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Computational Prediction for the Slopes of A_L-type Phase Solubility Curves of Organic Compounds Complexed With α-, β-, or γ-cyclodextrins Based on Monte Carlo Docking Simulations

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Abstract

A Monte Carlo (MC) docking method was introduced in order to predict the aqueous solubility of inclusion complexes composed of small organic compounds and various cyclodextrins. The slope (S) of the A_L-type phase solubility curve was accurately predicted by a combination of the interaction energy and nonpolar solvation free energy for each of the docked complexes. The regression equation for S, the slope of the phase solubility curve gives a fine correlation coefficient, r^2, of 0.913 and standard error of 0.028 for the 63 organic compounds complexed with cyclodextrins.

Introduction

Aqueous solubility is an important physical property that influences the release or transport of drugs in the human body [1]. Many poorly insoluble drugs have been physically or chemically modified to enhance their aqueous solubility and availability. Cyclodextrins (CDs) and their derivatives are common solubilizing agents for various drugs, food additives, and other hydrophobic small molecules [2, 3]. They form a water-soluble, host–guest type inclusion complex with small organic molecules. A-type phase-solubility profiles are obtained when the solubility of the guest compounds increases with increasing host cyclodextrin concentration. The most common type of phase-solubility diagram among A-type phase-solubility profiles is the A_L-type where one guest molecule forms a complex with one cyclodextrin molecule. The A_L-type phase-solubility curve is obtained when the complex is first order with respect to host and first or higher order with respect to guest [3]. Under A_L-type phase-solubility diagram, aqueous solubility of guest compounds complexed with cyclodextrin can be described with the slope (S) of the solubility curve and the intrinsic solubility (S_o) of the guests.

To improve the commercial applications of solubility enhancement by CDs, accurate computational method to estimate aqueous solubility of inclusion complex is highly desirable. Using a host–guest interaction model, numerous attempts have been made to elucidate and predict the solubilizing process of organic compounds by CDs. Connors predicted the association constants of α–CD complexes based on surface area estimation [4]. However, he did not explain the solvation effect on the complexation. Demian made a reliable prediction [5] on the slope of the solubility curve with two simple steric and hydrophobic parameters based on the QSPR (Quantitative Structure Property Relationship) approach. He found a significant relationship ($r^2 = 0.788$, $n = 19$) between the molecular descriptors and the solubility of inclusion complexes. Mura and coworkers explained the solubility of inclusion complexes with three theoretical parameters – docking energy, contact surface, and intermolecular interaction field [6]. They acquired the most accurate theoretical model ($r^2 = 0.805$, $n = 24$) for the computational prediction of the aqueous solubility of the inclusion complex.

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It is evident that the development of theoretical methods with general application has allowed reliable prediction of the complexation properties between guest and CD molecules. The present paper describes the theoretical model of solubility for the A_L-type guest/CD inclusion complexes in order to establish a precise prediction method for the aqueous solubility of inclusion complexes. Our method focuses on the most common CDs, namely, α-, β-, and γ-CDs. The slope of A_L-type phase-solubility curve of the inclusion complexes were explained by three computational parameters: host–guest interaction energy, host–guest nonpolar solvation free energy, and guest–guest nonpolar solvation free energy based on Monte Carlo docking simulations. It was interesting that consideration of the guest–guest interaction was decisive for an exact prediction of aqueous solubility. We obtained a finely predictable equation ($r^2 = 0.913$, $n = 63$) from the A_L-type aqueous solubility data [7] of 63-different inclusion complexes with the energy parameters.

Results and discussion

The experimentally determined slope of A_L-type phase solubility diagram and the predicted slope values for the 63-small organic molecules captured in CDs are presented in Table 1. The experimental solubility of each inclusion complex was taken from the published results [7] of other research groups. MC docking simulations were performed for these inclusion complexes, and then, solubility predictions were made based on the computational energy terms. All the energy terms were calculated for both the host–guest complex and guest–guest dimer. To this end, we estimated the interaction energy, polar solvation free energy, and nonpolar solvation free energy upon complexation based on MC docking simulations. The interaction energy is defined as a sum of the intermolecular van der Waals (vdW) and electrostatic energy arises from complex formation. The polar solvation energy terms, unexpectedly, could not contribute to the exact prediction of solubility (data not shown), and thus we did not consider this energy term in further analyses; the intermolecular electrostatic energies between host and guest appear to be nearly canceled by the polar solvation free energies, and therefore the use of polar solvation free energy terms for the prediction of solubility is not suggested. The nonpolar solvation contribution accounts for cavity creation in water and vdW interactions between the modeled nonpolar molecule and water molecules. This nonpolar solvation free energy term represents the change of solvent-accessible surface area upon complexation.

The most significant energy terms among the energy values were identified using a multivariate linear regression analysis and the best equation was obtained for the aqueous solubility of the inclusion complexes. The aqueous solubilities of the inclusion complexes were related with three energy values: the interaction energy between host and guest (ΔE_{h-g}), the difference between nonpolar components of free energy of solvation of the host–guest complex and those of individual host and guest molecules (ΔE_{np_h-g}), and the difference between nonpolar components of free energy of solvation of the guest–guest dimer and those of individual guest molecule (ΔE_{np_g-g}). The slope (S_{cal}) of the solubility curve could be expressed as the following equation:

$$S_{cal} = aE_{h-g} + bE_{np\_h-g} + cE_{np\_g-g} + d$$
$$(r^2 = 0.913, \mathrm{SD} = 0.084, n = 63)$$

where $a = -0.012$ mol/kcal, $b = +0.102$ mol/kcal, $c = +0.328$ mol/kcal, $d = +0.305$ mol/kcal.

The signs and relative magnitudes of the coefficients in the regression equation indicated that the complex solubility was directly related to the interaction energy and nonpolar solvation free energy for binding of the host–guest and guest dimer. A negative sign of the interaction energy term indicates that a strong host–guest interaction enhances the aqueous solubility of the inclusion complexes due to the gain of potential energy. On the other hand, a positive sign of nonpolar solvation free energy terms indicates that they impose a heavy penalty against favorable interaction energy between host and guest. The nonpolar solvations decrease the aqueous solubility of the complex due to the loss of solvent-accessible surface area of the host and guest upon complexation. The performance of the proposed regression model equation in estimating the slope of the solubility curve was shown in Figure 1. Some of the outliers, especially an experimental slope value below 0.01, could be a consequence of experimental errors. However, fine correlation coefficient ($r^2 = 0.913$) indicates the adequate reliability of this model in describing the variations of the solubility slope. The prediction accuracy of the solubility equation was expressed by the terms of standard error and significance level (Table 2). The standard error and significance level for each term of the regression equation were highly satisfactory for accurate prediction of the aqueous solubility of inclusion complexes. Their average values were 0.028 and 2.95×10^{-4}, respectively.

In conclusion, we predicted accurately the slope of phase solubility ($r^2 = 0.913$) by the introduction of the guest–guest interaction term as a supplement for the solubility equation based on Monte Carlo docking simulations. Our theoretical model and solubility equation might provide a powerful methodology as well as insight into the aqueous solubility prediction of inclusion complexes. In particular, our approach can be applied to the structurally diverse class of organic molecules and a broad range ($S = 0.01 \sim 1.0$) of aqueous solubility. In this respect, the MC docking simulations are highly recommended for the accurate explanation of solubility enhancement of hydrophobic molecules by CDs with the terminology of interaction energy and nonpolar solvation free energy.

Table 1. Host–guest type inclusion complexes and their experimental *versus* predicted slopes of the A_L-type solubility curves

Guest compounds	Host CD	Solubility slope (S)		Energy terms		
		S_{obs}	S_{cal}	ΔE_{inte_h-g}	ΔE_{np_h-g}	ΔE_{np_g-g}
Diphenyl *o*-phthalate[aa]	β-CD	0.001	0.036	−20.98	−1.95	−0.98
Natamycin[ab]	α-CD	0.001	0.000	−46.11	−1.65	−2.14
Camptothecin[ac]	β-CD	0.001	0.067	−25.27	−2.15	−0.98
Furnidipine[ad]	β-CD	0.002	0.000	−14.64	−1.41	−1.11
Mebendazole[ae]	γ-CD	0.002	0.067	−22.59	−2.13	−0.89
Meloxicam[af]	γ-CD	0.003	0.051	−23.35	−2.18	−0.95
Meloxicam[af]	α-CD	0.003	0.083	−23.40	−1.87	−0.95
Nimodipine[ag]	β-CD	0.003	0.000	−19.68	−2.05	−1.07
Meloxicam[af]	β-CD	0.004	0.089	−24.85	−1.99	−0.95
Indomethacin[ah]	β-CD	0.004	0.048	−30.15	−2.05	−1.25
Gliclazide[ai]	α-CD	0.005	0.050	−20.86	−1.42	−1.10
Rutin[aj]	γ-CD	0.010	0.000	−31.56	−1.55	−1.73
Cyproterone acetate[ak]	β-CD	0.013	0.095	−27.45	−1.85	−1.07
Natamycin[ab]	γ-CD	0.019	0.000	−57.26	−3.30	−2.14
Triflumizole[al]	β-CD	0.021	0.000	−25.43	−2.18	−1.25
Rutin[aj]	α-CD	0.022	0.000	−32.92	−1.69	−1.73
Di-*n*-butyl *o*-phthalate[aa]	β-CD	0.026	0.009	−22.29	−1.99	−1.10
Cyproterone acetate[ak]	γ-CD	0.032	0.033	−29.76	−2.73	−1.07
Rutin[aj]	β-CD	0.032	0.055	−47.84	−2.52	−1.73
Norplurazon[am]	β-CD	0.035	0.132	−23.33	−1.93	−0.78
Oleanoic_acid[an]	β-CD	0.038	0.000	−30.06	−2.15	−1.47
Melatonin[ao]	α-CD	0.039	0.141	−21.57	−1.67	−0.77
Natamycin[ab]	β-CD	0.048	0.031	−52.18	−1.94	−2.14
Hesperetin[ap]	β-CD	0.057	0.127	−23.20	−1.90	−0.80
Sulfaproxyline[aq]	β-CD	0.060	0.022	−25.23	−2.27	−1.08
Celecoxib[ar]	β-CD	0.063	0.041	−23.04	−2.21	−0.96
Oleanoic_acid[an]	γ-CD	0.065	0.091	−46.51	−2.84	−1.47
Melatonin[ao]	γ-CD	0.071	0.129	−22.90	−1.94	−0.77
Tolbutamide[as]	β-CD	0.075	0.156	−25.50	−2.05	−0.75
Miconazole[at]	α-CD	0.095	0.024	−22.75	−1.89	−1.10
Dexamethasone acetate[au]	β-CD	0.098	0.118	−26.81	−2.13	−0.89
Acyclovir[av]	β-CD	0.110	0.190	−22.82	−1.69	−0.66
Diallyl *m*-phthalate[aa]	β-CD	0.117	0.145	−23.39	−1.88	−0.76
α-bisabolol[aw]	β-CD	0.120	0.196	−21.91	−1.97	−0.52
Cinchonine[ax]	γ-CD	0.120	0.082	−24.42	−2.26	−0.87
Dexamethasone acetate[au]	γ-CD	0.126	0.149	−34.42	−2.72	−0.89
Norprogesterone[ay]	β-CD	0.143	0.104	−27.91	−2.46	−0.87
Gliquidone[az]	β-CD	0.146	0.039	−27.58	−2.15	−1.15
Melatonin[ao]	β-CD	0.149	0.158	−24.77	−1.88	−0.77
β-lapachone[ba]	β-CD	0.160	0.186	−16.15	−1.46	−0.50
Tenoxicam[bb]	γ-CD	0.160	0.103	−21.53	−1.97	−0.79
Nicardipine[bc]	β-CD	0.162	0.068	−31.98	−2.07	−1.25
Prochloraz[bd]	β-CD	0.168	0.059	−22.23	−1.75	−1.02
Phenylundecanoic acid[be]	β-CD	0.170	0.227	−49.68	−2.14	−1.39
Cinchonine[ax]	β-CD	0.190	0.120	−26.27	−2.11	−0.87
Podophyllotoxin[bf]	β-CD	0.200	0.156	−25.80	−2.31	−0.68
2-phenylphenol[bd]	β-CD	0.220	0.317	−18.65	−1.43	−0.20
tenoxicam[bb]	β-CD	0.240	0.136	−24.34	−1.98	−0.79
Bromazepam[bg]	β-CD	0.250	0.186	−23.67	−1.96	−0.62
Diethyl *o*-phthalate[aa]	β-CD	0.270	0.167	−23.20	−1.61	−0.77
Clofibrate[bh]	β-CD	0.278	0.207	−21.82	−1.76	−0.55
Alfaxalone[bi]	β-CD	0.310	0.251	−24.43	−1.67	−0.54
Carbofuran[bj]	β-CD	0.417	0.191	−25.54	−1.71	−0.75
Ibuproxam[bk]	β-CD	0.570	0.247	−25.88	−1.84	−0.55
Shikonin[bl]	β-CD	0.592	0.391	−30.90	−1.80	−0.31
Cinnamic acid[be]	β-CD	0.630	0.693	−44.14	−1.29	−0.03

Table 1. (Continued)

Guest compounds	Host CD	Solubility slope (S)		Energy terms		
		S_{obs}	S_{cal}	ΔE_{inte_h-g}	ΔE_{np_h-g}	ΔE_{np_g-g}
o-toluic_acid[be]	β-CD	0.720	0.771	−45.74	−1.20	0.12
Phenylvalreic acid[aa]	β-CD	0.800	0.768	−51.16	−0.55	−0.29
Phenylbutyric acid[aa]	β-CD	0.900	0.788	−49.16	−1.47	0.13
m-toluic acid[be]	β-CD	0.910	0.886	−43.80	−1.19	0.54
Salicyclic acid[be]	β-CD	0.910	0.935	−44.50	−1.08	0.63
Phenylpropionic acid[be]	β-CD	0.950	0.857	−48.10	−1.37	0.35
Benzoic acid[be]	β-CD	0.960	0.969	−43.56	−1.03	0.75

Experimental slope values were taken from various literatures (see ref. 7).

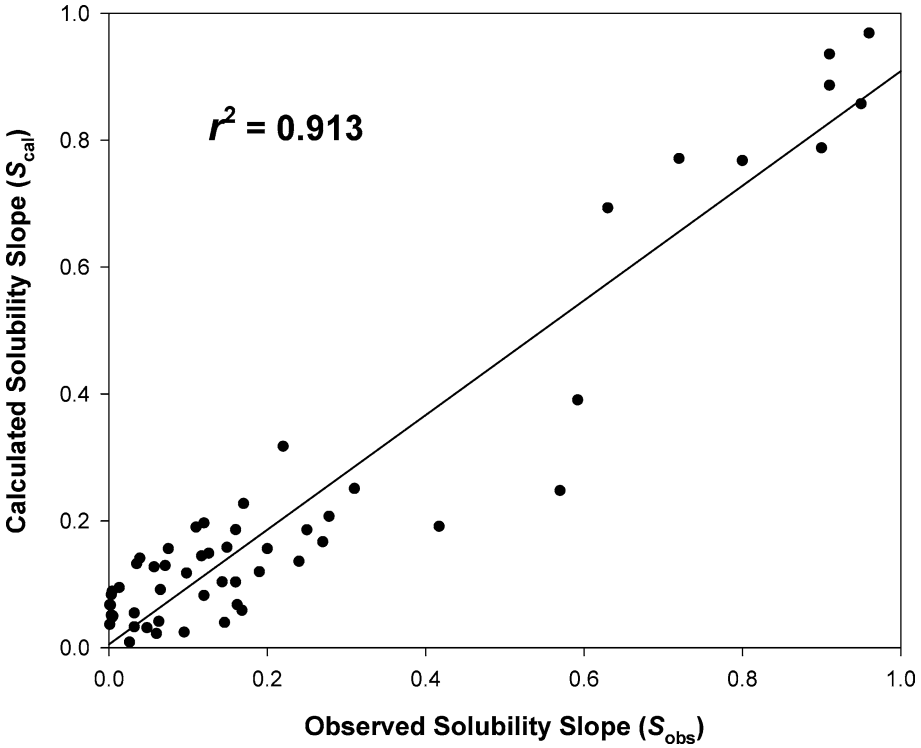

Figure 1. Plot of observed against predicted slope values of solubility diagram.

Computational method

Assumptions and aqueous solubility model of inclusion complex

All host CDs and guests are assumed to be chemically and physically stable. CDs are expected to complex with the guest and, once formed, the guest-CD complex is assumed to have a 1:1 stoichiometry; any dissolved compound does not appreciably alter the medium polarity. The specially designed computation on the self-association of each guest compound *via* dimerization was considered to reflect the effect of the molecular aggregation process in an aqueous solution. However, the association effect of whole inclusion complexes is not considered in this model. Our solubilization process model for the inclusion complex is as follows:

$$\text{CD} + \text{Guest} \underset{\text{solubility decrease}}{\overset{\text{solubility increase}}{\rightleftharpoons}} \text{Inclusion complex}$$

$$\text{Guest} + \text{Guest} \underset{\text{solubility increase}}{\overset{\text{solubility decrease}}{\rightleftharpoons}} \text{Guest dimer}$$

$$\text{Large solvent-accessible surface area} \underset{\text{solubility increase}}{\overset{\text{solubility decrease}}{\rightleftharpoons}} \text{Small solvent-accessible surface area}$$

Table 2. The standard errors and significance levels of each coefficient of solubility equation

Complex	Standard error	Significance level
Constant term	0.059	3.10×10^{-6}
$\Delta E_{\text{inte\_h–g}}$	0.001	8.19×10^{-18}
$\Delta E_{\text{np\_h–g}}$	0.030	1.18×10^{-3}
$\Delta E_{\text{np\_g–g}}$	0.023	4.87×10^{-21}
Average	0.028	2.95×10^{-4}

The A_L-type solubility isotherms at 298 K of the guest compounds in a CD aqueous solution can be described by a straight line in general [3]. The A_L-type aqueous solubility of the guest (C[guest]) is expressed with the terms of the slope of the solubility curve, the added host CD concentration (C[host]), and the intrinsic guest solubility (S_o), as follows:

$$\text{C[guest]} = \text{slope} \times \text{C[host]} + S_o$$

Thus, we can easily predict the increased solubility of guest compounds upon complexation if we know the slope of the solubility curve. In this study, we have developed a prediction method for the slope of the solubility curve based on MC docking simulations.

Construction of the molecular models and protocol of MC docking simulations

The starting configurations of the α-, β-, and γ-CDs for MC simulations were taken from the X-ray crystal structure. The InsightII/Builder module (version 2000, Accelrys Inc. San Diego, USA) was used to generate missing hydrogen atoms for the CDs used in the simulations. The atomic coordinates of the 63-guest compounds were obtained from Sci-Finder. All simulations were performed using a general molecular modeling program, CHARMM [8] (version 28b2), with a parm22 all-atom force field. The parameter values for the CDs were modified according to a revised carbohydrate parameter set (carbohydrate solution force field-CSFF [9]) of CHARMM. The MC docking simulations were performed using a 'MC' module of CHARMM. The short-range nonbonded interactions were truncated with a 13-Å cutoff. An implicit solvent water model was used with a distance-dependent dielectric constant. The docking process was assumed to be a 1:1 interaction between the CD and each guest or a dimeric association between guests during the MC runs. The initial configuration of each host and guest molecule was positioned arbitrarily within a neighboring distance. Trials to a new configuration were accomplished by changing each move set of a guest molecule. The MC move set for flexible docking was composed of rigid translations, rigid rotations, and rotations of freely rotatable dihedral angles of the guest. A single step consists of selecting a random conformer, making a random move, minimizing the energy of a new conformer, and then checking the energy with a Metropolis [10] criterion. This process uses a combined methodology consisting of the Metropolis criterion for global optimization and an energy minimization method for local optimization [11]. The CDs were weakly fixed using a harmonic positional restraint of CHARMM to maintain backbone integrity. The MC-minimized structures were saved every 20 steps for 20,000 trials. These MC processes produced various docked structures for each guest with a CD or guest dimer.

Calculation of interaction energy and solvation free energy

All the energy terms including interaction energy, polar solvation free energy, and nonpolar solvation free energy were calculated for both the CD-guest complex and the guest–guest dimer. The interaction energy ΔE_{inte} is the potential energy difference between a complex and each molecule and is defined as:

$$\Delta E_{\text{inte}} = \langle \Delta E_{\text{vdw}} \rangle + \langle \Delta E_{\text{elec}} \rangle$$

where $< >$ denotes an average over a set of snapshots along an MC trajectory. E_{vdw} and E_{elec} denote vdW and electrostatic energies, respectively. The polar contribution to the solvation free energy was calculated by solving the Poisson–Boltzmann equation with the PBEQ module of the CHARMM program. The nonpolar solvation free energy ΔE_{np} accounts for cavity creation in water and vdW interactions between the modeled nonpolar molecule and water molecules. This term can be conceptualized as transferring a nonpolar molecule with the shape of the host or guest from vacuum to water. This transfer free energy is described as [12]:

$$\Delta E_{\text{np}} = \gamma A + b$$

where A is the solvent-accessible surface area calculated by the CHARMM program, γ and b are 0.00542 kcal/mol Å^2 and 0.92 kcal/mol, respectively, which are derived from the experimental transfer energies of hydrocarbons [13]. The probe radius is 1.4 Å.

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