ELSEVIER

www.elsevier.nl/locate/carres

Carbohydrate Research 328 (2000) 635–639

CARBOHYDRATE RESEARCH

Note

Correlation of the solubility of several aromatics and terpenes in aqueous hydroxypropyl-β-cyclodextrin with steric and hydrophobicity parameters

Barbu A. Demian *

Philip Morris USA, Research Development and Engineering, PO Box 26583, Richmond, VA 23261-6583, USA

Received 6 October 1999; received in revised form 20 March 2000; accepted 27 March 2000

Abstract

The solubility isotherms of nineteen aromatics and terpenes in aqueous hydroxypropyl-β-cyclodextrin were determined to be straight lines. This is explained by the host–guest complexation which is characteristic for the whole class of cyclodextrins and derivatives. The slopes of the solubility isotherms correlate with Sterimol L and log P_{ow} as descriptors of the steric fit and hydrophobicity match, in accord with the qualitative representation of the phenomenon.

Keywords: Hydroxypropyl-β-cyclodextrin; Solubility; Host–guest complex; Quantitative structure–property relationship; Hydrophobicity; Steric fit

1. Introduction

Monoterpenes and monocyclic aromatics, that is, the majority of the compounds of interest in the flavor and fragrance field, form readily host–guest complexes with β-cyclodextrin (cyclomaltoheptaose). The use of β-cyclodextrin itself in formulations is limited, however, by its low water solubility. Several cyclodextrin derivatives, where the hydrogen of the hydroxyl groups is substituted by hydroxyethyl-, hydroxypropyl-, or methyl groups, exhibit a dramatic increase in solubility of up to 60% w/w in water. Such derivatives can play in flavor formulations simultaneously the function of solvent, fixative and stabilizer [1].

The present note reports the solubility data in aqueous solutions of hydroxypropyl-β-cyclodextrin of a group of aromatic compounds and terpenes. Taking advantage of the conceptual understanding of the host–guest complexation involving cyclodextrins [2–5], the derivation of a quantitative structure–property relationship (QSPR) is attempted.

2. Experimental

Materials.—Hydroxypropyl-β-cyclodextrin (CAS 94035-02-6) was a commercial product from American Maize-Products Comp., Hammond, IN, USA, sold under the trade name Encapsin™ HPB. It is manufactured under

* Fax: +1-804-2742468. Present address: Chrysalis Technologies Inc., PO Box 26583, Richmond, VA 23261-6583, USA.

E-mail address: barbu.a.demian@pmusa.com (B.A. Demian).

0008-6215/00/$ - see front matter
PII: S0008-6215(00)00139-7

license from Janssen Biotech N.V. The average degree of substitution, reported by the manufacturer, is 4.5. Anisole (CAS 100-66-3), *p*-anisaldehyde (CAS 123-11-5), *E*-anethole (CAS 4180-23-8), phenylethyl alcohol (CAS 60-12-8), phenylethyl acetate (CAS 103-45-7), ethyl phenylacetate (CAS 101-97-3), vanillin (CAS 121-33-5), ethyl vanillin (CAS 121-32-4), thymol (CAS 89-83-8), *E*-cinnamaldehyde (CAS 14371-10-9), *E*-cinnamyl acetate (CAS 103-54-8), acetophenone (CAS 98-86-2), methyl salicylate (CAS 119-36-8), *R*-(−)-carvone (CAS 6485-40-1), β-damascone (CAS 23726-92-3), linalool (CAS 78-70-6) and γ-nonalactone (CAS 104-61-0), were all of analytical purity, purchased from Aldrich Chem. Co., and used as received. Anisyl acetate (CAS 104-21-2) and anisyl phenylacetate (CAS 102-17-0) were of practical grade, purchased from Givaudan and Bell Flavors, respectively.

Solubilities.—The solubilities at 25 °C in water and 10, 20 and 30% w/w Encapsin™ HPB in water were determined by the shake-flask method. Excess of the solute was shaken overnight with the solvent on a thermostated shaker. The saturated solution was separated by filtration through 0.25-μm cut-off disposable filters. The concentration of the solute was determined by UV spectrophotometry after the appropriate dilution in methanol. The spectra in range of 200 to 400 nm were recorded at pathlengths of 0.2 to 1 cm, using a Varian DMS 100/DS-15 UV–Vis spectrophotometer. The absorbances at the λ_{max} of the solutes were used to compute the corresponding concentrations. Reference spectra of the solutes in MeOH were recorded under identical conditions. The solubility isotherms were calculated using the RS/1 software package [6].

The steric parameters of the solutes, Sterimol L [7] were calculated with the aid of the software suite ChemOffice [8]. The procedure used involved the following steps:

- draw the structure of the solute molecule in the ChemDraw module of the software suite;
- export the structure into the Chem3D module;
- execute a MM2 minimization;
- minimize the conformational energy using the quantum chemistry program MOPAC (Fujitsu), an integral part of the software package; this part of the procedure, run on a Pentium Pro PC at 133 MHz clock speed, took from 15 to 90 min, depending on the size of the molecule;
- read the coordinates of the most distant pair of atoms in the molecule;
- compute Sterimol L as the Euclidian distance between the extreme atoms plus the Van der Waals radii of the extreme atoms.

Experimental data for the octanol–water partition coefficients were available from the compilation of *C.* Hansch et al. [9] for eight solutes of the set. For eight compounds, the $\log P_{ow}$ were calculated using the semi-empirical Hansch–Fujita Π methodology [10,11]. Finally, for three terpenes, the $\log P_{ow}$ was calculated using the Rekker's fragmental constant approach [12].

The multiple linear regression calculations were carried out using the statistical software package SYSTAT [13].

3. Results and discussion

The solubility isotherms at 25 °C of the 19 solutes in aqueous hydroxypropyl-β-cyclodextrin are well described by straight lines. The host and guest concentrations are expressed in molar units:

$$C_{m[guest]} = \text{slope} \times C_{m[host]} + \text{intercept}$$

The hydroxypropyl-β-cyclodextrin–Encapsin™ HPB molecular weight was calculated based on an average degree of substitution of 4.5. The parameters of the lines and the pertinent statistics are listed in Table 1. The linear fit of the solubility data ranges from passable to excellent.

Two factors could account for the monotonic increase of the guest concentration as a function of the host concentration. First, the host–guest complexation; as the host concentration increases, more of the guest is transferred into the solution. The second, less obvious factor, is the hydrotropic effect. The hydrotropic effect is a phenomenological description of the simple fact that a solution is

not the same as the pure solvent. In other words, some increase of the solute concentration with the increasing hydroxypropyl-β-cyclodextrin concentration would be expected even in the absence of any complexation. In some cases, the hydrotropic effect can be significant. For example, the solubility isotherms of a number of aromatic compounds in methylated β-cyclodextrin are well represented by second-degree polynomials [14]. The upward curvature of the graphs is attributable to the hydrotropic effect. An alternative explanation is the formation of higher order complexes, like 1 × [guest]:2 × [host]. In this later case, again a curvature of the solubility isotherm is to be expected. The data of the present paper show a linear increase of the guest concentration as function of the host concentration. It is reasonable to assume that the dominant factor accounting for this dependence is the host–guest complexation.

The qualitative representation of the host–guest complexation implies two elements, the steric fit and the hydrophobicity match [4,5]: the guest has to fit into the cavity of the cyclodextrin host, and its hydrophobicity needs to match the relatively hydrophobic environment of the host's cavity.

The parameter chosen for the steric factor was Sterimol L [7]. The simplest description of it is the length of the rectangular box the molecule could fit into. The members of the guests set are all monocyclic aromatics or monoterpenes. The other dimensions of the 'box', the width–Sterimol B_1, B_2, etc., are about the same in this set of molecules.

The natural choice for the hydrophobicity parameter was the logarithm of the octanol–water partition coefficient, $\log P_{ow}$, by far the best documented and the most frequently used hydrophobicity parameter in QSAR studies. The steric and hydrophobicity parameters of the data set are listed in Table 2.

The two descriptors: Sterimol L and $\log P_{ow}$, are essentially noncorrelated (correlation coefficient 0.264). The quantitative structure–property relationship derived from the data set is:

$$\text{Slope} = 2.86 - 0.11 \times \text{Sterimol L} - 0.34 \times \log P_{ow}$$

Multiple R	0.788
Standard error of the estimate	0.336

Table 1
Solubility isotherms at 25 °C in aqueous hydroxypropyl-β-cyclodextrin (Encapsin™ HPB)

	Slope (mol/mol)	STD_{slope}	Intercept (mol/L)	$STD_{intercept}$	F ratio	P significance level
Acetophenone	1.973	0.088	0.096	0.011	502.5	0.001980
Anethole	0.416	0.006	0.001	0.001	4608.8	0.000217
Anisaldehyde	1.730	0.013	0.039	0.002	6882.5	0.000767
Anisole	0.924	0.023	0.010	0.003	1531.9	0.000652
Anisyl acetate	0.890	0.005	0.011	0.001	27529	0.000002
Anisyl phenylacetate	0.204	0.010	0.002	0.001	442.9	0.002250
Cinnamic aldehyde	0.984	0.014	0.014	0.002	4255.8	0.000235
Cinnamyl acetate	0.500	0.019	0.001	0.002	629.4	0.001580
Carvone	0.930	0.009	0.011	0.001	11757	0.000085
β-Damascone	0.314	0.050	0.001	0.008	393.2	0.001190
Ethyl phenylacetate	0.660	0.014	0.009	0.002	2377.7	0.000420
Ethyl vanillin	0.963	0.012	0.019	0.002	6442.8	0.000155
Linalool	0.920	0.011	0.012	0.001	6444.5	0.000155
Methyl salicylate	0.719	0.005	0.004	0.001	18280	0.000055
γ-Nonalactone	0.264	0.076	0.059	0.014	119.1	0.007470
Phenylethyl acetate	0.710	0.035	0.013	0.004	438.9	0.002270
Phenylethyl alcohol	1.850	0.043	0.172	0.005	1705.7	0.000586
Thymol	1.109	0.013	0.006	0.002	7619.4	0.000131
Vanillin	1.363	0.101	0.048	0.013	179.5	0.005520

Table 2
Steric and hydrophobicity data

Guest molecule	Sterimol L	log P_{ow}
Acetophenone	7.90	1.58 [a]
Anethole	10.57	3.33 [b]
Anisaldehyde	9.70	1.48 [b]
Anisole	7.64	2.11 [a]
Anisyl acetate	11.46	1.96 [b]
Anisyl phenylacetate	15.74	3.36 [b]
Cinnamic aldehyde	9.45	1.90 [b]
Cinnamyl acetate	11.75	1.98 [b]
Carvone	8.90	2.51 [c]
β-Damascone	9.67	4.36 [c]
Ethyl phenylacetate	11.00	2.39 [b]
Ethyl vanillin	8.89	2.39 [b]
Linalool	7.43	3.13 [c]
Methyl salicylate	8.34	2.34 [a]
γ-Nonalactone	10.82	2.16 [b]
Phenylethyl acetate	11.01	2.30 [a]
Phenylethyl alcohol	8.48	1.36 [a]
Thymol	8.55	3.30 [a]
Vanillin	7.69	1.21 [a]

[a] Experimental data [9].
[b] Using Hansch–Fujita method [10].
[c] Using Rekker's fragmental constants method [12].

The standard errors and the associated significance levels of the coefficients are:

	Standard error	P (significance level)
Constant term	0.42	0.000
Sterimol L coefficient	0.04	0.013
Log P_{ow} coefficient	0.10	0.004

While the QSPR is statistically valid it is not very strong. Several factors could account for that. First, the solubility data are relatively noisy. Second, the host is in fact a very complex mixture of positional isomers and diastereomers [15]. The observed behavior is the integrated response of those isomers: this will introduce a significant amount of noise. Third, as already discussed (vide supra), the hydrotropic effect is unaccounted for.

The negative sign of the coefficient associated with the steric fit term has a straightforward interpretation. The longer the molecule, the more of it protrudes from the host's cavity and is not protected from the polar environment of the bulk solvent. It is also possible that molecules with high Sterimol L are involved in 2:1 complexes, less favored entropically. The net effect is the higher the Sterimol L, the lower the solubility.

The hydrophobicity term also has a negative coefficient, something rather unintuitive. It is not the hydrophobicity, but the hydrophobicity match that counts. The cyclodextrin's cavity was estimated to correspond in hydrophobicity to ethanol or 1,4-dioxane, i.e., corresponding to a $\log P_{ow} \sim -0.3$ [5]. The range in hydrophobicity of the data set is from 1.2 to 4.4. For this particular set, the higher the hydrophobicity, the bigger the mismatch, and the lower the solubility.

In conclusion, the solubility of a set of 20 aromatics and terpenes in aqueous hydroxypropyl-β-cyclodextrin can be described by a quantitative structure–property relationship involving steric and hydrophobicity parameters. This is in accord with the representation of the phenomenon being controlled by the host–guest complexation.

References

[1] J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
[2] J. Szejtli, *Cyclodextrines and Their Inclusion Complexes*, Akad. Kiado, Budapest, 1982.
[3] F. Voegtle, *Supramolecular Chemistry*, Wiley, New York, 1991, pp. 135–140 (Chapter 4.2).
[4] M.V. Rekharsky, Y. Inoue, *Chem. Rev.*, 98 (1998) 1875–1917.
[5] K.A. Connors, *Chem. Rev.*, 97 (1997) 1325–1357.
[6] RS/1 Version 5.2, BBN Domain Corp., Cambridge, MA, 1996.
[7] A. Verloop, in E.J. Ariens (Ed.), *Drug Design*, Vol. III, Academic, New York, 1976, p. 133.
[8] ChemOffice Ultra™ 4.0, CambridgeSoft Corp., Cambridge, MA, 1996.
[9] C. Hansch, A. Leo, D. Hoekman, *Exploring QSAR. Hydrophobic, Electronic, and Steric Constants*, ACS Professional Reference Books, ACS, Washington, DC, 1995.
[10] T. Fujita, J. Iwasa, C. Hansch, *J. Am. Chem. Soc.*, 86 (1964) 5175–5182.
[11] C. Hansch, A. Leo, *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*, ACS Professional Reference Book, ACS, Washington, DC, 1995, pp. 103–118 (Chap. 4.4).

[12] R.F. Rekker, R. Manhold, *Calculation of Drug Lipophilicity. The Hydrophobic Fragmental Constant Approach*, VCH, Weinheim, 1992.
[13] SYSTAT 7.0, SPSS Inc., Chicago, IL, 1997.
[14] B.A. Demian, *Program Booklet and Abstracts*, *Volume 51*, 51st Tobacco Chemists' Research Conference, Winston-Salem, NC, September 14–17, 1997, Abstract 55, p. 58.
[15] L. Szente, C.E. Strattan, in D. Duchene (Ed.), *New Trends in Cyclodextrines and Derivatives*, De Sante, Paris, 1994, p. 64 (Chapter 2).