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INCLUSION, COMPLEXATION AND EFFICIENT ENANTIOMERIC DISCRIMINATION BY REGIOSPECIFIC OVERMETHYLATION OF A DIMETHYL-β-CYCLODEXTRIN

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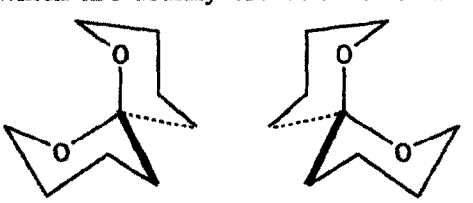
Summary
An unsymmetrically methylated β-cyclodextrin was prepared and allowed the chiral discrimination of the volatile included compound 1,7 dioxaspiro(5,5) undecane 1.

The resolution of racemates by the formation of diastereoisomeric inclusion complexes might offer two major advantages :
- It can be of wide scope, not just limited to enantiomers able to form a salt or an ester with the chiral resolving agent.
- This type of combination may allow an easy recovery of the resolving agent.
Cyclodextrins (CD) have a natural chirality due to both, sugar intrinsic chirality and to the conformation of the cyclodextrin cycle. The large number of stereogenic centers and the chiral conformation are not sufficient to achieve effective enantiomeric discrimination in solid state complexation. It should be pointed out that the chiral resolution, in solid state, recently described[1] is not total, both enantiomers being present at different positions. We recall that an important success of chiral resolution is the use of chromatography on cyclodextrins or modified cyclodextrins stationnary phase[2-5].
We are studying the preparation of inclusion complexes of pheromones in modified cyclodextrins. Inclusion complexes of pheromones are of interest since they can provide a continous source of pheromones which are usually too volatile for a practical use in agriculture.
1,7-Dioxaspiro(5,5) undecane 1 (Scheme 1) is the main component of the Dacus Oleae pheromone. This is one of the rare cases where both enantiomers are active as a pheromone but they exhibit a different qualitative and quantitative biological behaviour : R(-)1 is a long range attractant for males. S(+)1 is an arrestant for females[6].



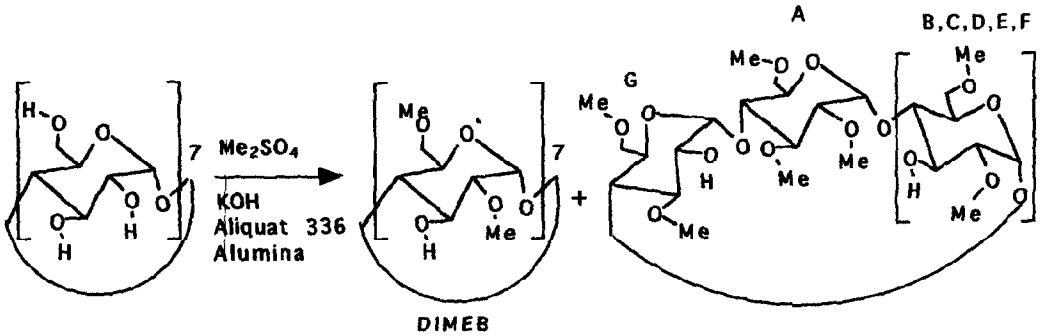
Scheme 1 : Enantiomers of 1,7-dioxaspiro(5,5) undecane 1

This compound has a two fold symmetry axis[7,8] and presents an intrinsic chirality. It has been the object of intensive studies both in laboratory and field experiments We present here the formation of inclusion complex obtained between 1 and a partially methylated CD derivative.

The synthesis of heptakis (2,6-di-O-methylated)-β-CD has been attempted by using solid-liquid phase transfer catalysis [9,10]. These conditions are simple, cheap and avoid the use of dipolar aprotic solvents.

The obtained product (Scheme 2) is a mixture of methylated derivatives which has been used to complex the racemic form of pheromone 1 in alcoholic solutions[11].

Scheme 2 : Alkylation of β-CD under solid-liquid PTC conditions.



The ^{1}H-NMR spectra of the isolated complex (Bruker 270MHz, $CDCl_3$, TMS) showed a 1:1:1 complex of a cyclodextrin derivative, a pheromone, and one molecule of solvent (ethanol or methanol).

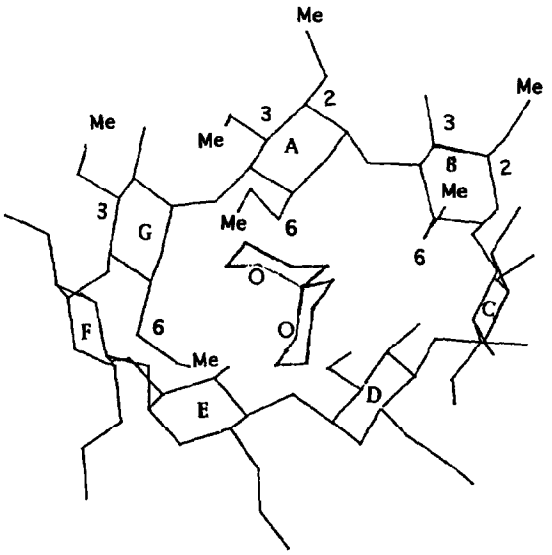
The pheromone isolated from the inclusion complex was the S(+) enantiomer (Ee : 96%).

The X ray crystal study[12] of the complex reveals several original achievements (Schemes 2 and 3) :

- Only one enantiomer of 1 is present on the Fourier difference maps. This enantiomer is of S configuration.
- To the best of our knowledge, it is the first crystallographic structure of an unsymmetrical (point modification) CD. The CD molecule differs from the expected heptakis(2,6-di-O-methyl)-βCD in two aspects :
- An additional methyl group has been introduced in position 3 on one residue (A).
- The glycosidic residue (G) next to the 2,3,6-tri-O-methylglucosyl-residue is methylated in position 3 instead of position 2

It is one of the rare case of an unambiguous (free of disorder) determination of the molecular structure of a volatile and liquid guest molecule which is also chemically inert.

The X ray crystal structure determination has shown without ambiguity the position of all the atoms of 1 within the CD cavity. The characteristics of the guest atoms (height of the peaks in the electron density, thermal motion parameters, etc...) are close to those of CD atoms. No disorder is detectable for the guest molecule The central spiranic atom is located very near (0,35 A) the center of the cyclodextrin glycosidic oxygen heptagon which is almost planar. The two fold axis of the guest lies on this plane.



Scheme 3 View of the complex from the secondary face. (Sybyl, Evans and Sutherland). The methyl groups (Me) in position 2, 3 and 6 are labelled for residue B, A and G. The molecule of methanol which was detected by NMR is not represented. It is located outside of the cavity. (between the units of CD).

Thus we are in presence of a real monomeric structure with one supramolecule of cyclodextrin-pheromone complex in the unit cell. It is a remarkable fact that this discrimination does not implicate any H bond. The Van der Waals contact between the additional methyl group of residue A, directed towards the cavity, and one of the oxygen atoms of 1, seems to play an important role in chiral resolution, clearly this methyl group greatly contributes to the complementarity of the host- guest association.

Although, the isolated yied was low, the procedure is considerably cheaper and simpler than the asymetric syntheses of 1[13-14].

The precise origin of the chiral discrimination needs further studies. Another overmethylated CD have been previously isolated as its per-benzoylated derivative and studied by NMR[15]. Efforts are under way to compare this product with the presently described molecule. Unsymmetricals CD might be useful knew tools for chiral resolution.

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10. A mixture of β-CD hydrate (2.70g, 2mmol), alumina 1g, finely ground potassium hydroxyde (2.28, 40mmol), aliquat 336 (mostly trioctymethylammonium chloride, 0,3g) was vigourously shaken for 10 min at room temperature. Dimethyl sulfate 3.80g, 30mmol) in 2 ml toluene was added within 5 min. The mixture was shaken for 4h then water 5ml was added. The mixture was extracted with methylene chloride (2x15ml) and washed with water (2x5ml). After drying, the methylene chloride solution was evapored to afford the crude methylated cyclodextrin (2,3 g) as a glass.
11. The crude mixture of methylated derivatives was dissolved in CH_3OH (10ml) and 1,7-Dioxaspiro(5,5)undecane 1 (0.625g, 4mmol) was added the solution was boiled a few minutes. The hot solution was introduced immediatly in a Dewar. The crystals (270mg) were separated by filtration. Yield : 8% (based on the starting β-CD). The crystals were disolved in water 5ml, and introduced in a micro-distilation apparatus. About half of the solution was distillated under partial vacuo (150mm). The distillate was extracted by diethylether(2x5ml) dried on sodium sulfate and evaporated under vacuo without heating. The isolated pheromone : 19mg, was disolved in pentane. $[\alpha]_D^{22} = +118$ (c=0.026) ; Lit[13] $[\alpha]_D^{23} = +123$ (c=0.234).
12. The best crystal was mounted in a capillary glass. Final value of refinement : R= 0.078. The complete crystallographic description will be published elsewhere.
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