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β-CD Inclusion Complexes: Relative Selectivity of Terpene and Aromatic Guest Molecules Studied by Competitive Inclusion Experiments

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Abstract. The relative inclusion selectivity of a series of 21 terpene and aromatic guest molecules with regard to β-CD have been measured in an aqueous environment, based on the interaction of 1:1 mixtures of the guest molecule with one equivalent of β-CD. The order for inclusion in β-CD, as determined by a statistical analysis of the total results is (-)borneol (**2**) > terpineol (**21**) > (+)camphor (**4**) > (-)carvone (**11**) = geraniol (**16**) = (±)linalool (**1**) = cineole (**3**) = (-)fenchone (**15**) > (+)isomenthol (**17**) = citral (**13**) = thymol (**10**) > (-)menthone (**19**) > (+)menthol (**18**) > *o*-cresol (**14**) > eugenol (**9**) > (+)limonene (**7**) = (-)bornyl acetate (**8**) > anethol (**12**) = (+)camphene (**5**) > (-)pinene (**6**) > myrcene (**20**). The relative selectivity obtained has little relation to previously measured association constants, but is consistent with selectivities obtained in solution from competition experiments.

Key words: β-cyclodextrin, guest selectivity, terpenes, aromatics, inclusion complexes.

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1. Introduction

The cyclodextrins are a class of cyclic oligosaccharides which are widely used for their ability to form inclusion complexes with a large range of substrate molecules [1]. They have found considerable application for separations in both chromatographic [2] and classical crystallisation techniques [3]. Much effort has been put into obtaining association constants using numerous physical methods [4], however, considerable disagreement exists between the results obtained using different methods on the same guest [5, 6]. We ourselves have observed that inclusion selectivity is extremely dependent on the precise experimental conditions [7, 8], and is in particular highly sensitive to cosolutes [7] or cosolvents [8]. Recently Ueno *et al.* have carried out a series of experiments on the binding of various substrates to modified cyclodextrins in which competition occurs between an environmentally sensitive molecular probe covalently attached to the CD and which is capable of intramolecular inclusion, and a second, 'free' guest molecule [9-11]; *this experiment occurs in the solution state.* In this publication we wish to describe

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the relative inclusion selectivity for a series of 21 terpenoid and aromatic guest molecules, which singly give 1:1 hostguest complexes; *our experiment occurs via precipitation and may be considered to be in the solid state.* The molecules studied are widely distributed in essential oils and information on their relative capacity for complexation will be of considerable use in the cosmetic formulation of CD-complexes. The basic experiment is extremely simple, a 1:1 mixture of two guest molecules was stirred with one equivalent of β-CD at a given rate of stirring, for a constant period of time, at a constant temperature. The resultant inclusion mixture was obtained by filtration, washed with constant volumes of water and ether, and dried under identical conditions. The identical treatment of all experiments rules out any possibility of environmental influence on selectivity. The use of a 21×21 experimental matrix allows some generalisation to be made concerning the results.

Hence:

(a) Complexation varies as alcohols > ketones > phenols > hydrocarbons.
(b) Cyclic systems are more readily complexed than linear systems, except in the case of alcohols.
(c) Little discrimination occurs between mono- or bicyclic molecules.
(d) As evidenced by a comparison of our results and those of Ueno *et al.* [9–11], little differentiation exists between purely solution-based competition based selectivities and those obtained from precipitation/'solid-state' selectivity experiments.

2. Experimental

In order to allow valid internal comparison of the results we decided to adopt a standardised procedure.

2.1. MATERIALS

β-Cyclodextrin was a gift from Roquette. The terpenes, aromatic molecules and DMSO-d_6 were purchased from Aldrich and were used without further purification. NMR spectra were recorded on a Bruker AC 200 Spectrometer (200 MHz).

2.2. METHODS

Determination of the Stoichiometry of the Inclusion Complexes

β-Cyclodextrin (1.25 g; 1.1×10^{-3} mol) was added to 25 mL of water and warmed to 40°C; terpene or aromatic guest molecules (2.2×10^{-3} mol) were added to the solution while stirring and were maintained at 40°C for 1 h. The precipitated complexes thus obtained were filtered, washed with water and diethyl ether, and dried under reduced pressure.

Inclusion Selectivity Measurements

β-Cyclodextrin (2.5 g: 2.2×10^{-3} mol) was added to 50 mL of water and warmed to 40°C. Equimolar mixtures of terpene or aromatic guests (2.2×10^{-3} mol of each) were added to the solution while stirring and were maintained at 40°C for 1 h. The precipitated complexes thus obtained were filtered, washed with diethyl ether, and dried under reduced pressure. The relative selectivity of the complexation of terpenes by β-cyclodextrin was measured by integration of the ^{1}H NMR spectra of the precipitated compounds in DMSO-d_6. Values have a ±5% uncertainty.

Yields of the mixture of inclusion complexes obtained were measured in all cases.

3. Results and Discussion

The structural formulae for the terpenoid and aromatic guests are given in Figure 1; initial binding experiments show formation of 1:1 complexes under our experimental conditions. Table I shows the relative percentages of each guest obtained in the mixture of inclusion compounds formed during the complexation experiment. A random sample of the experiments were repeated and in general the results obtained were identical. In a number of cases, however, certain results appeared to be aberrant (i.e. relative percentages were obtained that were wildly out of line with the relative selectivity obtained in the other 20 complexation experiments for the guest); here the complexation was repeated three times. In all cases the results obtained were identical, but different from the original value. These new values have been used in the analysis.

Typical ^{1}H-NMR spectra obtained for the two guest molecules **6** and **12** and for the inclusion mixture are shown in Figure 2. The use of DMSO as the solvent leads to complete decomplexation and allows easier comparison of the spectra. The accuracy of the results derived from spectral integration is considered to be ±5%. The order of relative inclusion selectivity for the complexation of the series of terpenes with β-CD is (-)borneol (**2**) > terpineol (**21**) > (+)camphor (**4**) > (-)carvone (**11**) = geraniol (**16**) = (±)linalool (**1**) = cineole (**3**) = (-)fenchone (**15**) > (+)isomenthol (**17**) = citral (**13**) = thymol (**10**) > (-)menthone (**19**) > (+)menthol (**18**) > *o*-cresol (**14**) > eugenol (**9**) > (+)limonene (**7**) = (-)bornyl acetate (**8**) > anethol (**12**) = (+)camphene (**5**) > (-)pinene (**6**) > myrcene (**20**).

It may be argued that the values obtained in these experiments simply reflect relative solubilities of the inclusion complexes; however, a comparison of the observed yields shows no correlation with the observed selectivity.

It has been suggested that 1 h is not sufficient to bring the system to equilibrium. This is in fact correct, since long-term selectivity experiments show that divergence of about 5% per 30 days is still occurring after stirring at 40°C for 60 days! However, as all systems were treated equally, this problem may be ignored. Since no variations are observed for samples treated for 1, 2 or 3 h we have chosen to

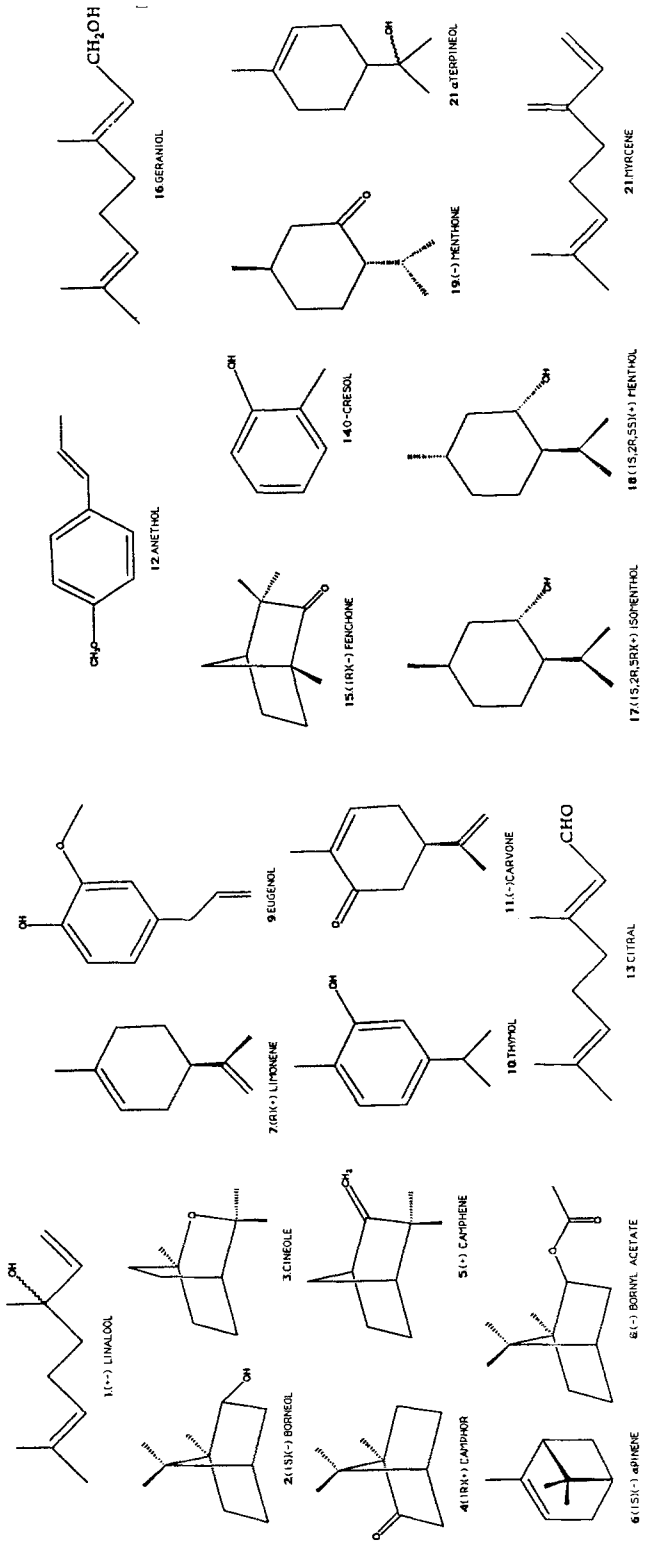

Fig. 1. Structure of terpene and aromatic guests.

TABLE Ia. Relative inclusion selectivities for β-CD/terpene complexes.

	ANETHOL	CITRAL	O-CRESOL	FENCHONE	GERANIOL	ISOMENTHOL	MENTHOL	MENTHONE	MYRCENE	TERPINEOL
LINALOOL	60-40	50-50	70-30	50-50	50-50	60-40	75-25	60-40	90-10	30-70
BORNEOL	75-25	80-20	80-20	70-30	60-40	80-20	75-25	90-10	80-20	80-20
CINEOLE	70-30	50-50	40-60	50-50	60-40	50-50	50-50	60-40	90-10	50-50
CAMPHRE	75-25	80-20	75-25	50-50	60-40	70-30	50-50	60-40	85-15	35-65
CAMPHENE	50-50	40-60	40-60	20-80	25-75	30-70	30-70	40-60	75-25	20-80
PINENE	50-50	30-70	30-70	25-75	25-75	10-90	15-85	15-85	60-40	20-80
LIMONENE	50-50	40-60	50-50	40-60	20-80	30-70	40-60	40-60	75-25	20-80
BORNYL AC	50-50	30-70	50-50	30-70	30-70	35-65	40-60	35-65	60-40	20-80
EUGENOL	50-50	25-75	50-50	35-65	15-85	40-60	40-60	25-75	70-30	10-90
THYMOL	70-30	50-50	50-50	50-50	50-50	40-60	40-60	50-50	70-30	25-75
CARVONE	70-30	60-40	50-50	70-30	60-40	50-50	70-30	70-30	80-20	30-70
ANETHOL	X	25-75	50-50	30-70	20-80	10-90	10-90	25-75	60-40	25-75
CITRAL	75-25	X	65-35	50-50	25-75	40-60	50-50	70-30	85-15	50-50
O-CRESOL	50-50	35-65	X	50-50	50-50	30-70	30-70	40-60	80-20	15-85
FENCHONE	70-30	50-50	50-50	X	60-40	60-40	60-40	70-30	80-20	70-30
GERANIOL	80-20	75-25	50-50	40-60	X	50-50	70-30	60-40	100-0	30-70
ISOMENTHOL	90-10	60-40	70-30	40-60	50-50	X		60-40	90-10	20-80
MENTHOL	90-10	50-50	70-30	40-60	30-70		X	30-70	70-30	15-85
MENTHONE	75-25	30-70	60-40	30-70	40-60	40-60	70-30	X	90-10	20-80
MYRCENE	40-60	15-85	20-80	20-80	0-100	10-90	30-70	10-90	X	0-100
TERPINEOL	75-25	50-50	85-15	30-70	70-30	80-20	85-15	80-20	100-0	X

TABLE Ib. Relative inclusion selectivities for β-CD/terpene complexes.

	LINALOOL	BORNEOL	CINEOLE	CAMPHRE	CAMPHENE	PINENE	LIMONENE	BORNYL AC	EUGENOL	THYMOL	CARVONE
LINALOOL	X	10-90	50-50	50-50	80-20	85-15	75-25	70-30	60-40	60-40	50-50
BORNEOL	90-10	X	50-50	50-50	75-25	80-20	85-15	70-30	60-40	60-40	70-30
CINEOLE	50-50	50-50	X	60-40	85-15	75-25	60-40	80-20	50-50	50-50	50-50
CAMPHRE	50-50	50-50	40-60	X	70-30	80-20	70-30	75-25	70-30	50-50	70-30
CAMPHENE	20-80	25-75	15-85	30-70	X	50-50	40-60	40-60	30-70	30-70	25-75
PINENE	15-85	15-85	25-75	20-80	50-50	X	35-65	50-50	40-60	20-80	20-80
LIMONENE	25-75	15-85	40-60	30-70	60-40	65-35	X	30-70	50-50	30-70	30-70
BORNYL AC	30-70	30-70	20-80	25-75	60-40	50-50	70-30	X	50-50	35-65	30-70
EUGENOL	40-60	40-60	50-50	30-70	70-30	60-40	50-50	50-50	X	50-50	30-70
THYMOL	40-60	40-60	50-50	50-50	70-30	80-20	70-30	65-35	50-50	X	40-60
CARVONE	50-50	30-70	50-50	30-70	70-30	80-20	70-30	70-30	70-30	60-40	X
ANETHOL	40-60	25-75	30-70	25-75	50-50	50-50	50-50	50-50	50-50	30-70	30-70
CITRAL	50-50	20-80	50-50	20-80	60-40	70-30	60-40	70-30	75-25	50-50	40-60
O-CRESOL	30-70	20-80	60-40	25-75	60-40	70-30	50-50	50-50	50-50	50-50	50-50
FENCHONE	50-50	30-70	50-50	50-50	80-20	75-25	60-40	70-30	65-35	50-50	30-70
GERANIOL	50-50	40-60	40-60	40-60	75-25	75-25	80-20	70-30	85-15	50-50	40-60
ISOMENTHOL	40-60	20-80	50-50	30-70	70-30	90-10	70-30	65-35	60-40	60-40	50-50
MENTHOL	25-75	25-75	50-50	50-50	70-30	85-15	60-40	60-40	60-40	60-40	30-70
MENTHONE	40-60	10-90	40-60	40-60	60-40	85-15	60-40	65-35	75-25	50-50	30-70
MYRCENE	10-90	20-80	10-90	15-85	25-75	40-60	25-75	40-60	30-70	30-70	20-80
TERPINEOL	70-30	20-80	50-50	65-35	80-20	80-20	80-20	80-20	90-10	75-25	70-30

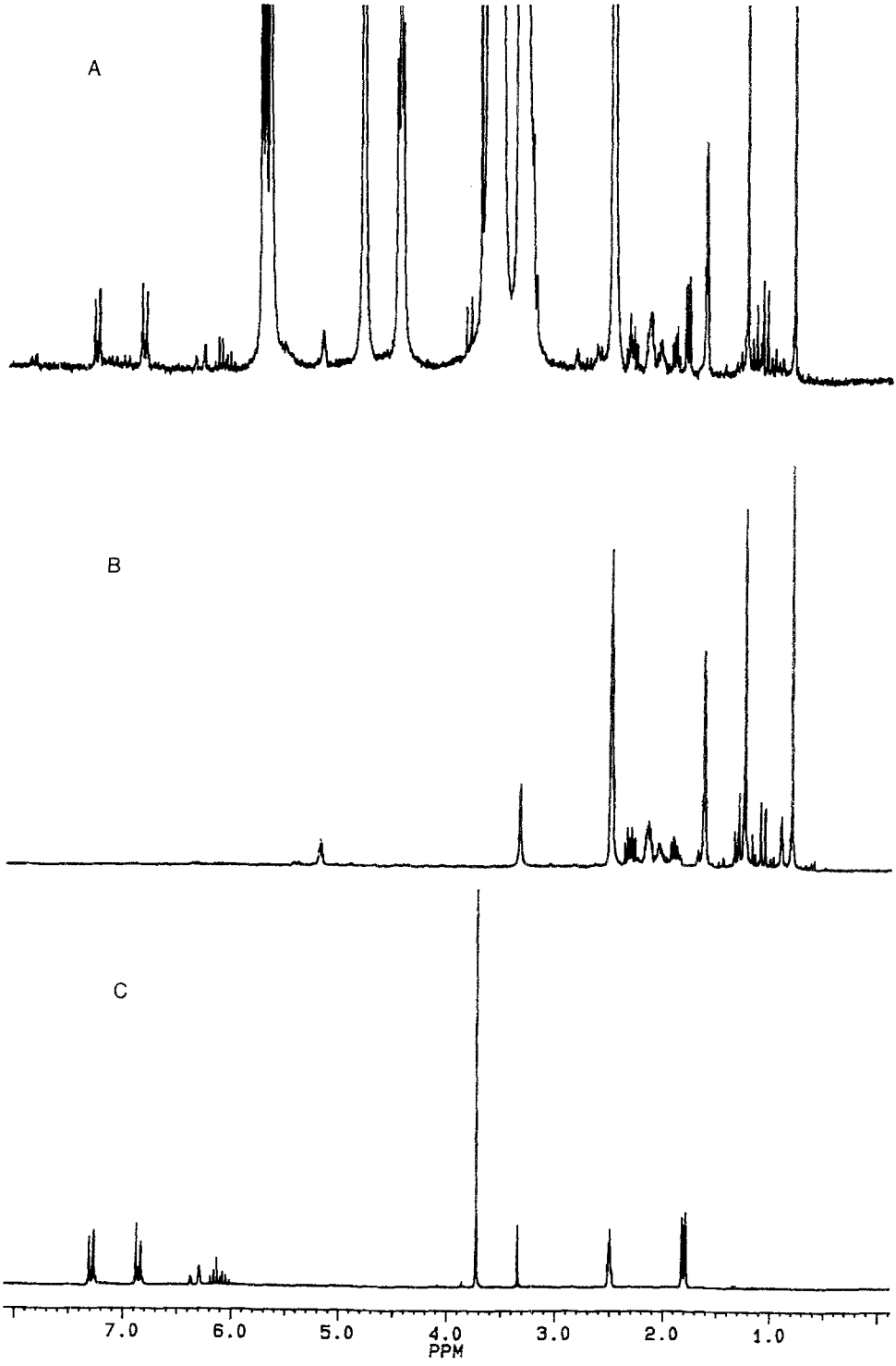

Fig. 2. (A) ^{1}H NMR spectrum of (−)pinene-anethol-β-CD inclusion complex. (B) ^{1}H NMR spectrum of (−)pinene. (C) ^{1}H NMR spectrum of anethol.

TABLE II. Ketones

	Camphor	Carvone	Citral	Fenchone	Menthone
Camphor	X	70-30	80-20	50-50	60-40
Carvone	30-70	X	60-40	70-30	70-30
Citral	20-80	40-60	X	50-50	70-30
Fenchone	50-50	30-70	50-50	X	70-30
Menthone	40-60	30-70	30-70	30-70	X

Table A1. Relative selectivity for ketone mixtures.

	Camphor	Carvone	Citral	Fenchone	Menthone
Camphene	30-70	25-75	40-60	20-80	40-60
Pinene	20-80	20-80	30-70	25-75	15-85
Limonene	30-70	30-70	40-60	40-60	40-60
Myrcene	15-85	20-80	15-85	20-80	10-90

Table A2. Relative selectivity for hydrocarbon/ketone mixtures.

	Camphor	Carvone	Citral	Fenchone	Menthone
Linalool	50-50	50-50	50-50	50-50	60-40
Borneol	50-50	70-30	80-20	70-30	90-10
Geraniol	40-60	40-60	75-25	40-60	60-40
Isomenthol	30-70	50-50	60-40	40-60	60-40
Menthol	50-50	30-70	50-50	40-60	30-70
Terpineol	65-35	70-30	50-50	30-70	80-20

Table A3. Relative selectivity for alcohol/ketone mixtures.

	Camphor	Carvone	Citral	Fenchone	Menthone
Eugenol	30-70	30-70	25-75	35-65	25-75
Thymol	50-50	40-60	50-50	50-50	50-50
O-Cresol	25-75	50-50	35-65	50-50	40-60
Anethol	25-75	30-70	25-75	30-70	25-75

Table A4. Relative selectivity for phenol/ketone mixtures.

	Camphor	Carvone	Citral	Fenchone	Menthone
Cineole	60-40	50-50	50-50	50-50	60-40
Bornyl Ac	25-75	30-70	30-70	30-70	35-65

Table A5. Relative selectivity for miscellaneous/ketone mixtures.

treat the system as static; again we wish to emphasize that in this publication a standardised method is used.

In order to facilitate analysis of the data we have broken down the guest molecules into a number of groups:

Ketones: camphor, fenchone, carvone, menthone, citral. (Tables II: A1, A2, A3, A4, A5.)

A general order of selectivity within the class of ketones is camphor > carvone > fenchone > citral > menthone. It is clear that the ketones have a much higher affinity

for β-CD than both the simple hydrocarbon and the phenolic structures. With regard to the alcohols it would appear that the first three in the series (camphor, carvone, fenchone) have somewhat higher affinities, whilst, citral and menthone have lower affinity.

For the two miscellaneous compounds, ketones are selectively preferred to bornyl acetate; whilst for the bicyclic ether cineol there is little difference in selectivity with regard to the ketones.

In general:

Ketones > Hydrocarbons

Ketones > Phenols

Ketones ≥ Alcohols

Hydrocarbons: camphene, pinene, limonene, mycrene. (Table III: B1, B2, B3, B4, B5.)

The only selectivity is that between the cyclic hydrocarbons and mycrene, a linear molecule, where there is a clear affinity against the linear system; thus limonene > camphene > pinene > mycrene. With regard to the other classes of compounds there is a constant selectivity disfavouring the hydrocarbon systems.

General order:

Hydrocarbons < Ketones

Hydrocarbons < Alcohols

Hydrocarbons < Phenols

Alcohols: linalool, borneol, geraniol, isomenthol, menthol, terpineol. (Table IV: C1, C2, C3, C4, C5.)

In contrast to the other systems there is no discrimination between linear and cyclic systems. In fact there is a slight favouring of the linear molecules, the internal order being: borneol > terpineol > linalool > geraniol > isomenthol > menthol. With regard to the other classes the alcohols are more strongly complexed than both the phenolic and hydrocarbon systems and also bornyl acetate. There is an approximate equivalence in the selectivity between them and the ketones, as is also observed with regard to cineole.

Hence:

Alcohols > Hydrocarbons

Alcohols > Phenols

TABLE III. Hydrocarbons

	Camphene	Pinene	Limonene	Myrcene
Camphene	X	50-50	40-60	75-25
Pinene	50-50	X	35-65	60-40
Limonene	60-40	65-35	X	75-25
Myrcene	25-75	40-60	25-75	X

Table B1. Relative selectivity for hydrocarbon mixtures.

	Camphene	Pinene	Limonene	Myrcene
Linalool	80-20	85-15	75-25	90-10
Borneol	75-25	80-20	85-15	80-20
Geraniol	75-25	75-25	80-20	90-10
Isomenthol	70-30	90-10	70-30	90-10
Menthol	70-30	85-15	60-40	70-30
Terpineol	80-20	80-20	80-20	100-0

Table B2. Relative selectivity for alcohol/hydrocarbon mixtures.

	Camphene	Pinene	Limonene	Myrcene
Camphor	70-30	80-20	70-30	85-15
Carvone	70-30	80-20	70-30	80-20
Citral	60-40	70-30	60-40	85-15
Fenchone	80-20	75-25	60-40	80-20
Menthone	60-40	85-15	60-40	90-10

Table B3. Relative selectivity for ketone/hydrocarbon mixtures.

	Camphene	Pinene	Limonene	Myrcene
Eugenol	70-30	60-40	50-50	70-30
Thymol	70-30	80-20	70-30	70-30
0-Cresol	60-40	70-30	50-50	80-20
Anethol	50-50	50-50	50-50	60-40

Table B4. Relative selectivity for phenol/hydrocarbon mixtures.

	Camphene	Pinene	Limonene	Myrcene
Cineole	85-15	75-25	60-40	90-10
Bornyl Ac.	60-40	50-50	70-30	60-40

Table B5. Relative selectivity for miscellaneous/Hydrocarbon mixtures.

Alcohols = Ketones

Phenols. (Table V: D1, D2, D3, D4, D5.)

Eugenol, thymol, *o*-cresol, anethol (strictly not a phenol but the structure is dominated by the phenyl-O functionality).

There is a general similarity in inclusion selectivity in this group, with a slight inferiority observed for the ether structure of anethole, giving an internal order: thymol > *o*-cresol ≥ eugenol > anethol. With respect to the other systems there is a higher selectivity for the phenolic molecules only in comparison to the hydrocarbons.

Hence:

TABLE IV. Alcohols

	Linalool	Borneol	Geraniol	Isomenthol	Menthol	Terpineol
Linalool	X	10-90	50-50	60-40	75-25	30-70
Borneol	90-10	X	60-40	80-20	75-25	80-20
Geraniol	50-50	40-60	X	50-50	70-30	30-70
Isomenthol	40-60	20-80	50-50	X	X	20-80
Menthol	25-75	25-75	30-70	X	X	15-85
Terpineol	70-30	20-80	70-30	80-20	85-15	X

Table C1. Relative selectivity for alcohol mixtures.

	Linalool	Borneol	Geraniol	Isomenthol	Menthol	Terpineol
Eugenol	40-60	40-60	15-85	40-60	40-60	10-90
Thymol	40-60	40-60	50-50	40-60	40-60	25-75
O-Cresol	30-70	20-80	50-50	30-70	30-70	15-85
Anethol	40-60	25-75	20-80	10-90	10-90	25-75

Table C2. Relative selectivity for phenol/alcohol mixtures.

	Linalool	Borneol	Geraniol	Isomenthol	Menthol	Terpineol
Camphene	20-80	25-75	25-75	30-70	30-70	20-80
Pinene	15-85	15-85	25-75	10-90	15-85	20-80
Limonene	25-75	15-85	20-80	30-70	40-60	20-80
Myrcene	10-90	20-80	10-90	10-90	30-70	0-100

Table C3. Relative selectivity for hydrocarbon/alcohol mixtures.

	Linalool	Borneol	Geraniol	Isomenthol	Menthol	Terpineol
Camphor	50-50	50-50	60-40	70-30	50-50	35-65
Carvone	50-50	30-70	60-40	50-50	70-30	30-70
Citral	50-50	20-80	25-75	40-60	50-50	50-50
Fenchone	50-50	30-70	60-40	60-40	60-40	70-30
Menthone	40-60	10-90	40-60	40-60	70-30	20-80

Table C4. Relative selectivity for ketone/alcohol mixtures.

	Linalool	Borneol	Geraniol	Isomenthol	Menthol	Terpineol
Cineole	50-50	50-50	60-40	50-50	50-50	50-50
Bornyl Ac	30-70	30-70	30-70	35-65	40-60	20-80

Table C5. Relative selectivity for miscellaneous/alcohol mixtures.

Phenols < Ketones

Phenols < Alcohols

Phenols > Hydrocarbons

During the course of this work monocrystalline samples were obtained for the inclusion complexes of borneol and camphor. The two compounds are isomorphous and belong to the general chess board-type [12] structure observed for β-CD inclusion compounds [13]. In this class the guest molecule is normally extremely disordered and, in view of this, structural resolution was not attempted. Both guest molecules are among those most strongly bound in terms of inclusion selectivity and until structural information becomes available for more weakly bound substrates no

TABLE V. Phenols

	Eugenol	Thymol	O-Cresol	Anethol
Eugenol	X	50-50	50-50	50-50
Thymol	50-50	X	50-50	70-30
O-Cresol	50-50	50-50	X	50-50
Anethol	50-50	30-70	50-50	X

Table D1. Relative selectivity for phenol mixtures.

	Eugenol	Thymol	O-Cresol	Anethol
Camphene	30-70	30-70	40-60	50-50
Pinene	40-60	20-80	30-70	50-50
Limonene	50-50	30-70	50-50	50-50
Myrcene	30-70	30-70	20-80	40-60

Table D2. Relative selectivity for hydrocarbon/phenol mixtures.

	Eugenol	Thymol	O-Cresol	Anethol
Linalool	60-40	60-40	70-30	60-40
Borneol	60-40	60-40	80-20	75-25
Geraniol	85-15	50-50	50-50	80-20
Isomentho l	60-40	60-40	70-30	90-10
Menthol	60-40	60-40	70-30	90-10
Terpineol	90-10	75-25	85-15	75-25

Table D3. Relative selectivity for alcolhol/phenol mixtures.

	Eugenol	Thymol	O-Cresol	Anethol
Camphor	70-30	50-50	75-25	75-25
Carvone	70-30	60-40	50-50	70-30
Citral	75-25	50-50	65-35	75-25
Fenchone	65-35	50-50	50-50	70-30
Menthone	75-25	50-50	60-40	75-25

Table D4. Relative selectivity for ketone/phenol mixtures.

	Eugenol	Thymol	O-Cresol	Anethol
Cineole	50-50	50-50	40-60	70-30
Bornyl Ac.	50-50	35-65	50-50	50-50

Table D5. Relative selectivity for miscellaneous/phenol mixtures.

conclusions concerning the effects of solid-state structure may be drawn. However it should be noted that if the more strongly selected molecules have disordered guests the fit between host and guest would seem to play a small role in the selectivity.

The above information allows an empirical statistical analysis of the relative inclusion selectivity to be made, and from such an analysis it becomes necessary only to carry out a limited number of complexation experiments to place any new compounds in the scale [14].

In order to attempt to explain the results obtained we have looked in detail at a number of parameters: guest solubility, previously determined association

TABLE VI. Stability constants of β-CD-terpene complexes.

	S (M/l)*	S(M/l)**	K (M^{-1}) [5]	K (M^{-1}) [6]
Linalool	$1{,}03.10^{-2}$			
Borneol	$4{,}1.10^{-3}$	$4{,}8.10^{-3}$	231 [11]	
Cineole	$2{,}3.\ 10^{-2}$	$1{,}3.\ 10^{-2}$		
Camphor	$1{,}03.10^{-2}$	$6{,}5.10^{-3}$	378	
Camphene				
Pinene				
Limonene	$6{,}39.10^{-5}$	$2{,}2.10^{-4}$	2230	
Bornyl Ac				
Eugenol	$1{,}50.10^{-2}$		140	650
Thymol		$5{,}1.10^{-3}$		180
Carvone		$8{,}8.10^{-3}$		180
Anethol	$7{,}49.10^{-4}$		1040	
Citral	$1{,}9.10^{-3}$			
o-Cresol		$28.\ 10^{-2}$		
Fenchone	$1{,}41.10^{-2}$	$3{,}29.10^{-3}$	140	
Geraniol				
Isomenthol				
Menthol	$2{,}92.10^{-3}$	$2{,}7.10^{-3}$	3850	2240
Menthone	$3{,}22.10^{-3}$	$4{,}5.10^{-3}$	546	
Myrcene				
Terpineol		$1{,}28.\ 10^{-2}$		

* "Solubilities of Inorganic and Organic Compounds", Edited by H. Stephen and T. Stephen, Pergamon Press LTD, London 1963.
** CRC Handbook of Chemistry and Physics.

constants and calculated dipole moments of the guest obtained from molecular graphics.

The guest solubilities are given in Table VIa and lead to an order: *o*-cresol > cineole > eugenol > terpineol > (±)linalool > (+)camphor = (-)fenchone > (-)carvone > thymol > (-)borneol > (-)menthone > (+)menthol > citral > anethol > (+)limonene. Comparison with the order of complexation: (-)borneol (**2**) > terpineol (**21**) > (+)camphor (**4**) > (-)carvone (**11**) = geraniol (**16**) = (±)linalool (**1**) = cineole (**3**) = (-)fenchone (**15**) > (+)isomenthol (**17**) = citral (**13**) = thymol (**10**) > (-)menthone (**19**) > (+)menthol (**18**) > *o*-cresol (**14**) > eugenol (**9**) > (+)limonene (**7**) = (-)bornyl acetate (**8**) > anethol (**12**) = (+)camphene (**5**) > (-)pinene (**6**) > myrcene (**20**), shows neither a direct nor an inverse relation. The possibility of the solubility of the guest molecules playing a role in the relative selectivity has been investigated by varying the quantity of guest available, in all experiments the same ratio of included molecule was found.

Similarily the association constants, where known, are given in Table VIb leading to an order: (+)menthol > (+)limonene > anethol > (-)menthone > eugenol >

TABLE VII. Calculated dipole moments for the terpene guest.

	x	y	z	dipole
RLinalool	0,440448	1,377064	-0,321461	1,481093
SLinalool	-0,277365	-1,542196	-0,416430	1,621331
Borneol	-1,170478	0,745289	-0,790970	1,597219
Cineole	-0,078733	-1,077032	-1,484411	1,835667
Camphor	1,006266	1,538705	-1,898921	2,643120
Camphene	0,041636	0,107014	0,104423	0,155209
Pinene	-0,021374	0,116516	-0,013520	0,119229
Limonene	-0,026447	-0,111487	-0,042036	0,122049
Bornyl Ac.	-1,903501	2,777856	0,346578	3,385250
Eugenol	0,012407	-0,459830	-0,001600	0,460000
Thymol	0,715213	-0,998509	0,515083	1,331863
Carvone	-1,979544	1,157077	0,991624	2,498147
Anethol	-1,272371	0,767621	0,818953	1,696719
Citral	-1,703258	-0,058676	1,664062	2,381939
Cresol	-1,302530	0,260481	0,340318	1,371223
Fenchone	0,996421	1,562364	-1,891037	2,647654
Geraniol	-0,483094	-0,021668	1,419270	1,499392
Isomenthol	1,231873	-0,858924	0,468186	1,573041
Menthol	1,264125	-0,819640	0,474388	1,579515
Menthone	2,209815	-1,198003	0,396016	2,544665
Myrcene	0,081258	-0,076268	-0,042905	0,119417
Terpineol	1,376872	-0,233982	-0,559579	1,504544

(+)camphor > (-)borneol > thymol > (-)carvone > (-)fenchone. In particular comparison with the experimentally observed relative selectivities shows *no correlation.*

In contrast to this lack of substantiation of the association constants as a valid tool for the determination of inclusion selectivity there exists close correlation between our results (precipitation/solid state) and the results obtained by Ueno for solution competition experiments involving pyrene, dansyl, or methyl red functions covalently bound to the cyclodextrin moiety and similar terpenoid molecules [9–11]. That in two separate and experimentally divergent situations, one series in solution (Ueno) and one in the 'solid-state' (this work), closely resembling orders for relative complexation abilities are observed and that these orders are widely divergent from the values one might predict from the published association constants suggests; (a) that there is a substansive basis for the use of relative inclusion selectivity; and (b) that there is reason to doubt that 'stability constants' may be applied to systems in which there is more than one guest species present.

Also one must cast doubt on the use of stability constants as a general measure, assumed to be independent of the experimental conditions under which the determination of the stability constant was carried out. The reasoning behind this is relatively simple; association constants are derived from an over simplistic view of the equilibria involved in the formation of inclusion compounds which does not take into account the aggregation of the cyclodextrins [15], or the possible effects of cosolvents used in the experiments on the fundamental properties of

water or cyclodextrin solutions [16], which cause association constants to vary in a substrate-dependent manner. Such a supposition is confirmed by a reversal in the values of the association constants of thymol and geraniol with β-CD as a function of methanol mole fraction [17].

The calculated dipole moments for the guest molecules are given in Table VII; these are derived from the energy minimised structures of the molecules obtained via the SYBYL molecular graphics package [18]. Once again, no correlation is found between the physical property and the experimentally observed inclusion selectivity.

4. Conclusion

It would thus appear that while an empirical scale of inclusion selectivity may be obtained from the analysis of the competitive complexation of a series of 21 guest molecules with β-CD, and that this scale is closely related to other experimentally determined complexation scales, the observed values are not easily correlated with the physical properties of the guest molecules. More importantly, there exists no correlation between the results of such competition experiments and the individually observed association constants.

We are currently investigating the effects of the presence of cosolvents on the relative inclusion selectivity of these guest molecules in order to 'fine tune' the separation possibilities of such systems.

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