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Theoretical Investigations of the Inclusion Processes of (4-tert-butylphenyl) (3-sulfonatophenyl) (phenyl) Phosphine in β-Cyclodextrin

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Abstract

Quantum mechanical calculations on the (4-tert-butylphenyl) (3-sulfonatophenyl) (phenyl) phosphine/β-cyclodextrin inclusion complex were carried out using semi-empirical calculations. Inclusion process pathways are described and the most probable structures of the 1:1 complex are sought through a global potential energy scan. The calculations suggest that the most stable structure is obtained when the aromatic ring bearing the tert-butyl group is included into the hydrophobic cavity of the β-cyclodextrin from the side of the primary hydroxyl groups.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with six (α-), seven (β-) or eight (γ-) D-glucopyranose units connected by α-(1,4) bonds. These compounds are truncated cone-shaped molecules with a hydrophobic cavity (Figure 1) [1]. The secondary hydroxyl groups (2-OH and 3-OH) of the respective glucose units are located at the wider side of the rim (the secondary face), and the primary 6-CH_2OH groups are located at the narrower side of the rim (the primary face) as seen in Figure 1b. These molecules are widely used as host molecules because of their properties, such as their solubility in water and the cavity created by the rim of oxygen atoms in the glycosidic function. They offer to guest molecules the possibility to penetrate and to accommodate and form inclusion complexes with a wide variety of organic compounds [2–3]. In particular, we have recently reported that β-cyclodextrin forms inclusion complexes with two well-known standard water-soluble ligands in aqueous-phase organometallic catalysis: the sodium salt of trisulfonated triphenylphosphine (P(m-$C_6H_4SO_3Na)_3$) [4–6] and the sodium salt of the monosulfonated triphenylphosphine (P(m-$C_6H_4SO_3Na$)($C_6H_5)_2$) [7]. The geometry for these inclusion complexes can be easily deduced from one and two-dimensional NMR experiments. So, it was demonstrated that the two phosphines are included into the hydrophobic cavity of the β-cyclodextrin from the side of the secondary hydroxyl groups. In the case of the monosulfonated triphenylphosphine, the NMR study fully prove that the inclusion occurs by one of the non-sulfonated aromatic rings.

Intensive theoretical works have been performed over the past few years on cyclodextrin inclusion complexes [8–19]. Theoretical approaches involve mainly Molecular Mechanics [8, 10, 11, 14] and Molecular Dynamics [13, 20] with various force fields approaches. For instance, stochastic Molecular Dynamics and Molecular Mechanics calculations [20–21] were used with empirical MM2 and AMBER force fields implemented in MACROMODEL [22]. MM3 calculations [20] indicate that only the local minimum can be found for a great number of positions of the guest in the host molecule. Quantum calculations seem to be the only route to achieve the search for the global minimum. However, such calculations are difficult to carry out because of the size of the molecular system. Early quantum calculations were performed with semi-empirical CNDO methods [23–24] followed by several semi-empirical quantum calculations [9, 25–27] with the use of the AM1 Hamiltonian [28] (Austin Model 1). Over the past few years all attempts made to investigate such processes have focused mainly towards CD complexation. At a higher level of quantum calculations, ab initio methods at the Hartree–Fock or the Density Functional Theory [16, 18] levels with a minimal basis set were carried out. However, all attempts made to date for the study of CD complexation were performed at several starting points rather than over a global search of the potential energy surface of the inclusion process. For other authors, the route of any investigation is to calculate the internal diameter formed by the rim of oxygen atoms in the glycosidic function followed by the inclusion process.

In the present paper, we describe a methodology to approach a complete potential surface scan of the inclusion process and apply it to the complexation of

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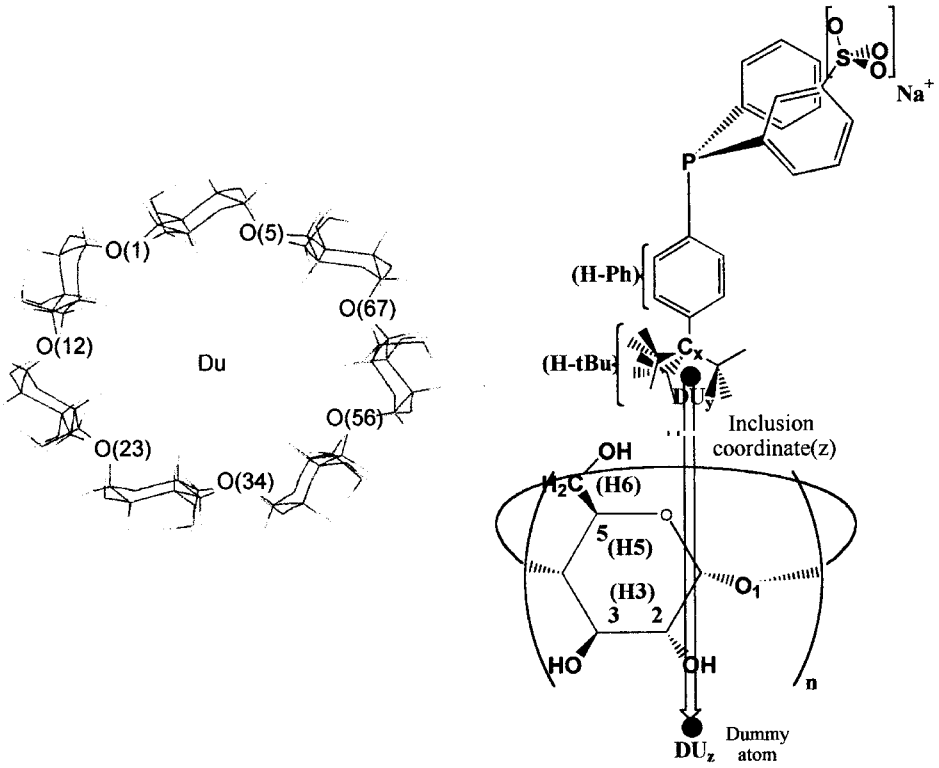

Figure 1. Structure (a) and shape (b) of β-cyclodextrin ($n = 6$ α-cyclodextrin, $n = 7$ β-cyclodextrin, $n = 8$ γ-cyclodextrin), Figure 1b. is the starting configuration of the inclusion process, z is the approaching distance between the two dummy atoms.

(4-tert-butylphenyl)(3-sulfonatophenyl) (phenyl)phosphine (TPPmSptBu) in β-cyclodextrin (Figure 2a). This theoretical study was initiated by the fact that a reliable NMR study of the inclusion process of this particular water soluble phosphine was impeded by aggregation phenomena. Indeed, in contrast to trisulfonated triphenylphosphine and to monosulfonated triphenylphosphine, TPPmSptBu is a highly surface active compound (cmc: 2 mM) and, consequently, the formation of molecular aggregates inducing alterations of the NMR signals and titration curves is difficult to avoid [29]. Thus, a theoretical approach to the inclusion process of this phosphine appears particularly interesting to obtain some information on the structure of the inclusion complexes. In our theoretical study, the inclusion by TPPmSptBu is first considered as isolated molecular systems in different conformations. In a second step, we investigate the inclusion pathway for the guest-host potential energy profile and the corresponding structures of the complexes obtained.

Calculation and methodology

Semi-empirical quantum calculations with the use of the AM1 Hamiltonian [28] (Austin Model 1) are performed in order to reproduce the potential energy scan of the inclusion process. The method is based on the NDDO (Neglect Diatomic Differential Overlap) approximation, part of the Gaussian 98, Revision A.7 [30]. Despite the limitations of semi-empirical methods characterized by the use of parameters derived from experimental data, they are commonly used for structure optimization of very large systems or for reactions involving large molecular systems. Such methods are a good starting point for calculations at a higher level of theory.

The host-guest inclusion process is investigated starting from optimized structures, as reported in Table 1. Different quantum calculation methods, such as the semi empirical AM1 or PM3 Hamiltonian and at the Hartree–Fock level with a 6-31G* basis set were used. Such calculations were performed in order to seek the most reliable starting configuration of the β-CD taking into account hydrogen-oxygen intra-molecular interactions. The obtained structures were compared to x-ray data as reported in Table 1. As far as structural properties are concerned, ab initio results at the Hartree–Fock level are close to experimental data as expected. Theoretical data can be enhanced by adding diffuse functions to the chosen basis set, however, this would lead to a considerable increase of CPU calculation time. An al-

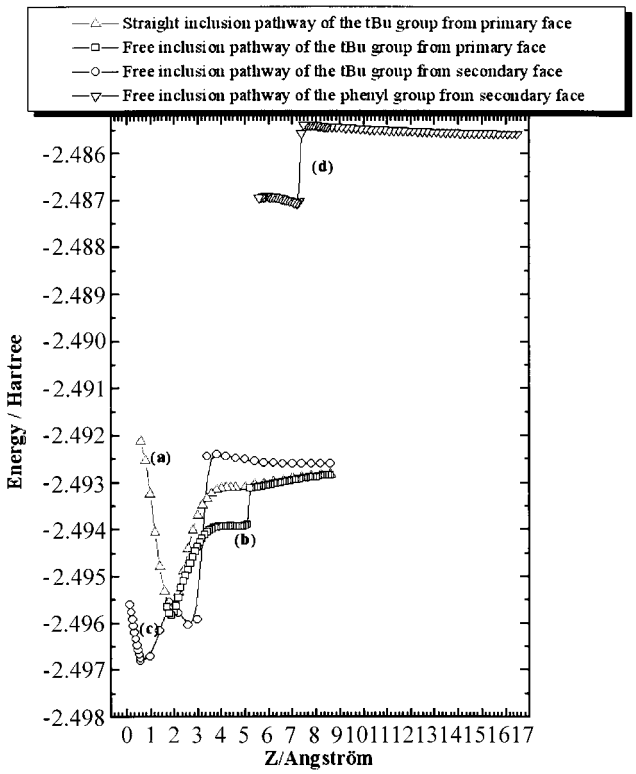

Figure 2. Potential energy profile of the inclusion process through the primary face (open triangles and open squares "curves (a) and (b) respectively") and the secondary face (open circles "curve (c)"). (a) Open triangles indicate a controlled inclusion process (straight inclusion). (b) Open squares indicate the potential energy of the inclusion process worked out with no restriction on the approach of the guest molecule. (c) Open circles indicate the potential energy profile for the inclusion process of the tBu group from the secondary face. (d) open down triangles indicate the potential energy profile of the phenyl group penetrating through the secondary face.

Table 1. Calculated and x-ray data of β-cyclodextrin. DU is the dummy atom located at the center of mass of the oxygen atoms in the glycosidic function.

Atomic distances (Å)	Theory level AM1	PM3	Hartree–Fock 6-31G	X-ray data[a]
DU—O_{23}	5.017	5.078	5.158	4.63
DU—O_{12}	5.017	5.078	5.158	5.18
DU—O_1	5.017	5.078	5.158	5.27
DU—O_5	5.017	5.078	5.158	4.57
DU—O_{67}	5.017	5.078	5.158	4.99
DU—O_{56}	5.017	5.078	5.158	5.35
DU—O_{34}	5.017	5.078	5.158	4.92
O_{23}—O_{12}	4.354	3.080	4.476	4.29
O_{23}—O_{34}	4.354	3.080	4.476	4.45
O_{12}—O_1	4.354	3.080	4.476	4.45
O_1—O_5	4.354	3.080	4.476	4.20
O_5—O_{67}	4.354	3.080	4.476	4.32
O_{67}—O_{56}	4.354	3.080	4.476	4.24
O_{56}—O_3	4.354	3.080	4.476	4.42

[a] Crystallographic studies. K. Harata, K. Otagiri, F. Hirayama and Y. Ohtani: *Bull. Chem. Soc. Jpn.* 1234 (1985).

ternative at this level of simple optimized structures seems to be found in the AM1 Hamiltonian. In order to examine in detail the reaction pathways and seek for a possible global minimum, we proceeded as follows.

The controlled reaction coordinate (z) of the inclusion process is the distance between a dummy atom located at the center of mass of the methyl groups of the tBu and a second dummy atom located at the center of the glycosidic oxygen atoms of the β-CD as illustrated in Figure 1. Dummy atoms are kept frozen at their initial position throughout the calculations. Performing a global search of inclusion complexes is a very tough job and we shall demonstrate that constraining and controlling some variables throughout the calculations may lead to different results and interpretations. For that purpose, we suggest the following scheme for an accurate global search of the inclusion process. Starting from optimized structures for the host and guest molecules, the calculations of the inclusion process are performed with a full optimization of every point. At this stage all atoms of the β-CD are frozen. In a second step, points of interests in the potential energy profile of the inclusion process are taken and fully optimized by releasing all variables of the β-CD on a step-by-step basis. We start with the release of hydrogen atoms of the primary 6-CH_2OH groups and oxygen of the glycosidic function, followed by a full optimisation of the whole inclusion complex with all variables free. As reported later, although we notice an important change in the energy of the inclusion complex, such a process does not influence in any manner the penetration level of the guest molecule within the complex.

Results of the inclusion process of TPPmSptBu in β-CD

The penetration of (4-tert-butylphenyl)(3-sulfonatophenyl) (phenyl)phosphine (TPPmSptBu) in β-CD is investigated. Since the inclusion process may take place on either side of the β-CD, a potential energy scan of the inclusion process is carried out through both sides of the guest molecule. Several mechanisms and orientation of the guest molecule may occur theoretically; either the SO_3^-, the tBu or the phenyl group may be directed towards the hydrophobic cavity of the β-CD. The hydrophilic character of the SO_3 group is not favorable to its penetration from either side of the β-CD. Therefore, for the two remaining groups (i.e., the tBu and the phenyl), the inclusion may occur either from the primary hydroxyl group (the primary face) or the secondary hydroxyl groups (the secondary face).

According to the methodology described earlier, we undertake the inclusion process of the guest molecule from the tBu group through either the primary or the secondary face. The potential energy profile of the inclusion process is reported in Figure 2. A controlled perpendicular penetration of the guest molecule (curve "a") into the β-CD leads to an overall process different from the one where the guest molecule is free to approach the host molecule (curve "b"). In the straight perpendicular insertion we kept the angle $C_xDU_yDU_z$ and the dihedral angle $C_xDU_yDU_z$ O_1 (Figure 1a) constant. Although the minima in both cases are identical, the potential energy profile is different, indicating

the arrangement of the guest molecule while it penetrates the β-CD. The well depth in the potential energy profile for a free inclusion gives evidence as reported in Figure 2, for an inclusion process of the tBu group occurring preferentially from the primary face and leading to a 1:1 inclusion complex.

Theoretical results do not eliminate any possible penetration of the tBu group from the secondary face as reported in Figure 2 (curve "c"). However, the potential energy profile gives evidence of the differences of energies involved between the two processes. Such results suggest that the penetration from the secondary face needs probably more energy to overcome the energy barrier and the penetration pathway predicts two penetration levels.

All calculation attempts to seek for possible inclusion of the phenyl group from the primary face have failed. The calculated energies not reported in the figure are beyond the scale of the present energies. However, the inclusion of the phenyl group through the secondary face remains possible as illustrated in Figure 2 (curve d).

Such results suggest that the inclusion process of (4-tert-butylphenyl) (3-sulfonatophenyl) (phenyl) phosphine (TPPmSptBu) in β-CD occurs through the primary face with the insertion of the tBu group into the hydrophobic cavity of the β-CD.

It is important to emphasize that the calculations were performed with all variables of the β-CD kept frozen. To what extent is such a hypothesis valid? The minima obtained were then optimized on a step-by-step basis releasing all constraints on hydrogens of the primary 6-CH_2OH groups and oxygens of the glycosidic function, followed by a full optimization. The complete full optimization of the first minimum in the potential energy profile leads to an important change in energy $\Delta E = 117.17$ kcal/mole. This energy is the difference between the partly optimised inclusion complex and the fully optimized inclusion complex. Despite such a difference, we find no major differences within the penetration level of the guest molecule as illustrated by Figures 3a and 3b, except for the structure of the guest molecule. It is well known that the parent structure of the β-cyclodextrin is sensitive to the hydrogen bonding network of the primary OH group and to the belt of acetal oxygen linking the oxygens together [21]. An analysis of the host-guest binding structures (Figure 3) shows that the primary 6-CH_2OH groups located at the narrower side of the rim (the primary face) act as a lock and the secondary face gets wider. This result is incompatible with previous assumptions [21] obtained from molecular mechanics calculations where the secondary OH group tilted inward, enhancing the hydrogen bonding network in the secondary rim, and consequently leading to a significant opening of the primary OH face of the cyclodextrin.

Our results may let us assume that the described process would help the formation of a 1:2 inclusion complex with a second inclusion guest molecule penetrating from the opposite face. This second inclusion probably occurs by the phenyl group. We have present experimental evidence [7] of an inclusion complex with one aromatic ring of the mono-sulfonated triphenylphosphine (TPPMS) inserted into the hydrophobic cavity from the secondary side of the CD rather the primary face. We expect a concerted inclusion process from both sides of the β-CD leading to a 1:2 inclusion complex (i.e., a phenyl penetration from the secondary face and the tBu group insertion from the opposite face) as illustrated by Figure 4.

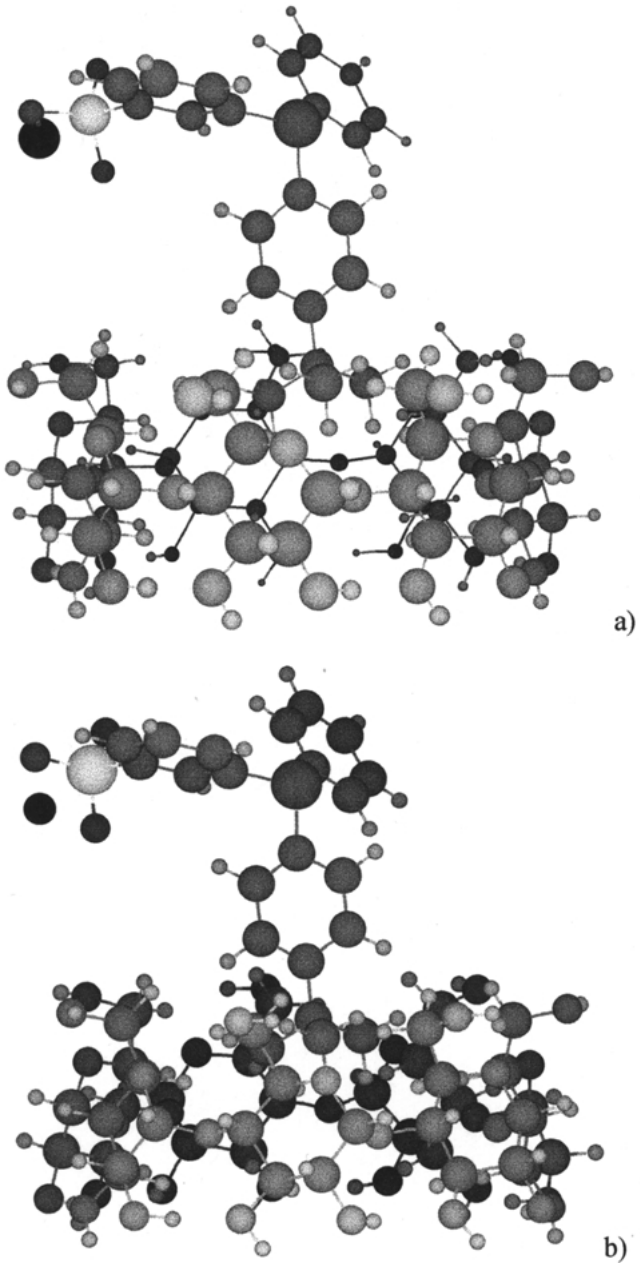

Figure 3. Structure of the inclusion complex for the 1st minimum of energy (curve "b" of Figure 2), "a" is a partial optimization, "b" is a full optimization.

All minima obtained in the different potential energy profiles of the penetration process were fully optimized and reported in Table 2 using two semi empirical methods with the AM1 and PM3 Hamiltonian. In order to evaluate the penetration depth, we have worked out the mean distance between the hydrogens of the tBu group (H-tBu) with the surrounding hydrogens of type H3, H5 and H6 (see Fig-

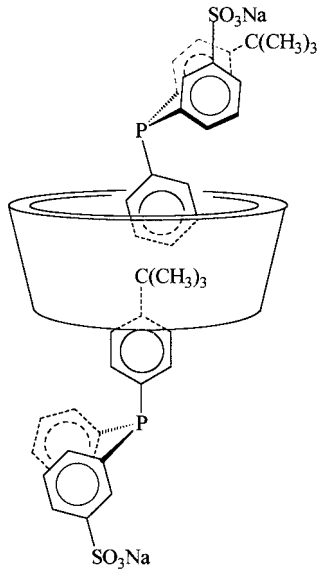

Figure 4. Concerted inclusion process from both sides of the β-CD leading to a 1:2 inclusion complex (i.e., a phenyl penetration from the secondary face and the tBu group insertion from the opposite face).

Table 2. Full optimization and calculated energies of selected minima in the potential energy profile plotted in Figure 2

	AM1-Calculated energy/Hartree	PM3-Calculated energy/Hartree
Min1 "Figure 2, curve (b)"	−2.6826955	−2.4077736
Min1 "Figure 2, curve (c)"	−2.6888366	−2.5193273
Min2 "Figure 2, curve (c)"	−2.693667	−2.5285924

ure 1b) in the β-CD. These results clearly show that the tBu group penetrates deep inside the host molecule and is close to hydrogens of type H5 and H3. Similar calculations of the mean distance of hydrogens of the phenyl group (H-Ph) of the TPPmSptBu to hydrogens of type H6 of the β-CD indicate that the phenyl group is surrounded by primary 6-CH_2OH groups.

Conclusion

This work has shown that the global search of the inclusion process may lead to complete mechanisms and illustrate in more detail all possible orientations or regioselective penetration involved in host-guest interactions than has been possible hitherto. The global search offers the possibility to carry out a full investigation of the overall process and to identify all stable complexes and possible transition states in more complex situations. The penetration process of the tBu group of the guest molecule occurs from the primary side of the β-cyclodextrin. Although the energies of the fully optimized inclusion complexes are different, the structure and the penetration level do not change when compared to the structure of the partial optimization. A complete penetration pathways needs to localise the transition states appearing in some cases such as the potential profile in Figure 2(c). Interestingly, the inclusion process leading to a 1:2 inclusion complex could be also promoted by the opening of the secondary face due to the inclusion of the tBu group.

Table 3. Calculated mean distance (Å) between hydrogen's (H-tBu) and (H-Ph) of the tBu and the phenyl group respectively in TPPmSptBu and hydrogens type H3, H5 and H6 (see Figure 1b) in β-CD

	Host hydrogen type H3	Host hydrogen type H5	Host hydrogen type H6
Guest (H-tBu)	5.925 Å	4.314 Å	5.208 Å
Guest (H-Ph)	14.175 Å	11.815 Å	10.881 Å

References

1. J. Szjetli: *Chem. Rev.* **98**, 11743 (1998).
2. E. Fenyvesi, L. Szente, N.R. Russell and M. McNammara: In J.L. Atwood, J.E.D. Davies, D.D. MacNicol and F. Vögtle (eds.), *Comprehensive Supramolecular Chemistry*, Vol. 3, Pergamon, Oxford (1996), p. 305.
3. K.A. Connors: *Chem. Rev.* **97**, 1325 (1997).
4. E. Monflier, S. Tilloy, C. Méliet, A. Montreux, S. Fourmentin, D. Landy and G. Surpateanu: *New. J. Chem.* **23**, 469 (1999).
5. E. Monflier, S. Tilloy, L. Caron, J.M. Wieruszeski, G. Lippens, S. Fourmentin, D. Landy and G. Surpateanu: *J. Incl. Phenom.* **38**, 361 (2000).
6. A. Da Costa, E. Monflier, S. Fourmentin, D. Landy and G. Surpateanu: *Surface Science* **470**, 275 (2001).
7. L. Caron, C. Christine, S. Tilloy, E. Monflier, S. Fourmentin, D. Landy and G. Surpateanu: *Supramol. Chem.* in press (2001).
8. B.S. Jursic, Z. Zdravkovski and A.D. French: *J. Mol. Struct. (TheoChem)* **366**, 113 (1996).
9. A. Botsi, K. Yannakopoulou, E. Hadjoudis and J. Waite: *Carbohydr. Res.* **283**, 1 (1996).
10. A. Entrena and C. Jaime: *J. Org. Chem.* **62**, 5923 (1997).
11. E. Cervello and C. Jaime: *J. Mol. Struct. (TheoChem)* **428**, 195 (1998).
12. J.M. Madrid, F. Mendicuti and W.L. Mattice: *J. Phys. Chem. B.* **102**, 2037 (1998).
13. T. Kozar and C. Venanzi: *J. Mol. Strut. (TheoChem)* **451**, 395 (1997).
14. X. Sanchez-Ruiz, M. Ramos and C. Jaime: *J. Mol. Struct.* **442**, 93 (1998).
15. E.B. Starikov, W. Saenger and T. Steiner: *Carbohydr. Res.* **307**, 343 (1998).
16. K.B. Lipkowitz: *Chem. Rev.* **98**, 1829 (1998).
17. N. Balabai, B. Linton, A. Nappet, S. Priyadarshy, R. Sukharevsky and D.H. Waldeck: *J. Phys. Chem. B.* **102**, 9617 (1998).
18. L. Liu, X.-S. Li, T.-W. Mu, Q.-X. Guo and Y.-C. Liu: *J. Incl. Phenom. Macrocycl. Chem.* **38**, 199 (2000).
19. D. Salvatierra, C. Jaime, A. Virgili and F.S. Ferrando: *J. Org. Chem.* **61**, 9578 (1996).
20. K.B. Lipkowitz, R. Coner, M.A. Peterson, A. Morreale and J. Shackelford: *J. Org. Chem.* **63**, 733 (1998).
21. K.B. Lipkowitz: *J. Org. Chem.* **56**, 6357 (1991).
22. F. Mohamdi, N.G.J. Richards, W.C. Guide, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W.C. Still: *Comp. Chem.* **11**, 440 (1990).
23. M. Kitagawa, H. Hoshi, M. Sakurai, Y. Inoue and R. Chujo: *Carbohydr. Res.* **163**, 1 (1987).
24. M. Sakurai, M. Kitagawa, H. Hoshi, Y. Inoue and R. Chujo: *Bull. Chem. Soc. Jpn.* **62**, 2067 (1989).
25. M.J. Huang, J.D. Watts and N. Bodor: *Int. J. Quant. Chem.* **64**, 711 (1997).
26. M.J. Huang, J.D. Watts and N. Bodor: *Int. J. Quant. Chem.* **65**, 1135 (1997).
27. N. Balabai, B. Linton, A. Nappet, S. Priyadarshi, R. Sukharevsky and D. H. Waldek: *J. Phys. Chem.* **B102**, 9617 (1998).

28. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy and J.J.P. Stewart: *J. Am. Chem. Soc.* **107**, 3902 (1985).
29. L. Caron, S. Tilloy, H. Bricout and E. Monflier: to be published.
30. Gaussian 98, Revision A.7, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle and J.A. Pople, Gaussian, Inc., Pittsburgh PA (1998).