtained from the Cambridge crystalographic database (CSD) [28, 29].

AM1 semi-empirical quantum mechanics calculations [30] of the inclusion complexes were performed using Gaussian 98 program [31]. The following initial steric conditions were applied for docking of mono-halogenbenzoic acids into the cyclodextrin cavity.

The glycosidic oxygen atoms of the cyclodextrin molecule were placed onto the XY plane and their center was defined as the center of the coordination system. The secondary hydroxyl groups of the CD were placed pointing toward the positive Z axis. The carboxyl group of the guest molecule was initially placed along the Z axis [32]. Two possible orientations of the guest molecule in complex were considered. For simplicity, the orientation in which the carboxyl group points toward oxygen atom in primary 6-hydroxyl group of CD was called the "head-first" orientation, the other, in which the carboxyl group points toward the oxygen in secondary 2- or 3-hydroxyl group of CD was called the "tail-first" orientation, see Fig. 1.

Optimization of the structure of the inclusion complex and calculation of the interaction energy (ΔE_{int}) of the system was performed according to Reference [13]:

1. Gradient optimization of the molecular geometry of cyclodextrin and calculation of its energy (E_{CD}).

Table 1 Interaction energies of the complexes of α-cyclodextrin with mono-halogenbenzoic acid

Complex	ΔE_{int}(kJ mol^{-1}) "head first"	ΔE_{int}(kJ mol^{-1}) "tail first"
o-F–BA + α-CD	−125.0	−113.7
m-F–BA + α-CD	−123.3	−105.3
p-F–BA + α-CD	−117.9	−120.8
o-Cl–BA + α-CD	−118.3	−120.0
m-Cl–BA + α-CD	−120.0	−101.2
p-Cl–BA + α-CD	−117.5	−104.1
o-Br–BA + α-CD	−102.8	−120.0
m-Br–BA + α-CD	−117.0	−117.0
p-Br–BA + α-CD	−116.6	−100.7
o-I–BA + α-CD	−102.8	−117.0
m-I–BA + α-CD	−113.3	−110.4
p-I–BA + α-CD	−116.2	−109.1

Table 2 Total number of intramolecular hydrogen bonds between secondary hydroxyles C(2)OH and C(3)OH and between primary hydroxyle C(6)OH and O(5) of glucose unit; intermolecular bonds between the secondary hydroxyl groups of α-cyclodextrin and $-COO^-$ group of quest. Orientation "head-first"

Inclusion complexes	No. of intramolecular hydrogen bonds between C(2)OH and C(3)OH hydroxyl groups of CD	No. of intramolecular hydrogen bonds between C(2)OH and C(3)OH hydroxyl groups of CD	No. of intermolecular hydrogen bonds
α-CD (X-ray) Reference [12]	5	2	–[a]
α-CD (AM1)	5	2	–[a]
o-F–BA + α-CD	5	2	0
m-F–BA + α-CD	6	2	1
p-F–BA + α-CD	6	2	0
o-Cl–BA + α-CD	5	2	1
m-Cl–BA + α-CD	6	2	1
p-Cl–BA + α-CD	5	2	0
o-Br–BA + α-CD	5	2	1
m-Br–BA + α-CD	6	2	1
p-Br–BA + α-CD	5	2	0
o-I–BA + α-CD	5	2	1
m-I–BA + α-CD	6	2	1
p-I–BA + α-CD	6	2	0

[a] not applicable

2. Gradient optimization of the molecular geometry of the guest molecule (mono-halogenbenzoic acid) and calculation of its energy (E_G).
3. Docking of the guest molecule into the cavity of cyclodextrin (*vide supra*), followed by the gradient optimization of the molecular geometry of the whole system and calculation of its energy (E_{CD-G}).

The interaction energy of the guest molecule (mono-halogenbenzoic acid) with CD (ΔE_{int}) was obtained as the difference between the energy of the inclusion complex ($E_{CD\text{-}G}$) and the sum of energies of the guest (E_G) and cyclodextrin (E_{CD}) Eq. (1):

$$\Delta E_{int} = E_{CD-G} - (E_{CD} + E_G) \quad (1)$$

Table 3 Total number of intramolecular hydrogen bonds between secondary hydroxyles C(2)OH and C(3)OH and between primary hydroxyle C(6)OH and O(5) of glucose unit; intermolecular bonds between the secondary hydroxyl groups of α-cyclodextrin and $-COO^-$ group of quest. Orientation "tail-first"

Inclusion complexes	No. of intramolecular hydrogen bonds between C(2)OH and C(3)OH hydroxyl groups of CD	No. of intramolecular hydrogen bonds between C(2)OH and C(3)OH hydroxyl groups of CD	No. of intermolecular hydrogen bonds
α-CD (X-ray) Reference [12]	5	2	–[a]
α-CD (AM1)	5	2	–[a]
o-F–BA + α-CD	4	1	4
m-F–BA + α-CD	4	0	3
p-F–BA + α-CD	4	2	2
o-Cl–BA + α-CD	3	1	4
m-Cl–BA + α-CD	3	2	2
p-Cl–BA + α-CD	4	1	2
o-Br–BA + α-CD	4	1	2
m-Br–BA + α-CD	3	0	3
p-Br–BA + α-CD	2	1	2
o-I–BA + α-CD	3	1	2

[a] not applicable

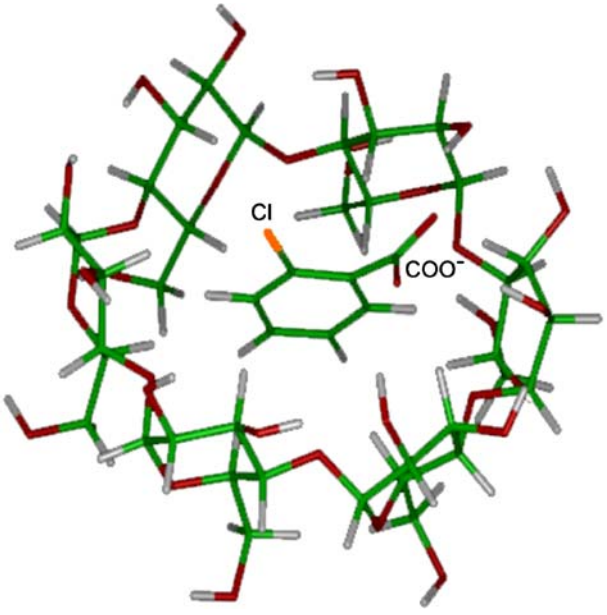

Fig. 2 Optimized inclusion complex of *ortho*-chlor benzoic acid with α-CD

Results and discussion

The AM1 semi-empirical method, used in this study, is still one of the most convenient tools for computing energies of large systems (i.e. inclusion complexes with cyclodextrins) [11, 14, 15, 33]. Systems of similar size are still too large

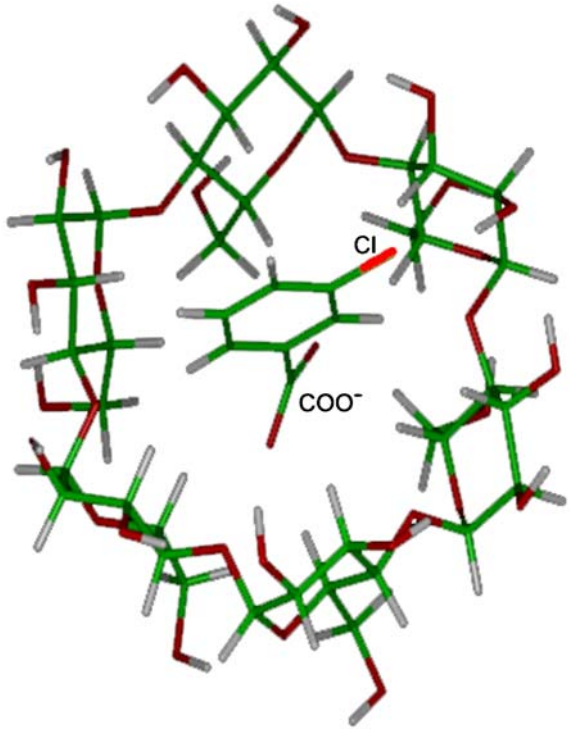

Fig. 3 Optimized inclusion complex of *meta*-chlor benzoic acid with α-CD

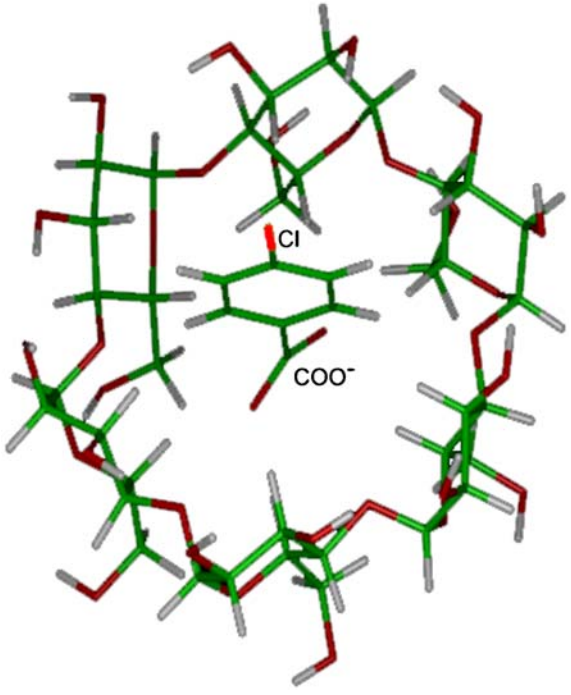

Fig. 4 Optimized inclusion complex of *para*-chlor benzoic acid with α-CD

for accurate ab initio calculations (especially when dealing with a greater number of systems of interest) [11].

Calculated interaction energies of α-cyclodextrin with a set of anions of mono-halogenbenzoic acids in "tail-first" and "head first" orientations are given in Table 1. The negative interaction energies together with the equilibrium geometries of the species studied obtained by the AM1 method demonstrate the ability of α-CD to form stable inclusion complexes with mono-halogenbenzoic acids, although we presume that these numbers would be smaller if solvation effects were included in the calculations. The magnitude of these values, corresponding to the non-bonded supramolecular complexation, is in agreement with other AM1 studies [25, 26]. From Table 1, we can conclude that the "tail-first" orientation is preferred in the case of

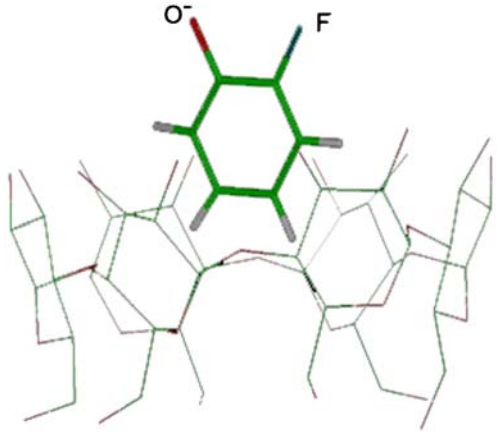

Fig. 5 Complex of *ortho*-fluorophenol with α-CD obtained from CSD

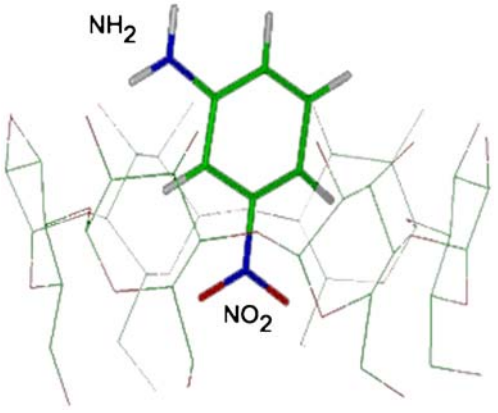

Fig. 6 Complex of *meta*-nitroaniline with α-CD obtained from CSD

ortho halogenbenzoic acids while the "head-first" orientation is preferred in the case of *meta* and *para* halogenbenzoic acids when the halogen is Cl, Br, or I. A notable exception is the case of the inclusion complexes of fluorobenzoic acids. However, this can be explained by the very low polarizibility of fluorine. Our results are consistent with these closely related published previously by Bodor's group [26, 27]. They found that the inclusion complex of α-cyclodextrin with benzoic acid is more stable in the "head-first" position, similarly to *meta*- and *para*-halogenbenzoic acids studied in our case. The different behavior of *ortho*-halogenbenzoic acids (which preferred the "tail-first" position) can be explained by steric effects.

Table 2 enumerates intramolecular and intermolecular hydrogen bonds of α-CD complexes obtained from crystalographic database [34] and by molecular modeling (AM1) in the "head-first" orientation; intramolecular hydrogen bonds are formed between secondary hydroxyls C(2)OH and C(3)OH and between primary hydroxyl C(6) OH and O(5) of the glucose unit; intermolecular bonds intervene between the secondary hydroxyl groups of α-cyclodextrin and the $-COO^-$ group of guest molecule. Table 3 shows the total numbers of hydrogen bonds involved in the "tail-first" orientation. The stabilization energy of each hydrogen bond is approximately 10–15 kJ mol^{-1}.

The graphic representation of the optimized inclusion complex shows the flexibility of the cyclodextrin ring,

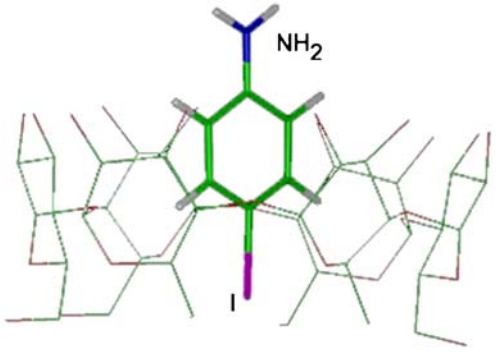

Fig. 7 Complex of *para*-iodaniline with α-CD obtained from CSD

which can change its shape according to the size of the quest molecule. The structure of α-CD–*o*–Cl-BA (energetically preferred orientation "tail-first") is shown in Fig. 2, the structure of α-CD–*m*–Cl-BA (energetically preferred orientation "head-first") is shown in Fig. 3, the structure of α-CD–*p*–Cl-BA (energetically preferred orientation "head-first") is shown in Fig. 4. All structures represent the equilibrium geometries obtained by AM1 calculations.

It would be beneficial to compare the geometries of the calculated inclusion complexes by the AM1 method with those obtained from CSD. Unfortunately, there is no crystallographic structure available directly for α-CD-halogenbenzoic acid inclusion complexes. However, there are available structures of α-CD inclusion complexes with guest molecules structurally similar to halogenbenzoates in the CSD. These inclusion complexes have orientations as predicted by our AM1 modeling. See α-CD–*o*–fluorophenol in Fig. 5 (orientation "tail-first", Reference [35]), α-CD–*m*–nitroaniline in Fig. 6 (orientation "head-first", more polar nitro group is in the "head" position, Reference [36]) and α-CD–*p*–iodaniline in Fig. 7, (orientation "head-first", more polar iodine group is in the "head" position, Reference [37]). For lucidity, the structures obtained from CSD are shown without hydrogen atoms and using a different type depiction. Crystallographic structures obtained from CSD show that the aromatic ring of the guest molecule is not localized exactly in the center of the cavity of CD, which is determined by the plane of the pyrazones. The results obtained by the AM1 method are in agreement with experimental observations.

Conclusion

Semi-empirical quantum chemical calculations (using the AM1 method) were successfully applied to the study of the complexation of α-CD with mono-halogenbenzoic acids and the energetically favorable inclusion structures were identified. The optimized structures of the resulting inclusion complexes were in a reasonable agreement with the structures obtained from the crystallographic database.

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References

1. Szejtli J (1982) Cyclodextrins and their Inclusion complexes. Akademjai Kiado, Budapest
2. Szejtli J (1998) Chem Rev 98:1743–1754
3. Hansen PE, Dettman HD, Sykes BD (1985) J Magn Reson 62:487–496
4. Pumera M, Matalova R, Jelinek I, Jindrich J, Juza J (2001) Molecules 6:221–229
5. Wan H, Blomberg LG (1995) J Chromatogr A 704:179–193
6. Pumera M, Felegel M, Lepša L, Jelínek I (2002) Electrophoresis 23:2449–2456
7. Zbrožek J, Pumera M, Felegel M (2002) J Chrom Sci 40:505–508
8. Pumera M, Jelinek I, Jindrich J (2001) Fresenius J Anal Chem 369:666–669
9. Pumera M, Jelinek I, Jindrich J (2000) J Chromatogr A 891:201–206
10. Pumera M, Jelinek I, Jindrich J, Benada O (2002) J Liq Chrom Relat Technol 25:2473–2484
11. Lipkowitz KB (1998) Chem Rev 98:1829–1874
12. Gilar M, Uhrová M, Tesařová E (1996) J Chromatogr B 681:133–141
13. Tesařová E, Gilar M, Hobza P, Kabeláč M, Deyl Z, Smolková-Keulemansová E (1995) J High Res Chrom 18:597–601
14. Sun M, Liu X, Yan L, Luo G, Zhao Y (2005) J Mol Model 9:419–422
15. Cai W, Yu Y, Shao X (2005) J Mol Model 11:186–193
16. Rauwolf C, Straßner T (1997) J Mol Model 3:1–16
17. Puchta R, Seitz V, van Eikema Hommes NJR, Saalfrank RW (2000) J Mol Model 6:126–132
18. Nishijo J, Nagai M (1991) J Pharm Sci 80:58–62
19. Tong WQ, Lach JL, Chin TF, Guillory JK (1991) Pharm Res 8:951–957
20. Tabushi I, Kiyosuke YO, Sugimoto U, Yamamura K (1978) J Am Chem Soc 100:916–919
21. Jones SP, Grant DJ, Hadgraft W, Parr GD (1984) Acta Pharm Technol 30:213–217
22. Orstan A, Ross JBA (1987) J Phys Chem 91:2735–2745
23. Zubiaur M, De Federico M, Burusco KK, Bea I, Virgili A, Sanchez-Ferrando F, Jaime C (2005) J Inclus Phenom Macrocycl Chem 51:241–247
24. Sakurai M, Kitagawa M, Hoshi H, Inoue Y, Chujo R (1988) Chem Lett 895–898
25. Huang M-J, Watts JD, Bodor N (1997) Int J Quant Chem 64:711–719
26. Huang M-J, Watts JD, Bodor N (1997) Int J Quant Chem 65:1135–1152
27. Bodor N, Huang MJ, Watts JD (1996) J Incl Phenom Mol Recogn Chem 25:97–102
28. Allen FH, Davies JE, Galloy JJ, Johnson O, Kennard O, Macrae CF, Mitchell EM, Mitchell GF, Smith JM, Watson DG (1991) J Chem Inf Comp Sci 31:187–204
29. CSD. Cambridge Crystallographic Data Centre, Cambrigdge, UK
30. Dewar MJS, Zoebish EG, Healy EF, Stewart JJP (1985) J Am Chem Soc 107:3902–3909
31. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (1998) Gaussian 98, Revision A.6., Gaussian Inc, Pittsburgh PA
32. Li XS, Liu L, Guo QX, Chu SD, Liu YC (1999) Chem Phys Lett 307:117–120
33. Nascimento CS, Anconi CPA, Dos Santos HF, De Almeida WB (2005) J Phys Chem A 109:3209–3219
34. Chacko KK, Saenger W (1981) J Am Chem Soc 103:1708–1715
35. Shibakami M, Sekiya A (1992) Chem Commun 1742–1743
36. Harata K (1980) Bull Chem Soc Jpn 53:2782–2786
37. Saenger W, Beyer K, Manor PC (1976) Acta Crystallogr B 32:120–128