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Dedicated to Prof. József Szejtli on the occasion of his 60th birthday

INVESTIGATION OF THE CYCLODEXTRIN COMPLEXES OF MANDELIC ACID DERIVATIVES

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Abstract

Racemic free mandelic acid and its methyl, ethyl, isoamyl and benzyl esters were found to form inclusion complexes with all the three studied natural cyclodextrins proved by thermoanalytical results. Differences between the solid state stability of guests were detected mainly by evolved gas analysis. Even signs of an eventual optical resolution by molecular inclusion were observed in several cases, but still not sufficiently proven. Due to the rather high volatility and low melting points of the majority of guest substances DSC technique was found to be suitable for studying the cyclodextrin complexes of mandelic acid.

Keywords: cyclodextrin complexes, DSC, mandelic acid derivatives

Introduction

The studies on molecular interactions between cyclodextrins and mandelic acid and its derivatives have always been dedicated to the possibility of enantiomer separation of racemic mixtures of different mandelates. The enantiomer separations of mandelates have been carried out primarily by using cyclodextrins as chiral recognition sites in different chromatographic systems and also by the enantioselective crystallization of solid cyclodextrin mandelate inclusion complexes.

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Harata reported on the successful optical resolution of racemic mandelic acid via cyclodextrin complex formation employing enantioselective crystallization [1]. It has been found that the two optical isomers can be crystallized separately when complexed by hexakis 2,3,6-tri-*O*-methyl-α-cyclodextrin.

The detailed crystal structure of *L* and *D*-mandelic acid permethyl-α-cyclodextrin complexes was described also by Harata *et al.* [2], even explaining their mode of inclusion into the CD cavity by the induced fit theory. In the *L*-mandelic acid complex the phenyl group is entrapped inside the permethyl-α-CD cavity, while the hydroxyl and carboxyl groups of the mandelic acid protrude from secondary side of the cyclodextrin. In the *D*-mandelic acid complex the guest molecule itself is hydrogen bonded to the oxygen atom of C2 of methylated α-CD. By the comparison of the two structures it has been suggested that the molecular inclusion of the guest induces a conformational change of the host molecule to accomodate *L* or *D*-mandelic acid more properly within the CD-cavity.

Sato and Suzuki successfully resolved racemic mandelic acid via selective cyclodextrin complexation followed by Sephadex gel chromatography [3].

Number of chromatographic methods have been published employing cyclodextrins either in eluents [4–6] or in the stationary phases [7–10] for the enantiomer separation of mandelic acid.

Hattori and Takahashi studied the asymmetric reduction of aromatic keto-acids. For instance the selective reduction of benzoyl-formic acid as substrate was studied in presence of different parent and chemically modified (taylor-made) cyclodextrins [11]. A 100% yield was reported for mandelic acid when it was previously complexed with 6-monodeoxy-amino-β-cyclodextrin.

The solid state characteristics of α-, β- and γ-cyclodextrin complexes of mandelic acid and its derivatives have not yet been studied in details. The present paper reports on the result of thermoanalytical investigations of the crystalline complexes, aiming at the comparison of the thermal stability of the complexes of different mandelates with different cavity size cyclodextrins.

Materials and methods

D,L-mandelic acid methyl ester, *D,L*-mandelic acid ethyl ester, *D,L*-mandelic acid isoamyl ester and *D,L*-mandelic acid benzyl ester were purchased from Sigma Co. St. Louis in analytical purity. Crystalline α-, β- and γ-cyclodextrins were produced by CYCLOLAB Ltd. Budapest. Their purity by HPLC was higher than 99.5%.

The inclusion complexes of mandelic acid and its derivatives were prepared by the solvent-free suspension technology described previously [12], reacting equimolar amounts of both the CD and guests. The mandelic acid content of solid inclusion complexes was determined by UV-spectrophotometry on a Varian DMS 100S UV-VIS photometer.

The TG and DSC runs were recorded in flowing argon (10 $l \cdot h^{-1}$) with 5 $deg \cdot min^{-1}$ heating rate, while in the EGA experiments nitrogen and heating rate of 8 $deg \cdot min^{-1}$ were applied. The initial mass of samples was about 3 mg.

Results and discussion

Composition of the mandelate cyclodextrin complexes

The compositions of solid, dry inclusion complexes of different racemic mandelates with the three parent cyclodextrins are listed in Table 1.

These data indicate that after filtration of the wet cyclodextrin complexes still a little amount of adsorbed guest is present, which can be removed by simple washing with ethanol. This means that in certain cases no 100% molecular encapsulation occurs, thus the cyclodextrin complex formation with the majority of studied mandelic acid esters does not appear to be quantitative.

Thermal behaviour of the solid mandelate/cyclodextrin complexes

The DSC technique is reliable in the characterization of solid free *D,L*-mandelic acid-cyclodextrin complexes. As shown in Fig. 1 the free *D,L*-mandelic acid has an endothermic peak at 122°C representing its melting process. This melting endothermic peak cannot be detected in case of either of the inclusion complexes, which is probably due to the molecular dispersed state of the included mandelic acid, thus due to the complex formation between mandelic acid and α-, β- and γ-cyclodextrins.

Because of the rather low melting point or the liquid state of the majority of the racemic mandelic acid esters involved in this study heat flow curves were not taken for the investigations of their cyclodextrin complexes.

Evolved Gas Analysis (EGA), however, proved to be an appropriate thermoanalytical technique to study the solid state characteristics of the mandelate ester/cyclodextrin complexes. Figure 2 illustrates that the racemic ethyl mandelate forms an incluson complex of moderate stability with α-cyclodextrin. Moreover, it is shown that ethanolic washing removes a small amount of the thermally less stable fraction of guest. Besides, it is visible, that a thermal es-

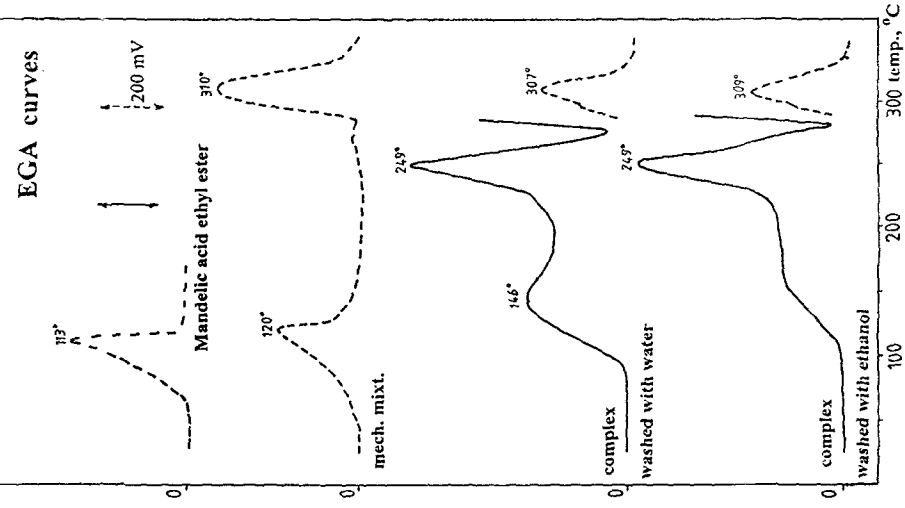

Fig. 2 EGA curves of mandelic acid ethyl ester - α-cyclodextrins

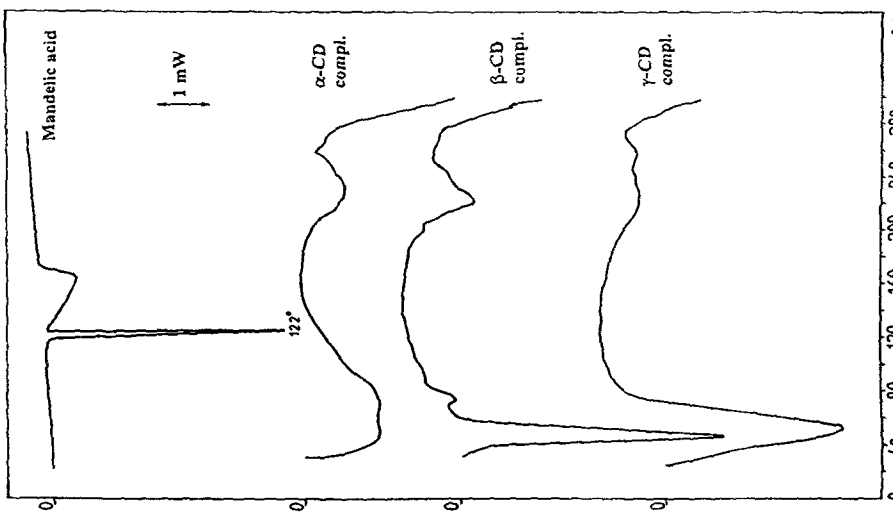

Fig. 1 DSC curves of mandelic acid cyclodextrins

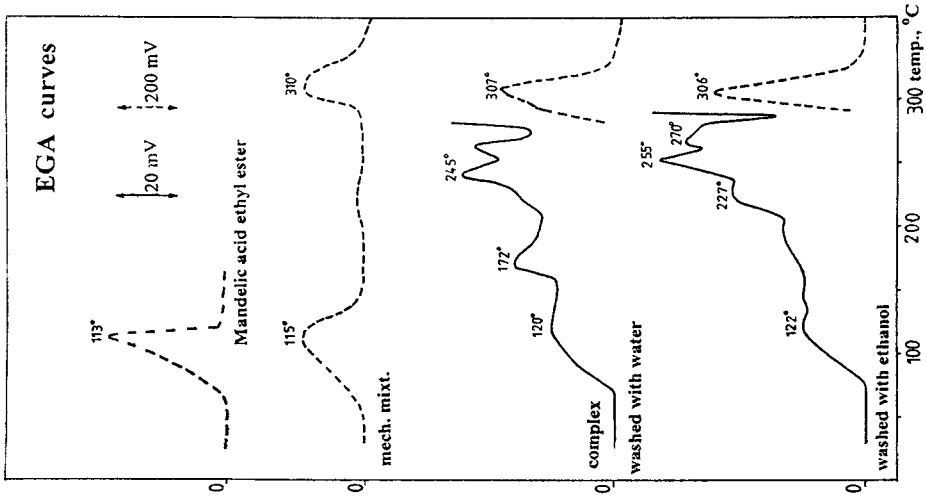

Fig. 3 EGA curves of mandelic acid ethyl ester - β-cyclodextrins

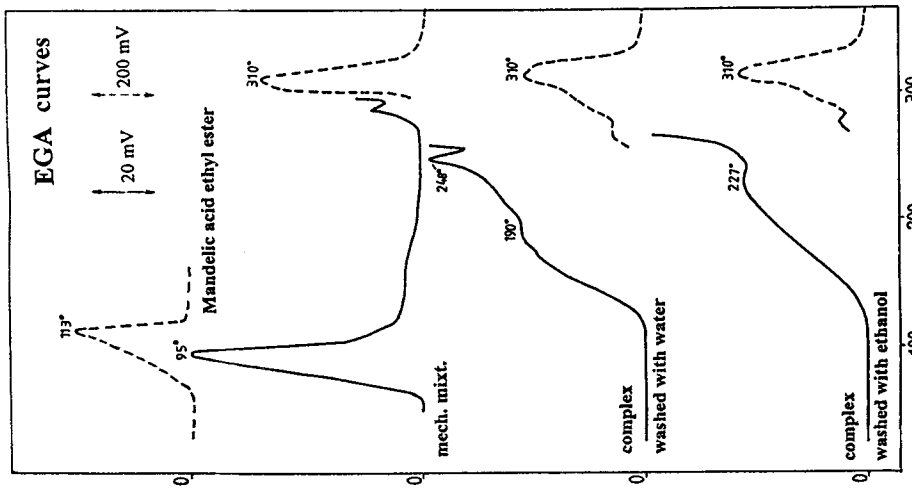

Fig. 4 EGA curves of mandelic acid ethyl ester - γ-cyclodextrins

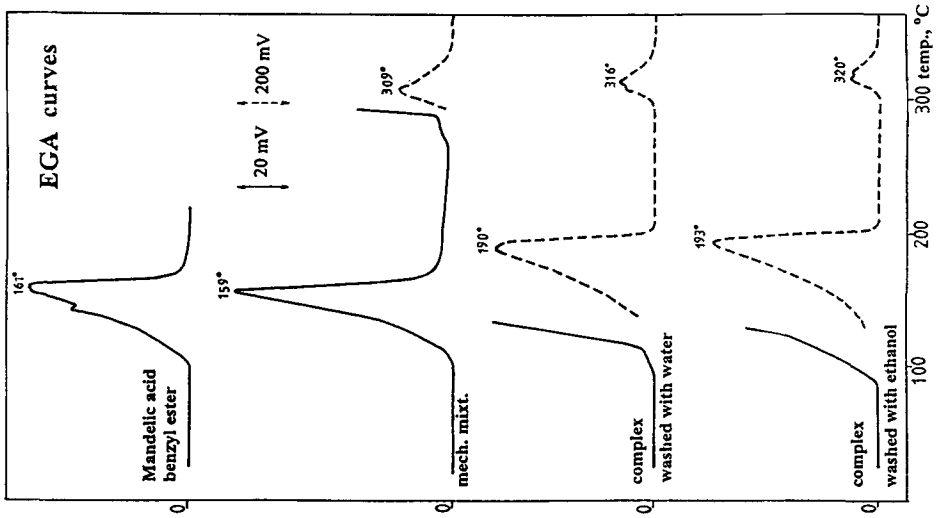

Fig. 5 EGA curves of mandelic acid benzyl ester - β-cyclodextrins

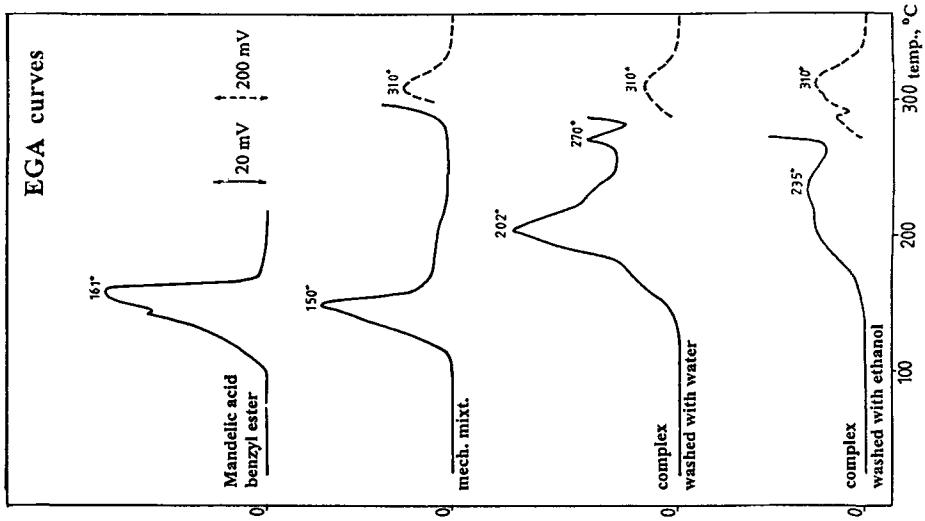

Fig. 6 EGA curves of mandelic acid benzyl ester - γ-cyclodextrins

cape of the complex sample appears at 249°C, which EGA response might be due to the decomposition of the complex still not fully explained. The thermal behaviour of the β-CD complex of ethyl mandelate was found to be different, also a partial molecular entrapment of the guest was detected, furthermore an eventual selectivity in the complex formation is also supposed (Fig. 3). The complexation of the racemic ethyl mandelate by γ-cyclodextrin was found to be complete, since no thermal release of the ester could be detected in the temperature range of 50–100°C, where the free/or adsorbed species got entirely lost. It is still noteworthy that neither aqueous not ethanolic washings removed a part of the input amount of ethyl mandelate (Fig. 4).

Table 1 Composition of inclusion complexes after aqueous and ethanolic washing

Samples	Active ingredient, %	
	Washed with water	Washed with ethanol
Mandelic acid - α-CD	9.9	7.8
Mandelic acid - β-CD	6.5	5.1
Mandelic acid - γ-CD	7.9	7.2
Mandelic acid benzyl ester - α-CD	*	*
Mandelic acid benzyl ester - β-CD	*	*
Mandelic acid benzyl ester - γ-CD	*	*
Mandelic acid ethyl ester - α-CD	10.4	4.2
Mandelic acid ethyl ester - β-CD	11.6	7.1
Mandelic acid ethyl ester - γ-CD	12.7	9.4
Mandelic acid isoamyl ester - α-CD	13.2	7.7
Mandelic acid isoamyl ester - β-CD	12.7	9.8
Mandelic acid isoamyl ester - γ-CD	13.4	9.3
Mandelic acid methyl ester - α-CD	10.2	10.4
Mandelic acid methyl ester - β-CD	11.0	8.0
Mandelic acid methyl ester - γ-CD	11.0	8.1

* Due to the complexation an intense increase of extinction coefficient of benzyl-mandelate was observed, and thus no reliable analytical data can be given for these complexes

Similar thermal behaviour was observed with the other mandelic acid esters, in terms of the effect of washing treatments on the thermal stability of the com-

Table 2 Quantitative evaluation of the thermoanalytical studies of mandelic acid and mandelic acid ester cyclodextrins

Cyclodextrin	Mandelic acid	Benzyl mandelate	Ethyl mandelate	Isoamyl mandelate	Methyl mandelate
α-CD	complexed washing does not affect	complexed washing does not affect	slightly selective complexation washing reduces the thermally less stable fraction	partial complex washing removes free part	probably selective complexation washing does not affect
β-CD	complexed washing does not affect	partial complex washing removes free part	partial complex eventual selectivity washing reduces the amount of guest	partial complex washing removes free part	probably selective complexation washing does not affect
γ-CD	complexed washing does not affect	slightly selective complexation washing affects active content	complexed washing does not affect	complexed washing slightly reduces the amount of guest	probably selective complexation washing reduces the thermally less table fraction

plexes. In the evaluation of the EGA curves of mandelic acid isoamyl ester CD complexes (curves here are not presented) partial complexation was found when in that case where α- and β-cyclodextrins were the host molecules (ethanolic washing removed the free part of the guest). Almost total complexation was observed upon the use of γ-CD. The case of methyl mandelate was found however unique as the cyclodextrin complexation of this substance showed a pronounced selectivity (EGA curves here are not presented). This means that upon the molecular inclusion of methyl mandelate a probable partial enrichment of a given enantiomer takes place, which is indicated by a multistep-type thermal release of the solid complexes during heating. This phenomenon was also seen in the EGA curves of the benzyl mandelate β- and γ-cyclodextrin complexes (Figs 5 and 6). On the basis of the facts mentioned above, further studies are needed to elucidate whether the resolution of the enantiomers of the studied mandelates is possible by cyclodextrin complexation.

Conclusions

The quantitative evaluation of the thermoanalytical studies discussed above are summarised in Table 2.

Other analytical investigations are still needed to elucidate if there is any chance for an eventual possibility of a solid state transesterification upon heating, that would lead to the multistep appearance of the EGA curves. In this case the formation of free alcohol and the corresponding cyclodextrin ester would take place. This is a theoretical possibility as solid state acyl transfer by heating has already been reported by Wernick *et al.* [12].

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Zusammenfassung — *DL*-Mandelsäure und verschiedene (methyl-, ethyl-, isoamyl- und bensylester Derivaten) wurden mit drei natürlichen (α-, β- und γ-CD) Cyclodextrinen komplexiert. Der molekularverkapselte Zustand der Gastmoleküle wurde mittels thermoanalytischen Untersuchungen bewiesen. Es wurde auch festgestellt, dass im Pulverform die Stabilität der Cyclodextrin Komplexe von Mandelsäure und Derivaten wurde mit Evolved Gas Analyse gezeigt, aber noch nicht völlig bewiesen. Infolge der niederen Schmelzpunktbereich der Mandelsäure-ester-Derivaten DSC-Methode war anwendbar nur bei der thermoanalytischen Untersuchung der Cyclodextrin Komplexe der freien *DL*-Mandelsäure.