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Evidence of the Existence of 2:1 Guest–Host Complexes between Diclofenac and Cyclodextrins in D_2O Solutions. A ^1H and ^{13}C NMR Study on Diclofenac/β-Cyclodextrin and Diclofenac/2-Hydroxypropyl-β-cyclodextrin Systems

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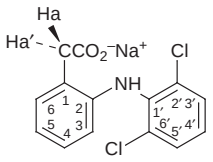
The interaction of diclofenac sodium salt (DCFNa) and two cyclodextrins, β-cyclodextrin (βCD) and 2-hydroxypropyl-β-cyclodextrin (HPβCD), studied in D_2O solution with different NMR techniques (^1H, ^{13}C NMR, ROESY experiments, NMR titrations), shows the existence of multiple equilibria involving 1:1 and 2:1 guest–host complexes.

β-Cyclodextrin (βCD) and its derivative 2-hydroxypropyl-β-cyclodextrin (HPβCD) belong to a class of torus shaped molecules, which can form supramolecular complexes with a variety of guests.[1,2] This inclusion process can be exploited in the pharmaceutical field to enhance the stability and solubility of drugs.



2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid, diclofenac, is widely employed as non-steroidal anti-inflammatory drug and the interaction of its sodium salt (DCFN a) with βCD has been studied both in solution[3,4] and in the solid state.[5] To improve the solubility, stability and bioavailability of drugs,[6] an alternative to βCD is HPβCD, that enables toxic effects of parenteral application to be avoided.[7]

The two systems DCFNa/HPβCD and DCFNa/βCD were first studied through the observation of ^1H and ^{13}C NMR complexation shifts (Tables 1 and 2, see full text) but the results were contradictory. The proton shifts seemed to suggest a stronger interaction between DCFNa and βCD than between DCFNa and HPβCD, whereas the carbon shifts seemed to suggest a weaker interaction.

A rotating-frame Overhauser effect (ROESY) study was then undertaken in order to gain further information of the supramolecular interactions. The ROE study on the DCFNa/HPβCD system (Fig. 2) shows that both rings are involved in the complexation process but the dichlorophenyl ring is preferentially included, because the intermolecular ROEs between the dichlorophenyl moiety and HPβCD are higher than those between HPβCD and the aromatic protons of the phenylacetate group. A similar but clearer situation is found for the DCFNa/βCD system (Fig. 3). In this case, the C-4′/4′-H side of the dichlorophenyl ring of DCFNa enters the cyclodextrin cavity through the secondary hydroxy rim (case **c** Scheme 1). It is less easy to understand what happens to the phenylacetate ring. 3-H and 4-H of DCFNa appear to be close to 3-H of βCD (3-H closer than 4-H) whereas

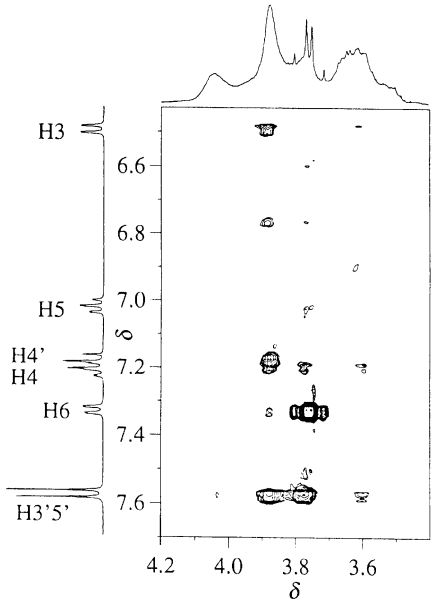


Fig 2 ROESY spectrum obtained at 1:1 DCFNa/HPβCD molar ratio in D_2O solution with a mixing time of 200 ms

6-H of DCFNa seems nearer to 5-H than to 3-H of βCD and 5-H of DCFNa give only very low ROE cross-peaks. These results cannot be readily interpreted on the basis of a unique structure and strongly suggest the presence of different 1:1 complexes in solution or mixtures of complexes of different stoichiometry.

Further information on stoichiometry can be derived from NMR titrations. The complexation process was monitored through the measurement of ^1H and ^{13}C complexation shifts of DCFNa, in the DCFNa/HPβCD system, owing to the complexity of HPβCD spectra. A more classical approach was instead used in the DCFNa/βCD system monitoring the changes of ^1H and ^{13}C chemical shifts of βCD upon addition of DCFNa. From these data the presence of multiple equilibria involving both 1:1 (GH) and 2:1 (G_2H) guest–host species can be observed in both systems. G_2H complexes are rather unusual for β-cyclodextrins but they have been isolated for troponoids.[22] The complexation shifts were simulated using different approaches (details are given in the Appendix, see full paper). K_{11} values of 310, 260 and 234 $dm^3\,mol^{-1}$

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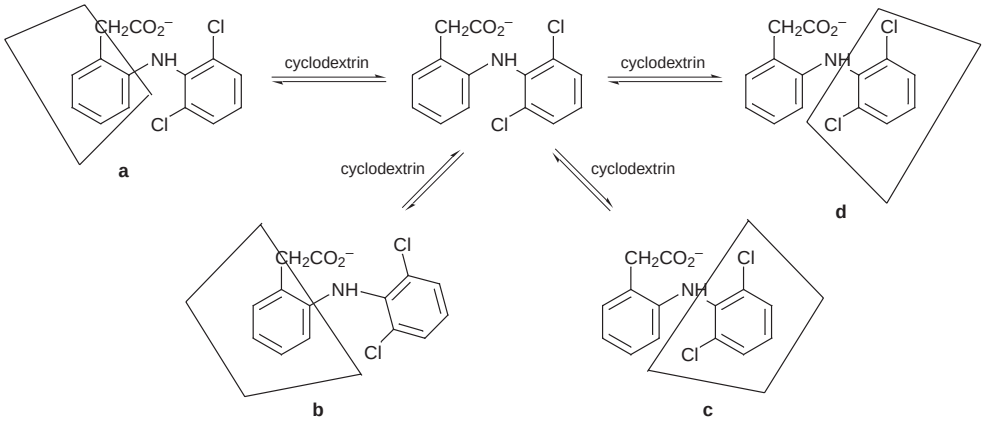

Scheme 1 Possible relative host–guest orientations of cyclodextrins and DCFNa in 1:1 inclusion complexes

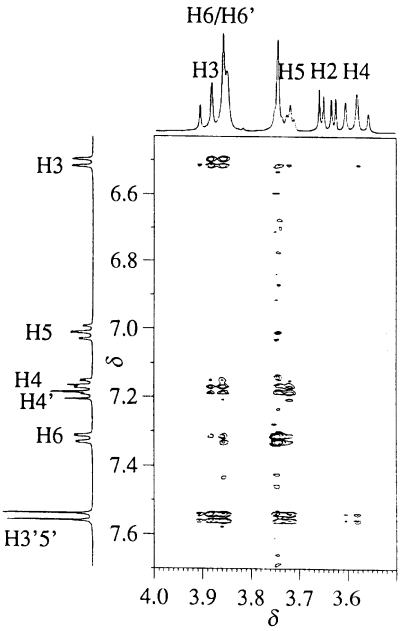

Fig. 3 ROESY spectra obtained at 2:1 DCFNa/βCD molar ratio in D_2O solution with a mixing time of 200 ms. The singlet at δ 3.75 (partially overlapped to the βCD HS) is due to DCFNa methylene protons which remain isochronous in the presence of βCD.

were obtained applying models, A, B and C, respectively, whereas K_{21} was found to be *ca.* 50 $dm^3\,mol^{-1}$. Δv^{lim} for GH and G_2H complexes have the same relative sign for all carbons (except C-5), but opposite sign for all protons (except 3-H). For the DCFNa/βCD system, K_{11} (170 $dm^2\,mol^{-1}$ and K_{21} (22 $dm^3\,mol^{-1}$) are lower than those obtained in DCFNa/HPβCD system, indicating a lower complexation ability of βCD towards DCFNa. This is probably a consequence of the higher rigidity of the βCD cavity with respect to that of HPβCD, where the original hydrogen bond framework is partially disrupted by hydroxypropyl groups.

An exchange process was also observed for the CH_3 signal of HPβCD, probably related to a conformational adjustment of the HPβCD ring induced or, more likely, slowed down by the interaction of the two DCFNa molecules in the 2:1 complex DCFNa/HPβCD.

This study shows that for these two systems, carbon complexation shifts and nuclear Overhauser experiments should be preferred when possible, to proton complexation shifts. As far NMR titrations, it should be underlined that the presence of G_2H species in solution would have probably been neglected if only the strongly shifted signals (*e.g.* dichloroaminophenyl carbons) had been taken into account in the DCFNa/HPβCD system.

Techniques used: ^1H and ^{13}C NMR, ROESY-TPPI, NMR titrations

References: 26 Tables: 2 Figs: 12

Appendix: Elucidation of complexation constants

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References cited in this synopsis

1 G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 803.
2 V. T. D'Souza and K. B. Lipkowitz, *Chem. Rev.*, 1998, **98**, 1741.
3 D. V. Whittaker, L. J. Penkler, L. A. Glintenkamp, M. C. B. van Oudtshoorn and P. L. Wessels, *J. Incl. Phenom.*, 1996, **25**, 177.
4 S. Astilean, C. Ionescu, G. Cristea, S. I. Farcas, I. Bratu and R. Vitoc, *Biospectroscopy*, 1997, **3**, 233.
5 M. R. Caira, V.-J. Griffith, L. R. Nassimbeni and B. van Oudtshoorn, *J. Chem. Soc., Chem. Commun.*, 1994, 1061.
6 M. Otagiri, T. Imai, N. Matsuo and K. Uekama, *Acta Pharm. Suec.*, 1983, **20**, 1.
7 F. Leroy-Lechat, D. Wouessidjeve, J. P. Andreux, F. Puisieux and D. Duchêne, *Int. J. Pharm.*, 1994, **101**, 97.
20 D. Neuhaus and M. P. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH, New York, 1989.
22 H. Takeshita, M. Kumamoto and I. Kouno, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1006.
25 A. A. Bothner-BY, R. L. Stephens, J.-M. Lee, C. D. Warren and R. W. Jeanloz, *J. Am. Chem. Soc.*, 1984, **106**, 811.