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Analytical Survey

Cyclodextrins as versatile chiral recognition reagents for use in a variety of optical and separative analyses

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Abstract: A short overview is presented covering the actual and potential use of cyclodextrins and some of their derivatives in analytical chemistry. The contributions in separation science, including HPLC, GC, CE and MEKC are noted, together with applications in circular dichroism and luminescence techniques, including fluorescence and phosphorescence.

Keywords: *Cyclodextrin; HPLC; capillary electrophoresis; GC; fluorescence; luminescence; photophosphorescence; circular dichroism.*

Introduction

It has been noted that β-cyclodextrin appears in connection with a variety of widely differing analytical techniques, such as circular dichroism, chromatography of enantiomers and luminescence [1].

Circular dichroism (CD), that is the measurement of the difference in absorption of light between left- and right-handed polarized light, can be used for the direct determination of L-cocaine in street drug samples with minimal sample preparation [2]. Even though the usual additives, lidocaine, procaine and benzocaine contain a benzene chromophore and absorb in the same spectral region, they do not interfere with the CD measurement because they are non-chiral. Lactose, the common diluent, is chiral but it does not absorb in the same region and is not CD-active. Opium alkaloids are also CD-active [3].

In the search for even greater specificity Purdie and co-workers have examined solute-induced CD-spectropolarimetry; for example, using β-cyclodextrin it was possible to identify cocaine and phencyclidine [4]. The same co-solute has been used with a great variety of achiral drugs and assays developed for meperidine in tablets [5] and seconal sodium suppositories [6]. The problems of interference in the determination of achiral analytes have also been discussed [7].

Cyclodextrins in Chiral Discrimination

Since great differences exist between the physiological properties of enantiomeric forms of drugs, considerable interest in the quantitative resolution of racemates [8] has been expressed during the past decade. Cyclodextrins, which have been utilized for many years in the conventional resolution of racemates and for chiral induction in organic synthesis [9] have now been used to form bonded stationary phases for use in high-performance liquid chromatography [10, 11]. Using such phases it is now possible to obtain excellent separations of diastereomers and of individual isomers for a range of drugs [10] such as prostaglandins, vitamin D_2, and sterols, as well as for general chemicals [11], mycotoxins, polycyclic aromatic hydrocarbons, quinones and heterocyclic compounds [12], dansyl amino acids, barbiturates [13] and isomers of disubstituted benzene derivatives [14]. Methylated β-cyclodextrin-bonded stationary phases show superior resolution compared to unmodified β-cyclodextrin for disubstituted benzene derivatives [15] which may also be resolved via α- and β-cyclodextrin inclusion complexes using reversed-phase HPLC [16]. The advantage of a β-cyclodextrin bonded chiral stationary phase compared to other chiral stationary phases is in its ability to function with highly polar mobile phases [17].

The separation of metallocene enantiomers of iron, ruthenium and osmium has also been reported [18] and is of particular interest to inorganic chemists.

The formation of inclusion compounds of γ-cyclodextrin with chemical preservatives, herbicides, polycyclic aromatic hydrocarbons, phthalic acid esters, organochlorine and organophosphorous insecticides and PCBs, has been shown to be valuable in the solvent extraction clean-up of a variety of food samples [19]. The polarographic assay of cyclodextrins in turbid dextrin mixtures may be achieved using linoleate–cyclodextrin complex formation, which does not react in the lipoxygenase reaction [20].

The induction of circular dichroism and the ability to separate racemates are attributable to the bonding and structural properties of the cyclodextrins, which are cyclic sugar molecules formed by the degradation of starch. Their doughnut-shaped assemblies have different internal diameters, depending on the number of glucose residues which are linked together [21]. The β-cyclodextrin molecule contains, for example, 35 stereogenic centres and guest solutes that can interact via van der Waals forces with its hydrophobic cavity. In most cases the binding in the cavity is too symmetrical to induce large enantioselectivity and other points of interaction are necessary to achieve chiral recognition. β-Cyclodextrin has a C_7 symmetry axis and 14 hydroxyl groups around the mouth of the cavity, seven clockwise and seven counter-clockwise; the opposite rim has seven primary hydroxyl groups, hence a number of potential interactions are possible between these and a guest enantiomer in addition to any repulsive steric interactions [22]. Dalgliesh was the first to enumerate the three-point interaction requirement of a stationary phase–solute interaction to achieve stereochemical specificity [23] and hence optical resolution.

Chiroptical Spectroscopy and Luminescence Techniques

The chirality of cyclodextrin is also a vital feature in the induction of circular dichroism, with the additional requirement that the guest molecule must contain a chromophore. Hence circular dichroism can be used to determine achiral drugs. Cyclodextrins acting as hosts also enhance the luminescence properties of selected molecules which can form inclusion complexes [24]. Fluorescence is enhanced by shielding the excited singlet species in the dextrin cavity from the quenching and non-radiative decay processes which take place in free solution. Phosphorescence, which occurs from the triplet state, is completely quenched for molecules in solution, but may be observed in solids or from other highly ordered media [25]. Cyclodextrins provide suitable microscopically ordered media to permit phosphorescence from excited molecules held within the cavity, particularly in the presence of heavy-atom-containing species, which promote the rate of inter-system crossing, singlet to triplet. Methods have been developed for the determination of polynuclear aromatic hydrocarbons [26], nitrogen heterocycles and bridged biphenyls [27] and a variety of licit and illicit drugs [28]. Sensitized room-temperature biacetyl phosphorescence via molecular organization of donors such as polynuclear aromatic hydrocarbons ensuring close proximity to the acceptor, biacetyl, in the cyclodextrin host has been demonstrated [29]. The size of the cyclodextrin cavity affects the sensitization [30] and also fluorescence enhancement of hallucinogenic drugs, such as mescaline and ibogaine [31]. Sample preparation procedures for the measurement of true fluorescence enhancement using cyclodextrins and micelles have been described; these avoid the possible effects of enhanced concentration via solubilization [32]. β-Cyclodextrin has also been shown in micelle-enhanced chemiluminescence to be useful in the determination of biological reductants using Lucigenin [33].

Future Perspectives

To date, the major interest in analytical applications of organized molecular assemblies has been focused on micelles, reversed micelles and micro-emulsions [34]. Further work by Armstrong *et al.* [35, 36] on the application of cyclodextrins and their derivatives for the separation of enantiomers in HPLC has extended the range of application of these important molecules. Moreover, König's group [37] has demonstrated the valuable use of derivatized cyclodextrins as media in gas chromatography separations. More recently, Terabe *et al.* [38, 39] have demonstrated the separation of enantiomers using cyclodextrins added to the buffer in capillary electrophoresis

and micellar electrokinetic chromatography. This brief survey of some applications of cyclodextrins should indicate the potential of other homogeneous yet micro-structured media in many areas of analytical chemistry.

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