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Infrared spectra of monosubstituted toluene derivatives in cyclodextrin: Orientation of guest molecules in included complexes

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ABSTRACT

Infrared spectroscopy was applied to determine the orientations of guest molecules (*m*- and *p*-chlorotoluene, *m*- and *p*-tolunitrile, and *m*- and *p*-toluidine) in cyclodextrin (α-, β-, or γ-cyclodextrin (CD)). Some bands of the guest molecules were found to shift by several wavenumbers upon formation of inclusion complexes or upon variation of the diameters of CD. The shifts could be explained by the steric hindrance imparted on the guest molecules in the CD cavities. Moreover, the bands were thought to be due to the vibrations of the moieties of guest molecules in the cavity of CD. The bands were assigned with the aid of quantum chemical calculations, which revealed that chlorotoluene, tolunitrile, and *p*-toluidine were able to enter the CD cavity, respectively, from the Cl, CN, and CH_3 sides. On the other hand, both the CH_3 and NH_2 groups of *m*-toluidine direct to the outside of the CD ring. The orientation of a guest molecule in a CD cavity was found to be determined by the charge distribution in the guest molecule; the negatively charged moiety of a guest molecule is attracted to the inside of CD.

1. Introduction

Cyclodextrin (CD) is a cyclic oligosaccharide consisting of six (α), seven (β), and eight (γ) α-D-glucose units connected through glycosidic α-1,4 bonds. CD, as a host, is able to include a number of guest compounds that fit into a hydrophobic cavity of 4.5–8.5 Å in diameter. The inclusion ability can be widely applied in numerous fields including the food and cosmetic industries, as well as the pharmaceutical industry. CD also is used in the field of analytical chemistry, where it is used for molecular recognition and enantioseparation in chromatographic methods. Understanding of the intermolecular interactions between the host and guest molecules is of great help in the development of further applications. Small shifts can be observed for some bands in Raman and infrared-absorption spectra of the guest molecules of various types upon formation of inclusion complexes. These shifts have been discussed from the standpoint of intermolecular interactions in the complexes [1–8]. Although changes in the FT-Raman spectra of some fundamental aromatic guest molecules such as *o*-, *m*-, and *p*-chlorostyrene [9] and *o*-, *m*-, and *p*-nitrophenol [10] have been reported upon complex formation with CD and upon variation of the host molecule, neither the interactions between the host and guest molecules nor the orientation of guest molecule in the host cavity has been discussed. The present study provides new experimental results including vibrational spectra of a number of other aromatic molecules in the CD. A discussion of the intermolecular interactions and the orientation of the guest molecule in the host cavity are also presented.

Herein, infrared-absorption spectra of monosubstituted toluenes, such as *m*- and *p*-chlorotoluene, *m*- and *p*-tolunitrile, and *m*- and *p*-toluidine, included in α-, β-, or γ-CD were measured. Some of the IR bands were observed to shift upon variation of the ring size of CD. The moieties of the guest molecules that suffer from intermolecular interactions were identified by assigning the shifted bands using quantum chemical calculations. Experimental results are shown in detail together with a discussion of the orientation of the guest molecules in the inclusion complexes.

2. Experimental

Host compounds, α-, β-, and γ-CD (Wacker), were generously provided by CycloChem Co., Ltd., Japan, and the guest compounds (reagent grade) were purchased from Wako Chemicals Inc., Japan. All reagents were used without further purification. Water distilled after deionization was used as the solvent.

A typical host–guest experiment was carried out as follows. A guest compound was added to a saturated aqueous solution of CD so that the molar concentration of the guest compound in the solution was half that of CD. The mixture was treated with supersonic waves to promote the inclusion. The inclusion complex was obtained as a precipitate, which was separated by centrifugation

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and subsequent filtration. The complex was then dried in the air at the room temperature prior to spectroscopic measurements. The amount of obtained precipitate differed greatly among complexes of different host–guest combinations, presumably due to the difference in the binding constant. Band shifts in the IR spectra upon precipitate formation both for the host and guest compounds support the formation of inclusion complexes.

IR absorption spectra of the precipitates in KBr pellets were measured using an FT-IR spectrophotometer (Shimadzu, FT-IR8400) equipped with a DTGS detector. Preparation of KBr pellets was not thought affect the quality of the inclusion complexes; repeated preparation of disks and their spectral measurements for a host–guest combination gave the same spectra. Further, we assumed that the interaction of KBr with sample compounds was so small that it did not affect the results.

Spectra were recorded in the 4000–400 cm^{-1} spectral region with the accumulation number of 40. A spectral resolution of 2 cm^{-1} was applied. The interval of spectral data under these conditions is about 0.96 cm^{-1}, therefore, we can examine qualitative band shifts greater than about 1 cm^{-1}.

DFT calculations were performed with the GAUSSIAN03 package [11] using the 6-31G* basis set. Becke's three-parameter hybrid density-functional in combination with the Lee–Yang–Parr correlation functional (B3LYP) was used to optimize the geometrical structures and estimate the vibrational wavenumbers.

3. Results

In the observed spectra of the inclusion complexes, bands due to CD were prominent. However, some bands attributed to the guest molecules could also be observed. Since intense broad bands due to CD often interfere with the observation of weak bands due to guest molecules, two spectral regions (1700–1450 and 850–600 cm^{-1}) were selected for a more detailed examination. In this region, bands due to CD were not as dominant and bands attributed to the guest molecules were more obvious. Characteristic aromatic C=C stretching modes and the CH_3-bending modes were observed in the 1700–1450 cm^{-1} region, and the band due to the aromatic CH-bending mode was observed in the 850–600 cm^{-1} region. A band around 2250 cm^{-1} could be observed, which was assigned to the CN-stretching of tolunitrile.

3.1. FT-IR spectra of *m*- and *p*-chlorotoluene included in α-, β-, or γ-CD

Fig. 1 shows IR absorption spectra of *m*-chlorotoluene included in α-, β-, and γ-CD in the 1650–1450 and 800–600 cm^{-1} spectral regions. The spectra shown in Fig. 1 (and in all figures appearing later) are depicted with shifted baselines, so that they do not overlap. Bands marked with asterisks are attributed to CD. The dashed lines in the figure help visualize the band shifts more clearly. See tables for quantitative shifts which are hardly seen in figures.

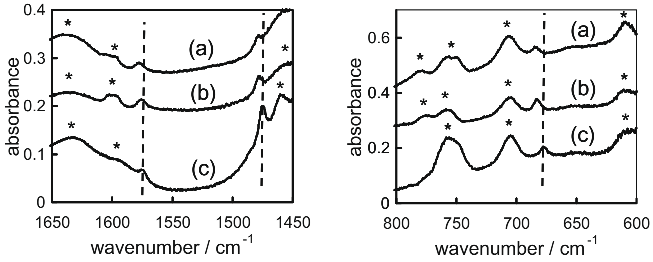

Fig. 1. IR absorption spectra of *m*-chlorotoluene included in (a) α-, (b) β-, and (c) γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the band shifts.

The band around 1580 cm^{-1} was assigned to the aromatic C=C stretching mode, and was observed to shift upon variation of the host. A reduction of the ring size of CD caused a shift of several wavenumbers towards a higher wavenumber; α-CD > β-CD > γ-CD. The bands around 1480 and 680 cm^{-1} were assigned to the CH_3-bending and the aromatic CH-bending modes, respectively, and were found to shift in the same way as the band around 1580 cm^{-1}.

Fig. 2 shows IR absorption spectra of *p*-chlorotoluene included in α-, β-, and γ-CD in the 1650–1450 and 900–700 cm^{-1} spectral regions. The band observed around 805 cm^{-1} assigned to the aromatic CH-bending mode was found to shift to a higher wavenumber with a decrease in the cavity size of CD. On the other hand, the wavenumber of the band observed at 1490 cm^{-1} assigned to the CH_3-bending mode was found to be independent of the cavity size of CD.

The observed wavenumbers of bands attributed to *m*- and *p*-chlorotoluene in CD are summarized in Table 1, where the results of the DFT calculations for isolated chlorotoluenes and the observed wavenumbers for the liquid film samples are also shown. Calculated wavenumbers were higher than those observed because they are not scaled.

3.2. FT-IR spectra of *m*- and *p*-tolunitrile included in α-, β-, or γ-CD

Fig. 3 shows the IR absorption spectra of *m*-tolunitrile included in α-, β-, and γ-CD in the 2300–2100 and 710–670 cm^{-1} spectral regions. The bands observed around 2230 and 685 cm^{-1} were assigned to the CN-stretching and the aromatic CH-bending modes, respectively, and were found to shift to higher wavenumbers upon a decrease in the ring size of CD; α-CD > β-CD $\geqslant$ γ-CD.

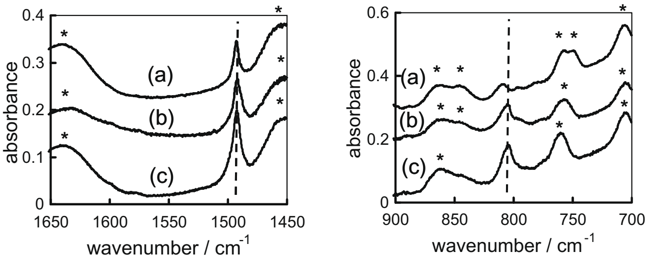

Fig. 2. IR absorption spectra of *p*-chlorotoluene included in (a) α-, (b) β-, and (c) γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the bands shift.

Table 1
Wavenumbers of IR bands of *m*- and *p*-chlorotoluene included in α-, β-, and γ-CD.

	Aromatic C=C stretching (cm^{-1})	CH_3-bending (cm^{-1})	Aromatic CH-bending (cm^{-1})
m-Chlorotoluene			
Monomer (calc.)[a,b]	1632	1529	696
Liquid film[b]	1577	1477	682
Included in α-CD	1579	1478	685
Included in β-CD	1576	1476	682
Included in γ-CD	1575	1475	676
p-Chlorotoluene			
Monomer (calc.)[a,b]		1522	822
Liquid film[b]		1492	806
Included in α-CD	–[c]	1490	806
Included in β-CD	–[c]	1490	805
Included in γ-CD	–[c]	1490	804

[a] Calculated by the DFT method using B3LYP/6-31G*. Not scaled.

[b] Those wavenumbers are shown to confirm the assignments of bands of included complexes.

[c] Not observed.

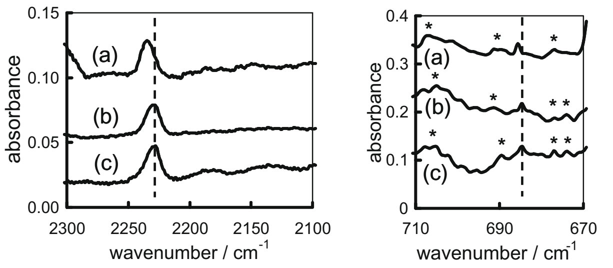

Fig. 3. IR absorption spectra of *m*-tolunitrile included in (a) α-, (b) β-, and γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the bands shift.

Fig. 4 shows the IR absorption spectra of *p*-tolunitrile included in α-, β-, and γ-CD in the 2300–2100 and 840–800 cm^{-1} spectral regions. The bands observed around 2230 and 817 cm^{-1} were assigned to the CN-stretching and the aromatic CH-bending modes, respectively, and were found to shift higher wavenumbers in the same manner as *m*-tolunitrile in CD; α-CD > β-CD ≈ γ-CD.

The wavenumbers of bands observed for *m*- and *p*-tolunitrile in CD are summarized in Table 2, where the results of DFT calculations and liquid-film observations are also shown.

3.3. FT-IR spectra of m- and p-toluidine included in α-, β-, or γ-CD

Fig. 5 shows IR absorption spectra of *m*-toluidine included in α-, β-, and γ-CD in the 1650–1450 cm^{-1} spectral region. In the spectra on the right-hand side which show the 1650–1600 cm^{-1} spectral region in expanded scales, weak bands due to *m*-toluidine included in CD are observed at 1627 cm^{-1} on the intense broad bands of CD. Neither the band at 1627 cm^{-1} assignable to the NH-bending mode nor the band at 1497 cm^{-1} assignable to the CH$_3$-bending mode was found to shift upon variation of the cavity size of CD.

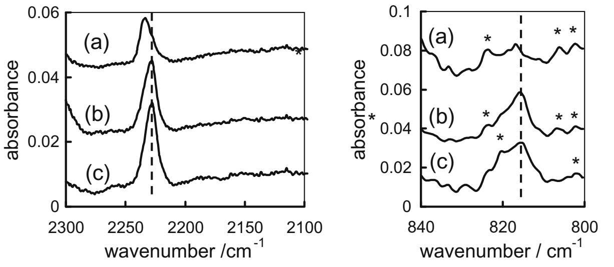

Fig. 4. IR absorption spectra of *p*-tolunitrile included in (a) α-, (b) β-, and (c) γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the bands shift.

Table 2
Wavenumbers of IR bands of *m*- and *p*-tolunitrile included in α-, β-, and γ-CD.

	CN-stretching (cm^{-1})	Aromatic CH-bending (cm^{-1})
m-Tolunitrile		
Monomer (calc.)[a,b]	2348	705
Liquid film[b]	2228	686
Included in α-CD	2234	686
Included in β-CD	2230	684
Included in γ-CD	2227	684
p-Tolunitrile		
Monomer (calc.)[a,b]	2347	836
Liquid film[b]	2228	817
Included in α-CD	2233	817
Included in β-CD	2227	815
Included in γ-CD	2227	815

[a] Calculated by the DFT method using B3LYP/6-31G*. Not scaled.

[b] Those wavenumbers are shown to confirm the assignments of bands of included complexes.

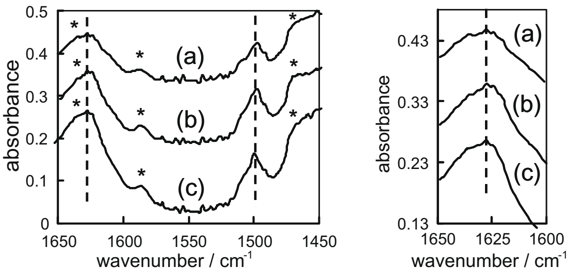

Fig. 5. IR absorption spectra of *m*-toluidine included in (a) α-, (b) β-, and (c) γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the bands shift. The 1650–1600 cm^{-1} spectral region is expanded on the right-hand side to show a weak band at 1627 cm^{-1}, which can be observed on the intense broad bands of CD.

Fig. 6 shows IR absorption spectra of *p*-toluidine included in α-, β-, and γ-CD in the 1700–1500 cm^{-1} spectral region. In the spectra on the right-hand side which show the 1650–1600 cm^{-1} spectral region in expanded scales, weak bands due to *p*-toluidine included in CD are observed at 1627 cm^{-1} on the intense broad bands of CD. No shift upon variation of the ring size of CD was observed for the band at 1627 cm^{-1} which was assigned to the NH-bending mode, while the band around 1520 cm^{-1} assigned to the CH$_3$-bending mode was found to shift to the higher wavenumber with the decrease of the ring size of CD; α-CD > β-CD ≈ γ-CD.

The wavenumbers of bands observed for *m*- and *p*-toluidine in CD are summarized in Table 3, where the results of DFT calculations and the wavenumbers observed under the liquid-film or in the KBr-pellet are also shown.

4. Discussion

Three functional groups, chloro, cyano, and amino, are well known to affect the stereoelectronic properties of a benzene ring in different ways [12]. In tolunitrile, the cyano group functions to pull electron density out of the benzene ring due to the mesomeric effect. This causes the electronic polarization with the negatively charged cyano group and the positively charged benzene ring. The electron-withdrawing inductive effect of the chloro group exceeds the electron-donating mesomeric effect, thus resulting in electronic polarization with the negatively charged chloro group and the positively charged aromatic ring. The amino group in toluidine, which is an electron donor to benzene ring through the res-

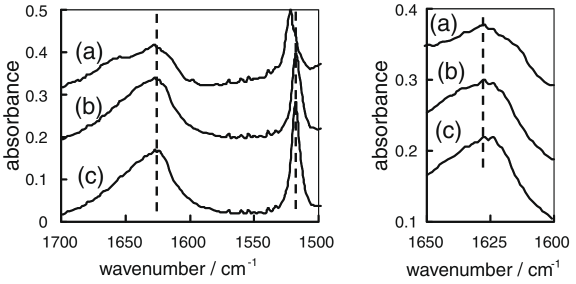

Fig. 6. IR absorption spectra of *p*-toluidine included in (a) α-, (b) β-, and (c) γ-CD. Bands marked with asterisks are those attributed to CD. Dashed lines help visualize the band shifts. The 1650–1600 cm^{-1} spectral region is expanded on the right-hand side to show a weak band at 1627 cm^{-1}, which can be observed on the intense broad bands of CD.

Table 3
Wavenumbers of IR bands of *m*- and *p*-toluidine included in α-, β-, and γ-CD.

	NH-bending (cm^{-1})	CH_3-bending (cm^{-1})
m-Toluidine		
Monomer (calc.)[a,b]	1649	1532
Liquid film[b]	1622	1495
Included in α-CD	1627	1497
Included in β-CD	1627	1497
Included in γ-CD	1627	1497
p-Toluidine		
Monomer (calc.)[a,b]	1696	1571
KBr pellet[b]	1627	1517
Included in α-CD	1627	1521
Included in β-CD	1627	1517
Included in γ-CD	1627	1517

[a] Calculated by the DFT method using B3LYP/6-31G*. Not scaled.

[b] Those wavenumbers are shown to confirm the assignments of bands of included complexes.

onance effect, causes the electronic polarization with the positively charged amino group.

All IR absorption spectra observed in this work could be explained with these charge distributions in the guest molecules by assuming that negatively charged moieties of the guest molecules are preferentially drawn into the cavity of the CD, because the electron withdrawing OH groups at the exterior of the cyclic CD molecule are expected to cause a cavity with high electric potential where is preferable for a negatively charged moiety of guest molecule. Orientations of inclusions are shown schematically in Fig. 7, where the structures of the host and guest molecules are calculated using the B3LYP/6-31G* method and are shown in a same scale together with the arrows representing the orientations of the inclusions.

Chlorotoluene presumably enters from the chloro-group side into a CD ring, because the chloro group is the most negatively charged part of the molecule. Therefore, the methyl group of *p*-chlorotoluene leaves the outside of the cavity. No shift of the band due to the methyl group is expected upon variation of the ring size of CD. On the other hand, the methyl group of *m*-chlorotoluene in CD inevitably interacts with CD because the distance between the chloro and methyl groups in *m*-chlorotoluene is smaller than that in *p*-chlorotoluene, and is expected to be in the CD cavity. The wavenumber for the band due to the CH_3-bending mode, therefore, depends on the CD cavity size; the larger steric hindrance in a smaller cavity causes the shift of the band from 1475 in γ-CD to 1478 cm^{-1} in α-CD (Table 1). The benzene ring is included in the cavity of CD, therefore, the bands due to the aromatic C=C stretching and aromatic CH-bending modes also shift upon variation of the cavity size of CD (Table 1).

Tolunitrile enters CD from the cyano-group side bearing a highly negative charge. The cyano group of included tolunitrile is always in the CD cavity, therefore, its wavenumber depends on the cavity size. The bands attributed to the CN-stretching mode of the *m*- and *p*-tolunitrile shift, by 7 or 6 cm^{-1}, respectively, towards the higher wavenumber upon a decrease in the cavity size of CD (Table 2). The band due to aromatic CH-bending modes of *m*- and *p*-tolunitrile included in CD also shifts upon variation of the cavity size of CD (Table 2); the benzene rings of these molecules are included in the CD cavity. No bands due to the methyl group of *m*- and *p*-tolunitrile are observed in the IR spectra, therefore, no information on the interaction between the methyl group of tolunitrile and CD was obtained.

The wavenumbers of the observed bands for the NH-bending of *m*- and *p*-toluidine were found to be independent of the cavity size of CD (Figs. 5 and 6). The positively charged amino group hardly enters the cavity of CD, whereas toluidine enters the CD from the opposite side of the amino group. In the case of *m*-toluidine, the wavenumber of the aromatic CH-bending mode also was found to be independent of the cavity size of CD, suggesting that *m*-toluidine enters the CD only shallowly and interacts weakly with CD. On the other hand, the wavenumber of the aromatic CH-bending mode of *p*-toluidine was found to shift upon variation of the cavity size of CD. The dipole moment of *p*-toluidine was calculated to be 1.535 D and to direct from the methyl group to the amino group; the methyl group is negatively charged compared with the amino group. Therefore, *p*-toluidine is included in the CD from the methyl-group side. The straight structure of *p*-toluidine enables deep inclusion into CD only with the small steric hindrance, which results in the shift of the aromatic CH-bending band upon variation in the size of the CD ring.

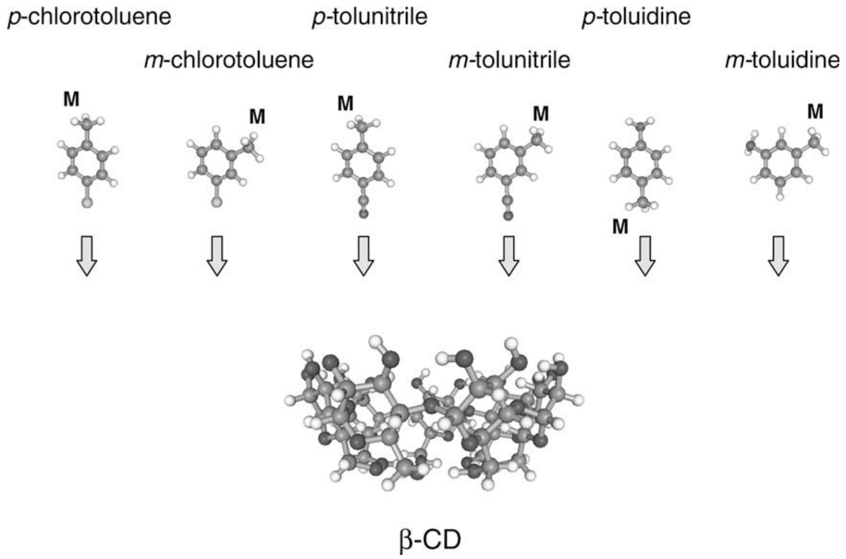

Fig. 7. Molecular structures calculated using the B3LYP/6-31G* method shown together with the arrows representing the orientations of inclusions. "M" denotes a methyl group.

5. Conclusions

A detailed investigation of the band shifts upon formation of the inclusion complex and upon a change in the cavity size of CD revealed that the charge distribution of monosubstituted toluene derivatives determines the orientations and depths of inclusion in the CD cavity. The orientation of a guest molecule in CD is determined not by the steric effect of the functional group, but mainly by the electronic character of the functional group. This finding is expected to be useful in discussing the guest orientation in CD. Future work will involve measuring Raman spectra of the inclusion complexes to confirm the present conclusions. Only the band shifts of the guest molecules were examined in the present study, because they were expected to contain information on the orientation of the guest in CD. Examination of the observed shifts in the bands due to the host molecules will also be examined in the future.

Acknowledgements

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References

[1] F.L. Dickert, S. Landgraf, R. Sikorski, J. Mol. Model. 6 (2000) 491.
[2] J.C. Netto-Ferreira, V. Wintgens, L.F.V. Ferreira, A.R. Garcia, L.M. Ilharco, M.J. Lemos, J. Photochem. Photobiol. A Chem. 132 (2000) 209.
[3] O. Rajabi, F. Tayyari, R. Salai, S.F. Tayyari, J. Mol. Struct. 878 (2008) 78.
[4] A. Bertoluzza, M. Rossi, P. Taddei, E. REdenti, M. Zanol, P. Ventura, J. Mol. Struct. 480 (1999) 535.
[5] V. Barillaro, G. Dive, P. Bertholet, B. Evrard, L. Delattre, E. Ziémons, G. Piel, Int. J. Pharm. 347 (2008) 62.
[6] L. Zhou, Z. Lin, C.J. Welch, Z. Ge, D. Ellison, Chirality 18 (2006) 306.
[7] N. Grancher, F. Kedzierewicz, V. Venard, A. Marsura, C. Finance, J. Le Faou, Incl. Phenom. Macrocycl. Chem. 51 (2005) 149.
[8] L. Vrielynck, C. Lapouge, S. Marquis, J. Kister, N. Dupuy, Spectrochim. Acta 60A (2004) 2553.
[9] S.-H. Choi, J.-W. Seo, S.-I. Nam, M.-S. Lee, K.-P. Lee, J. Incl. Phenom. Macrocycl. Chem. 40 (2001) 279.
[10] S.-H. Choi, E.-N. Ryu, J.J. Ryoo, K.-P. Lee, J. Incl. Phenom. Macrocycl. Chem. 40 (2001) 271.
[11] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Takajima, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchan, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochteraki, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacomb, P.M. W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.
[12] J. McMurry, Organic Chemistry, seventh ed., Thomson Brooks/Cole, Belmont, CA, 2008 (Section 16).