PRACE NAUKOWE Akademii im. Jana Długosza w Częstochowie
Seria: CHEMIA I OCHRONA ŚRODOWISKA 2008, XII, 155-162

Barbara Mianowska[a]
Wanda Śliwa[b]

[a]Wroclaw College of Humanities, Techno-Economic Faculty,
54-062 Wroclaw, ul. Stabłowicka 95
[b]Jan Długosz University, Institute of Chemistry and Environmental Protection,
42-201 Częstochowa, Armii Krajowej Ave 13/15, e-mail: w.sliwa@ajd.czest.pl

Cyclodextrins as drug carriers

Abstract: In the paper selected examples of cyclodextrin inclusion complexes with drugs are presented, pointing out advantages of their encapsulation.

Keywords: cyclodextrin, drug, inclusion complex, solubility

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides containing 6, 7 or 8 α-D-glucose units linked by 1–4 glycosidic bonds, *i.e.* α-, β- or γ-CDs, respectively [1,2]; it should be mentioned that higher CDs are also known [3]. CDs have hydrophilic outer surface and hydrophobic inner cavity; they may encapsulate organic and inorganic molecules. Due to this ability they are widely used in industrial, pharmaceutical and chemical fields and are a topic of an intense investigation [4-13]; the theme of our research group concerns chemical and physicochemical properties of CDs [14-19].

CDs influence chemical reactions [20, 21] and show catalytic properties [22]; they affect stability of guest molecules and may cause their chemical changes, *e.g.* they increase photofading resistance of free azo dyes and dyes anchored to cotton fibers [23]. Encapsulation in CD cavities alters properties of guest molecules, for example their solubility in water is significantly improved, this fact being of value for better accessibility of lipophilic drugs from alimentary canal [24].

CDs are used in drug delivery systems; the encapsulation of poorly soluble drug in CD cavity results in its increased solubility and bioavailability. It should be pointed out that orally administered drugs as a majority are poorly soluble. The use of CDs as drug carriers allows to avoid such difficulties in drug formulation as their sensitiveness to destruction and their side effects, *e.g.* toxicity or irritation of skin; the understanding of CD/drug interaction is of a great importance in the control of the rate of release [25]. The encapsulation

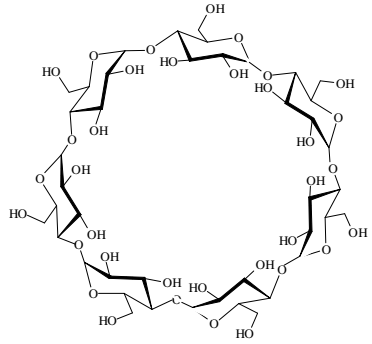
of drugs in CD cavities by weak binding forces provides a useful model to mimic the interaction of drugs with hydrophobic pockets of biological substrates [9].

Since CDs are nontoxic, they may be added to drugs and foods; their easy and environmentally friendly preparation by enzymic degradation of starch enables their wide use in a variety of fields. CDs are chiral, therefore they can form a diastereomeric pair with included racemate; they are useful as chiral selectors in many areas of chemistry and biology [26, 27].

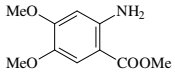
The number of reports concerning CDs is enormous; in the present paper only several selected examples of CD complexes with drugs are described.

Examples of CDs as drug carriers

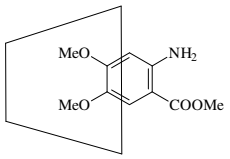
It was established that β-CD forms 1:1 inclusion complex with anesthetic **1**. The investigation of UV-Vis absorption and picosecond emission spectra has shown that upon encapsulation the emission intensity and the fluorescence lifetime increase [28]. This study is of importance for the better understanding of the photochemistry of encapsulated drugs and is of value in the search for species useful in phototherapy.



β-CD

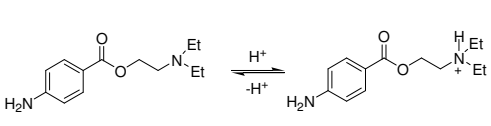


1

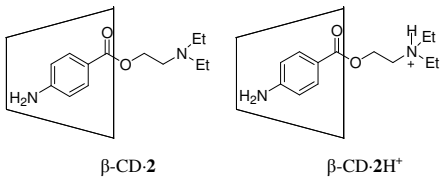


β-CD·**1**

The formation of 1:1 inclusion complexes of β-CD with novocaine **2** and its monoprotonated form **2**H^+ has been studied using steady-state fluorescence and UV-Vis spectroscopies [29, 30]. Novocaine is a local anesthetic existing as a neutral molecule **2** and as a monoprotonated form **2**H^+.

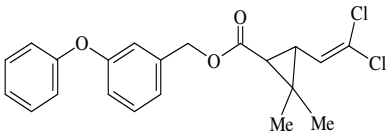


2 **2** H^+

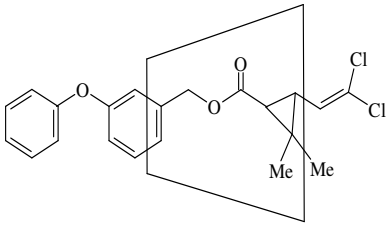


β-CD·**2** β-CD·**2**H^+

The interaction of β-CD with permethrin **3** affords two inclusion complexes: β-CD·**3** and (β-CD)$_2$·**3**, which coexist in aqueous solution [31, 32]. Permethrin is a synthetic pyrethroid, used as a drug in the prevention of malaria, in treatment of HIV and as an insecticide. Permethrin is poorly soluble in water; inclusion into β-CD cavity improves its solubility and increases insecticidal activity, these facts being promising for its more effective use in medicine and in agriculture.

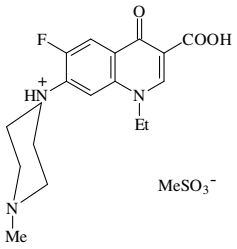


3

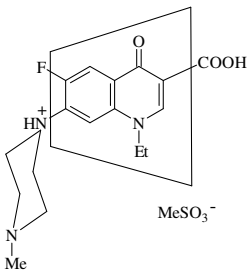


β-CD·**3**

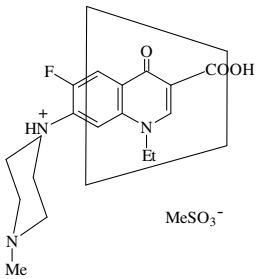
It was observed that α-CD, β-CD and HP-β-CD (hydroxypropyl-β-CD) form 1:1 inclusion complexes with the drug pefloxacin **4**; as a result the aggregates of **4** may break [33]. The complexation was studied by ^{1}H NMR, ^{13}C NMR and fluorescence spectroscopy methods. Spatial characterization based on 2D NMR technique allowed to propose two models of complexes.



4



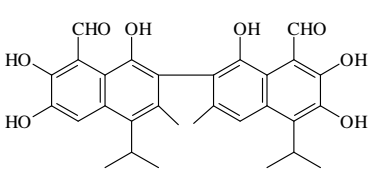
α-CD·**4**
or
HP–β-CD·**4**



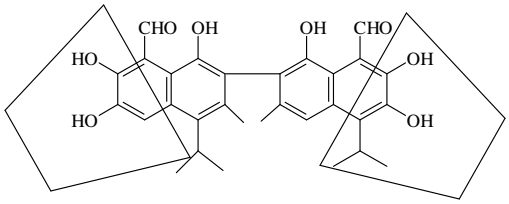
β-CD·**4**

The interaction of β-CD with gossypol **5** leads to 2:1 complex; due to complexation the solubility and thermal stability of drug increases [34]. Gossypol is present in root bark and in seeds of gossypium. Gossypol is clinically used to resist tumor and fungal pathogens and to reduce plasm cholesterol, it

shows however some side effects on human body; the inclusion into CD cavity enables their decrease.

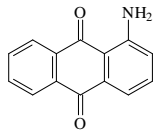


5

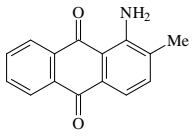


(β - CD)2· **5**

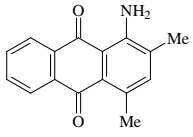
Treatment of β-CD with antraquinone derivatives **6–9** affords 1:1 inclusion complexes; their stability decreases in the order **9** > **6** > **7** > **8** [35]. Antraquinone derivatives are drugs used in the treatment of cancer.



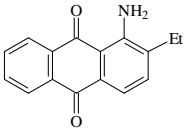
6



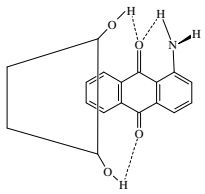
7



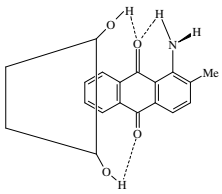
8



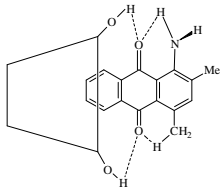
9



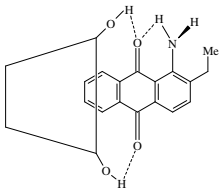
β-CD·**6**



β-CD·**7**

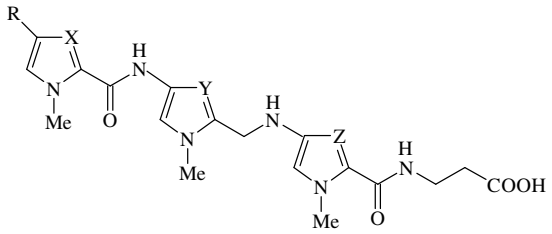


β-CD·**8**



β-CD·**9**

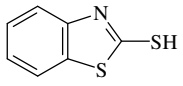
The formation of 1:1 inclusion complexes of β-CD with polyamide acids **10-14** has been investigated using electrospray ionization (ESI) mass spectrometry [36, 37]. Polyamides containing *N*-methylpyrrole and *N*-methylimidazole units have anticancer properties. The binding affinities of **10–14** in complex decrease in the order **13** > **12** > **11** > **10** > **14** [36, 38].



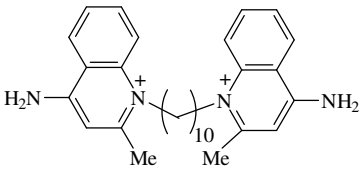
	R	X	Y	Z
10	H	CH	CH	CH
11	H	N	CH	CH
12	H	N	CH	N
13	H	N	N	N
14	NO_2	CH	CH	CH

It was observed that β-CD forms the 1:1 inclusion complex with 2-mercaptobenzothiazole **15** [39]. This compound is used in medicine as antifungal drug, it also serves as biocorrosion inhibitor, as additive in rubber industry and as a coating agent of metallic surfaces. **15** is volatile, it is present in waste water of rubber additive plants; its toxicity is harmful for the environment. The complexation of **15** by β-CD is very promising for the environment protection.

The ability of CDs to form inclusion complexes may be of use in analytical chemistry due to change of physical properties of guest molecules upon complexation. As an example may serve the flow injection spectrofluorometric method [40, 41] for determination of dequalinium chloride **16** in tablets and in serum. Compound **16** is an antibacterial and antifungal drug used in pharmaceuticals in infections of mouth and throat, as well as in cosmetics of oral hygiene.



15



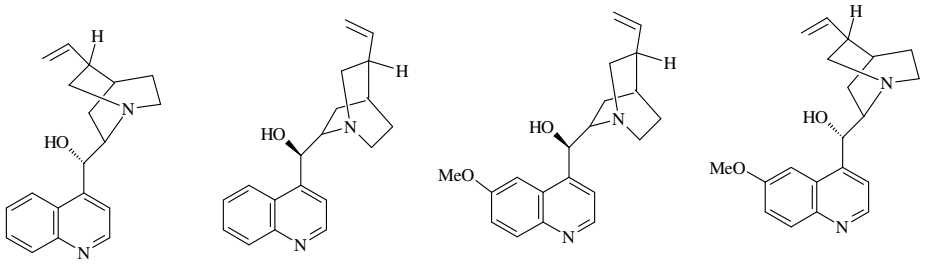
16

When β-CD is added to aqueous solution of **16**, a strong increase of fluorescence intensity occurs, this fact enabling the above analysis [42]. In this process β-CD forms with **16** the 1:1 inclusion complex.

Inclusion complexes of β-CD, DM-β-CD, *i.e.* heptakis(2,6-di-*O*-methyl)-β-CD and TM-β-CD, *i.e.* heptakis(2,3,6-tri-*O*-methyl)-β-CD with four cinchona alkaloids **17–20** were investigated [43]. Cinchona alkaloids **17–20**, *i.e.* cinchonine **17**, cinchonidine **18**, quinine **19** and quinidine **20** are antimalarial drugs; moreover quinidine **20** is useful as a sodium channel blocker in the treatment of cardiac arrhythmias.

Cinchona alkaloids **17–20** are encapsulated in CD cavity in acidic medium and may be released in a neutral medium; therefore β-CD, DM-β-CD and TM-β-CD may serve as carriers for these drugs [44].

The inclusion of **17–20** into CD cavities improves their water solubility. It is known that methylated β-CDs, such as DM-β-CD or TM-β-CD have a deeper cavity than native β-CD, therefore methylated β-CDs are more efficient receptors for cinchona alkaloids than β-CD.



17 **18** **19** **20**

CDs protect **17–20** at acidic pH, since CDs bind **17–20** more strongly at acidic pH (like that of the gastric acid), and release **17–20** at neutral pH (like that of serum). The explanation of this fact involves hydrogen bond interactions. At acidic pH the nitrogen atoms of **17–20** are protonated, and show strong hydrogen bond interactions with numerous oxygen atoms of CDs. At neutral pH however, these hydrogen bonds are weaker due to deprotonation, and as a result the binding between host and guest decreases.

Conclusion

Chemistry of CDs is a rapidly developing research area, this fact having its reflection in numerous works [45, 46]; among them those concerning CD inclusion complexes with drugs deserve a special attention [47-50]. The present paper is not meant to be exhaustive, but simply highlights the main features of CDs useful as drug carriers.

References

1. J. Szejtli, *J. Incl. Phenom. Macrocycl. Chem.,* 2005, **52**, 1.
2. J. Szejtli, *Pure Appl. Chem.,* 2004, **76**, 1825.
3. H. Dodziuk, A. Ejchart, W. Anczewski, H. Ueda, E. Krinichnaya, G. Dolgonos, W. Kutner, *Chem. Commun.,* 2003, 986.
4. W.S. Cai, Y.M. Yu, X.G. Shao, *J. Mol. Model.,* 2005, **11**, 186.

5. W.S. Cai, X.X. Yao, X.G. Shao, Z.X. Pan, *J. Incl. Phenom. Macrocycl. Chem.,* 2005, **51**, 41.
6. E. Luboch, Z. Poleska-Muchlado, M. Jamrógiewicz, J.F. Biernat, *Cyclodextrin Combinations with Azocompounds,* in: *Macrocyclic Chemistry, Current Trends and Future Perspectives,* K. Gloe (ed.), Springer; Dordrecht–Berlin–Heidelberg–New York, 2005, 203.
7. K. Kano, R. Nishiyabu, R. Doi, *J. Org. Chem.,* 2005, **70**, 3667.
8. A.J. Baer, D.H. Macartney, *Org. Biomol. Chem.,* 2005, **3**, 1448.
9. A. Douhal, *Chem. Rev.,* 2004, **104**, 1955.
10. S. Funasaki, S. Ishikawa, S. Neya, *J. Phys. Chem.,* 2004, **108B**, 9593.
11. N. Funasaki, *J. Incl. Phenom. Macrocycl. Chem.,* 2004, **50**, 43.
12. A. Koralewska, W. Augustyniak, A. Temeriusz, M. Kańska, *J. Incl. Phenom.,* 2004, **49**, 193.
13. J. Bascuas, L. Garcia-Rio, J.R. Leis, *Org. Biomol. Chem.,* 2004, **2**, 1186.
14. T. Girek, W. Śliwa, *Chemistry of Cyclodextrins*, Jan Długosz University of Częstochowa, 2006.
15. W. Śliwa, *Cyclodextrins,* Pedagogical University, Częstochowa, 2001.
16. W. Śliwa, T. Girek, *Chem. Heterocycl. Compounds,* 2005, 1603.
17. W. Śliwa, T. Girek, *Prace Naukowe Wyższej Szkoły Pedagogicznej w Częstochowie, Chemia i Ochrona Środowiska (Pedagogical University Issues, Chemistry and Environmental Protection),* 2005, **9**, 77.
18. W. Śliwa, T. Girek, J.J. Kozioł, *Current Org. Chem.,* 2004, **8**, 1445.
19. W. Śliwa, T. Girek, *Heterocycles,* 2003, **60**, 2147.
20. M.C.D. Manickam, S. Annalakshmi, K. Titchumani, C. Srinivasana, *Org. Biomol. Chem.,* 2005, **3**, 1008.
21. C.J. Easton, S.F. Lincoln, L. Barr, H. Onagi, *Chem. Eur. J.,* 2004, **10**, 3120.
22. N.S. Krishnaveni, K. Surendra, V.P. Kumar, B. Srinivas, C.S. Reddy, K.R. Rao, *Tetrahedron Lett.,* 2005, **46**, 4299.
23. E. Arunkumar, C.C. Forbes, B.D. Smith, *Eur. J. Org. Chem.,* 2005, 4051.
24. 2nd Asian Cyclodextrin Conference, Sapporo, Japan: *J. Incl. Phenom.,* 2004, **50**, 1.
25. O. Csernak, A. Buvari-Barcza, J. Samu, L. Barcza, *J. Incl. Phenom. Macrocycl. Chem.,* 2005, **51**, 59.
26. Y. Xu, M.E. McCarroll, *J. Phys. Chem.,* 2005, **109B**, 8144.
27. W. Anczewski, H. Dodziuk, A. Ejchart, *Chirality,* 2003, **15**, 654.
28. L. Tormo, J.A. Organero, A. Douhal, *J. Phys. Chem.,* 2005, **109B**, 17848.
29. E. Iglesias, *J. Org. Chem.,* 2006, **71**, 4383.
30. E. Iglesias, I. Brandariz, F. Penedo, *Chem. Res. Toxicol.,* 2006, **19**, 594.
31. G.-F. Yang, H.-B. Wang, W.-C. Yang, D. Gao, C.-G. Zhan, *J. Phys. Chem.,* 2006, **110B**, 7044.
32. G.M. Florio, T.L. Werblowsky, T. Miller, B.J. Berne, G.W. Flynn, *J. Phys. Chem.,* 2005, **109B**, 4520.
33. J.-B. Chao, H.-B. Tong, D.-S. Liu, S.-P. Huang, *Spectrochim. Acta,* 2006, **64A**, 166.
34. Y.-L. Shen, S.-H. Yang, L.-M. Wu, X.-Y. Ma, *Spectrochim. Acta,* 2005, **61A**, 1025.
35. M. Shamsipur, A. Yari, H. Sharghi, *Spectrochim. Acta,* 2005, **62A**, 372.
36. H. Li, J. Zhou, F. Tang, G. Yuan, *J. Am. Soc. Mass Spectrom.,* 2006, **17**, 9.

37. V. Gabelica, N. Galic, E. De Pauw, *J. Am. Soc. Mass Spectrom.,* 2002, **13**, 946.
38. K. De Vriendt, K. Sandra, T. Desmet, W. Nerinckx, J. Van Beeumen, *J. Am. Soc. Mass Spectrom.,* 2004, **18**, 3061.
39. F. Zha, R.H. Lu, *Polish J. Chem.,* 2005, **79**, 1461.
40. S. Petr, K.P. Chridtoforos, A.K. Michael, E.E. Constantinos, *Anal. Chim. Acta,* 2001, **438**, 131.
41. M.F.C. Martin, T. Oi Ling, *Anal. Chim. Acta,* 2000, **432**, 229.
42. B. Tang, B. Jia, X. Shi, *Spectrochim. Acta,* 2005, **61A**, 2203.
43. Y. Liu, G.-S. Chen, Y. Chen, F. Ding, J. Chen, *Org. Biomol. Chem.,* 2005, **3**, 2519.
44. O. Dechy-Cabaret, F. Benoit-Vical, C. Loup, A. Robert, H. Gornitzka, A. Bonhoure, H. Vial, J.-F. Magnaval, J.-P. Séguéla, B. Meunier, *Chem. Eur. J.,* 2004, **10**, 1625.
45. M. Jamrógiewicz, J.F. Biernat, *Polish J. Chem.,* 2006, **80**, 753.
46. N. Funasaki, S. Ishikawa, S. Hirota, *Anal. Chim. Acta,* 2006, **555**, 278.
47. D. Bongiorno, L. Ceraulo, M. Ferrugia, F. Filizzola, A. Ruggirello, V.T. Liveri, *ARKIVOC,* 2005, **14**, 118; *Chem. Abstr.,* 2006, **144**, 70029.
48. N. Beheshti, H. Bu, K. Zhu, A.-L. Kjøniksen, K.D. Knudsen, R. Pamies, J.G.H. Cifre, J.G. de la Torre, B. Nyström, *J. Phys. Chem.,* 2006, **110B**, 6601.
49. Y. Yu, C. Chipot, W. Cai, X. Shao, *J. Phys. Chem.,* 2006, **110B**, 6372.
50. C. Galant, A.-L. Kjøniksen, G.T.M. Nguyen, K.D. Knudsen, B. Nyström, *J. Phys. Chem.,* 2006, **110B**, 190.

Barbara Mianowska
Wanda Śliwa

Cyklodekstryny jako przenośniki leków

Streszczenie: W artykule przedstawiono wybrane przykłady kompleksów inkluzyjnych cyklodekstryn z lekami, podkreślając pozytywne zmiany właściwości leków spowodowane ich kompleksowaniem.

Słowa kluczowe: cyklodekstryna, kompleks inkluzyjny, lek, rozpuszczalność