Combination of 2D-, 3D-Connectivity and Quantum Chemical Descriptors in QSPR. Complexation of α- and β-Cyclodextrin with Benzene Derivatives

Ernesto Estrada,* Iliana Perdomo-López, and Juan J. Torres-Labandeira

Faculty of Pharmacy, Department of Organic Chemistry and Department of Pharmacy and Pharmaceutical Technology, University of Santiago de Compostela, 15706 Santiago de Compostela, Spain

Received May 1, 2001

Quantitative models are found to describe the complexation of α- and β-cyclodextrin with mono- and 1,4-disubstituted benzene derivatives by using combinations of 2D-, 3D-connectivity and quantum chemical molecular descriptors. The association constants (K_a) for the inclusion complexation of cyclodextrins and benzene derivatives are calculated by the models found with a high degree of precision. These models also permit the interpretation of the driving forces of such complexation processes. In the case of the complexation of α-cyclodextrin with benzene derivatives these driving forces are mainly the electronic repulsion between frontier orbitals of the host and guest molecules. However, the complexation of β-cyclodextrin with benzene derivatives is controlled by topological and topographic parameters indicating the relevance of the van der Waals and hydrophobic interactions. We also carried out molecular modeling studies showing that for α-cyclodextrin complexes the benzene ring is outside the cavity of the cyclodextrin, while in β-cyclodextrin they penetrate deeply into the apolar and hydrophobic cavity of the host, which explain the differences in the driving forces for both complexation processes.

INTRODUCTION

The study of quantitative relationship between physicochemical properties and the chemical structure (QSPR) has become an important area of research in computational chemistry.[1−4] This kind of studies has two main objectives. The first is to provide a way for estimating the studied property for novel compounds with an acceptable degree of precision. The second, but not less important, is to make structural interpretations of the physicochemical property studied. At present there exist a great number of molecular descriptors that can be used in QSPR studies.[5] Despite these descriptors, and the procedures employed for their definitions are of different nature, they try to account for the topological (2D), geometric (3D), and electronic features of molecules. Some of these descriptors, however, account for physicochemical more than for structural features of molecules. They include those based on experimentally determined physicochemical properties, such as most of the hydrophobic, electronic, and steric substituent constants.[6] In contrast, the so-called topological indices (TIs) accounts for structural information contained in a two-dimensional representation of molecules, the molecular graph, without consideration of any physicochemical molecular feature.[7,8] Most of these molecular descriptors can be considered as structure-explicit ones. Another group of descriptors, the so-called quantum chemical ones,[9] maintain encrypted the molecular structure and describe electronic features of molecules based on the use of the molecular wave function. Geometrical descriptors account for the 3D structural features of molecules in an explicit way,[10] such as bond distances, bond angles, and torsion angles or in an implicit way in the form of topographic descriptors.[11]

The topographic molecular descriptors are based on molecular graphs with appropriate weights to account for 3D molecular features. The pioneering works in this direction were done by Milan Randić at the end of 1980s.[12−14] In these works Randić proposed the use of topographic distance matrices, first based on graph embedded into a hexagonal lattice and then into a 3D diamond lattice. A further work of Bogdanov et al.[15] proposed a 3D distance matrix to compute a 3D Wiener index. The other direction in the search of topographic indices was followed by Estrada using quantum chemical parameters as vertex and edge weights for building topographic adjacency matrices.[16−18] This author defined in 1993 topographic connectivity indices based on bond order weighted molecular graphs.[16] Further, this type of weighted graphs was used to define a topographic edge adjacency matrix (3D bond matrix) as well as a 3D-bond connectivity index.[17] In a parallel approach Estrada introduced molecular graphs with vertices weighted by electron charge density on atoms to define a 3D adjacency matrix and a set of topographic connectivity descriptors.[18] In more recent years different authors have defined other types of topographic descriptors.[19−22]

Up to now there are not extensive applications of topographic descriptors in QSPR/QSAR studies. In a previous work we demonstrated the good possibilities of 3D-connectivity indices in QSPR/QSAR studies in comparison to 2D-connectivity and quantum chemical descriptors.[23] However, it has been previously demonstrated that the best possibilities of molecular descriptors in QSAR/QSPR come from the combined used of different classes of them accounting for several structural features. Consequently, we will study here the complexation of α- and β-cyclodextrin with benzene derivatives by using a combination of 2D-, 3D-connectivity indices and quantum chemical descriptors.

* Corresponding author phone: 34-981-563100 ext 14938; fax: 34-981-594912; e-mail: estrada66@yahoo.com.

10.1021/ci0100402 CCC: $20.00
Published on Web 09/28/2001

MOLECULAR DESCRIPTORS

Here we will find QSPR models to describe the complexation of α- and β-cyclodextrin with benzene derivatives by using a combination of topological (2D-connectivity), topographic (3D-connectivity), and quantum chemical descriptors. The QSPR models to be obtained are of the following form

$$\text{property} = a_0 + a_1x_1 + a_2x_2 + \cdots + a_nx_n$$

in which x_i are the topological, topographic, and quantum chemical molecular descriptors. The 2D connectivity indices are defined as follows[24−26]

$$^h\chi_t = \sum_{s=1} (\delta_i\delta_j \cdots \delta_{h+1})_s^{-0.5} \quad (1)$$

where $^h\chi_t$ is the connectivity index of type t and order h. The product is over the $h + 1$ vertex degrees in the subgraph having h edges, and the summation is carried out over all subgraphs of type t in the molecule. The different types of subgraphs studied in the molecular connectivity scheme are as follows: path, clusters, path-clusters, and chains, which are designed as *p*, *C*, *pC*, and *Ch*, respectively, according to their original definitions.

The valence connectivity indices are calculated in a similar way but using valence degrees instead of simple vertex degrees[25,26]

$$^h\chi_t^v = \sum_{s=1} (\delta_i^v\delta_j^v \cdots \delta_{h+1}^v)_s^{-0.5} \quad (2)$$

with the valence degree of an atom defined as follows:

$$\delta_i^v = Z_i^v - h_i \text{ for second row elements} \quad (3)$$

$$\delta_i^v = \{(Z_i^v - h_i)\}/\{(Z_i - Z_i^v - 1)\} \text{ for the rest of the atoms} \quad (4)$$

where Z_i^v is the number of valence electrons, h_i is the number of hydrogen atoms bonded to the atom, and Z_i is the atomic number.

Bond connectivity indices have been defined as follows[27−30]

$$^h\epsilon_t = \sum_{s=1} (\delta(e_i)\delta(e_j) \cdots \delta(e_h))_s^{-0.5} \quad (5)$$

where $\delta(e_i)$ is the bond degree and the sum is over all edges of the subgraph t.

The 3D-connectivity indices used in the current work have been introduced by using the same graph invariant that for the 2D-connectivity indices but using quantum chemical properties as vertex and edge weights. These topographic descriptors can be classified in two different groups. The first is that of descriptors based on bond order-weighted molecular graphs. The other group is formed by descriptors based on electron charge density-weighted molecular graphs.

Bond order weighted vertex connectivity indices $^h\Omega_t$ are calculated from expression (1) but using bond order weighted vertex degrees instead of simple vertex degrees.[16] The bond order weighted vertex degrees are defined as follows[16]

$$\delta_i(\rho) = \sum_i \rho_{ij} \quad (6)$$

where ρ_{ij} is the bond order or valence index of bond $i-j$, and the sum is over all non-hydrogen atoms adjacent to i.

The bond connectivity indices based on bond order weighted molecular graphs $^h\epsilon_t(\rho)$ are calculated from expression (5) but using the following definition of bond degrees[17]

$$\delta(e_k) = \delta_i(\rho) + \delta_j(\rho) - 2\rho_{ij} \quad (7)$$

where the bond e_k is incident to vertices i and j.

Connectivity indices based on electron charge density $^h\Omega_t(q)$ are calculated from expression (1) but using the following vertex degrees[18]

$$\delta_i(q) = q_i - h_i \quad (8)$$

where q_i is the electron charge density on atom i. A correction for hydrogen atoms is introduced in this scheme to calculate the indices $^h\Omega_t^c(q)$ according to the following approach

$$\delta_i^c(q) = q_i - \sum_j q_{hj} \quad (9)$$

where q_{hj} is the electron charge density of the jth hydrogen atom bonded to the atom i.

A series of quantum chemical molecular descriptors was also computed by following the procedure explained in the following section. This set of descriptors was calculated only for the atoms of the phenyl ring, which is the structural pattern repeated in all compounds of these data set. It includes the electronic charge on atoms and the energy of the highest occupied molecular orbital (HOMO) and of the lowest unoccupied molecular orbital (LUMO) as well as superdelocalizability indices, such as electrophilic and nucleophilic superdelocalizabilities of σ and π electrons in the molecule. For the definition of these terms see ref 31. A resume of the symbols and names of the topological, topographic, and quantum chemical descriptors to be used in the current work is given in Table 1.

Data Sets and Computations. Two data sets of benzene derivatives were studied in the current work. The first data set is formed by 56 mono- and 1,4-disubstituted benzenes for which the association constants (K_a) for the inclusion complexation with α-cyclodextrin were determined experimentally and further compiled by Liu and Guo.[32] The second data set is formed by the association constants for the inclusion complexation of 46 mono- and 1,4-disubstituted benzene derivatives with β-cyclodextrin.[32]

2D vertex and edge molecular connectivity indices of different types and orders were calculated by the computer system MODEST for Windows.[33] In computing 3D connectivity indices full geometry optimization of the benzene derivative structures was carried out by the semiempirical quantum chemical method AM1.[34] Then the output files were used as input for the system MODEST[33] in order to compute the topological, topographical, and quantum chemical descriptors (the software can be obtained free upon request to E. Estrada). The full geometry optimization calculations were done with MOPAC 6.0[35] by using the keyword PRECISE in order to obtain better precision. Two other keywords used were VECTORS to generate the eigenvectors of the wave function and the word BONDS to obtain the bond orders and valencies of the correspondent bonds and atoms in the molecules, which are used in the definition of 3D connectiv-

Table 1. Symbols for Topological, Topographic, and Quantum Chemical Descriptors and Their Definitions

${}^h\chi_p$	path connectivity index of order $h = 0-6$
${}^h\chi_C$	cluster connectivity index of order $h = 3-6$
${}^h\chi_{pC}$	path-cluster connectivity index of order $h = 4-6$
${}^h\chi_p^v$	valence path connectivity index of order $h = 0-6$
${}^h\chi_C^v$	valence cluster connectivity index of order $h = 3-6$
${}^h\chi_{pC}^v$	valence path-cluster connectivity index of order $h = 4-6$
${}^h\epsilon_p$	path bond connectivity index of order $h = 1-6$
${}^h\epsilon_C$	cluster bond connectivity index of order $h = 3-6$
${}^h\epsilon_{pC}$	path-cluster bond connectivity index of order $h = 4-6$
${}^h\Omega_p$	path bond-order-based topographic connectivity index of order $h = 0-6$
${}^h\Omega_C$	cluster bond-order-based topographic connectivity index of order $h = 3-6$
${}^h\Omega_{pC}$	path-cluster bond-order-based topographic connectivity index of order $h = 4-6$
${}^h\Omega_p(q)$	path charge-based topographic connectivity index of order $h = 0-6$
${}^h\Omega_C(q)$	cluster charge-based topographic connectivity index of order $h = 3-6$
${}^h\Omega_{pC}(q)$	path-cluster charge-based topographic connectivity index of order $h = 4-6$
${}^h\Omega_p^c(q)$	path hydrogen-corrected charge-based topographic connectivity index of order $h = 0-6$
${}^h\Omega_C^c(q)$	cluster hydrogen-corrected charge-based topographic connectivity index of order $h = 3-6$
${}^h\Omega_{pC}^c(q)$	path-cluster hydrogen-corrected charge-based topographic connectivity index of order $h = 4-6$
${}^h\epsilon_p(\rho)$	path bond-order-based topographic bond connectivity index of order $h = 1-6$
${}^h\epsilon_C(\rho)$	cluster bond-order-based topographic bond connectivity index of order $h = 3-6$
${}^h\epsilon_{pC}(\rho)$	path-cluster bond-order-based topographic bond connectivity index of order $h = 4-6$
$Q(i)$	electronic charge on atom i
$B(i-j)$	local dipole character of the bond $i-j$
$ES_\sigma(i)$	σ electrophilic superdeslocalizability on atom i
$ES_\pi(i)$	π electrophilic superdeslocalizability on atom i
$ES_T(i)$	total electrophilic superdeslocalizability on atom i
$NS_\sigma(i)$	σ nucleophilic superdeslocalizability on atom i
$NS_\pi(i)$	π nucleophilic superdeslocalizability on atom i
$NS_T(i)$	total nucleophilic superdeslocalizability on atom i
E_{HOMO}	energy of the highest occupied molecular orbital
E_{LUMO}	energy of the lowest unoccupied molecular orbital

ity indices. A total number of 41 topological, 55 topographic connectivity indices, and 51 quantum chemical descriptors were calculated according to the definitions given before and in Table 1.

The quantum chemical descriptors were calculated for atoms in the phenyl ring, which is the structural pattern that is repeated in all structures studied. The atoms in the phenyl ring are numbered in the clockwise sense starting from the carbon supporting the substituent X.

The statistical processing to obtain the QSPR models was carried out by using the forward stepwise regression method, where the independent variables are individually added or deleted from the model at each step of the regression depending on the Fisher ratio values selected to enter and to remove until the "best" model is obtained.

Molecular mechanics calculations of the complexation of α- and *β*-cyclodextrin with some benzene derivatives were carried out using the MM2 force field and full-geometry optimization with the Hyperchem software.[36] The molecules of the guest were introduced in the host by the two possible orientations, and the minimum energy was determined in both cases. These orientations are (a) introducing the substituent to the widest cavity of the cyclodextrin or (b) introducing the phenyl ring to the widest cavity of the cyclodextrin. In all cases the orientation (a) resulted the most stable.

QUANTITATIVE STRUCTURE ASSOCIATION CONSTANT RELATIONS

The association constants (K_a) for the inclusion complexation of α-cyclodextrin with 56 benzene derivatives have been compiled by Liu and Guo.[32] This data set includes 25 mono- and 31 1,4-disubstituted benzene derivatives. The values of ln K_a were described by multivariate linear regression analysis using a combination of 2D-, 3D-connectivity indices and quantum chemical descriptors: the best QSPR model obtained is given below together with its statistical parameters

$$\ln K_a(\alpha - CD) = -11.226 - 1.472(E_{HOMO}) + 1.888(E_{LUMO}) + 13.099[B(3-4)] + 29.054[ES_\sigma(1)] + 33.119[{}^3\Omega_C^c(q)] + 1.311({}^4\epsilon_p) - 22.318({}^3\chi_C^v) \quad (10)$$

$$N = 56,\ R = 0.9332,\ R_{CV} = 0.9230,\ s = 0.44,\ RMSECV = 0.50,\ F = 46.3$$

where N is the number of compounds, R is the correlation coefficient, R_{CV} is the correlation coefficient for the leave-one-out cross-validation procedure, s is the standard deviation of the regression, *RMSECV* is the root of the mean square error of the cross-validation, and F is the Fisher ratio for the regression.

Similarly we have described the association constants of *β*-cyclodextrin with 23 mono- and 23 1,4-disubstituted benzene derivatives with a combination of topological, topographic and quantum chemical descriptors. The best QSPR model found is given below together with the statistical parameters of the regression:

$$\ln K_a(\beta\text{-}CD) = 1.519 + 2.397({}^3\chi_p^v) + 79.865({}^6\chi_p^v) - 477.712({}^5\chi_C^v) - 37.016[{}^4\Omega_p(q)] - 102.470[{}^6\Omega_p(q)] + 547.198[{}^5\Omega_C(q)] + 45.286[{}^4\Omega_p{}^c(q)] - 1.603[{}^6\Omega_{pC}{}^c(q)] \quad (11)$$

$$N = 46,\ R = 0.9406,\ R_{CV} = 0.9272,\ s = 0.23,\ RMSECV = 0.27,\ F = 35.5$$

Table 2. Experimental and Calculated Values of the Association Constant (ln K_a) for the Complexation of α-Cyclodextrin with Mono- and 1,4-Disubstituted Benzene Derivatives as Well as Residuals of the Regression and Cross-Validation

X	Y	ln K_a (obsd)	ln K_a(calc)	residual	CV-residual
F	H	3.68	4.51	−0.83	−0.99
Cl	H	4.72	4.61	0.11	0.12
Br	H	6.29	5.74	0.55	0.59
I	H	7.09	6.51	0.58	0.65
Cl	Cl	5.42	5.37	0.05	0.06
Br	Br	6.93	7.14	−0.21	−0.26
I	I	8.34	8.57	−0.23	−0.35
Cl	F	4.17	5.08	−0.91	−0.98
Br	F	5.52	6.32	−0.80	−0.85
I	F	6.89	7.15	−0.26	−0.30
OCH_3	OCH_3	4.02	4.18	−0.16	−0.18
OEt	OEt	4.85	5.03	−0.18	−0.26
CO_2Me	CO_2Me	6.14	6.19	−0.05	−0.07
CH_3	NH_2	4.05	4.51	−0.46	−0.54
Cl	NH_2	5.53	5.61	−0.08	−0.09
CN	NH_2	6.11	5.52	0.59	0.67
NO_2	NH_2	6.45	5.91	0.54	0.68
I	OH	7.75	7.17	0.58	0.66
Cl	OH	5.61	5.07	0.54	0.57
Br	OH	6.56	6.38	0.18	0.19
CN	OH	5.06	5.07	−0.01	−0.01
NO_2	OH	5.99	5.33	0.66	0.68
COOH	$NHCH_3$	7.17	6.77	0.40	0.49
COOH	F	6.22	6.17	0.05	0.05
NO_2	COOH	5.86	6.06	−0.20	−0.22
SCH_3	CH_2OH	4.44	4.95	−0.51	−0.62
Br	SCH_3	5.74	5.93	−0.19	−0.23
SCH_3	Cl	5.04	4.48	0.56	0.77
SCH_3	NH_2	4.62	4.56	0.06	0.07
CH_3	H	3.60	3.75	−0.15	−0.17
H	H	3.35	3.56	−0.21	−0.26
Et	H	4.60	4.48	0.12	0.13
CH_3	CH_3	4.28	3.72	0.56	0.74
i-Pr	H	4.56	4.56	0.00	0.00
OCH_3	H	4.95	4.66	0.29	0.32
OEt	H	5.14	5.08	0.06	0.07
CH_2OH	H	4.57	4.96	−0.39	−0.43
CH_2Cl	H	5.32	4.48	0.84	0.88
CHO	H	4.62	4.50	0.12	0.14
COMe	H	4.94	5.09	−0.15	−0.16
CO_2Me	H	5.36	5.41	−0.05	−0.06
CO_2Et	H	5.89	5.96	−0.07	−0.09
CN	H	4.36	4.53	−0.17	−0.19
NHEt	H	4.85	4.92	−0.07	−0.08
H	NHMe	4.42	4.43	−0.01	−0.01
NMe_2	H	5.15	5.39	−0.24	−0.29
NHCOMe	H	4.63	4.99	−0.36	−0.40
C C	H	4.46	3.92	0.54	0.58
CH_3	OH	3.92	4.04	−0.12	−0.14
H	OH	3.61	3.85	−0.24	−0.27
OH	OH	3.18	3.05	0.13	0.17
COOH	H	5.82	5.41	0.41	0.44
COOH	OH	6.07	5.98	0.09	0.10
COOH	NH_2	6.22	6.40	−0.18	−0.20
CHO	OH	4.20	5.24	−1.04	−1.15
H	NH_2	4.03	4.10	−0.07	−0.08

Observed and calculated values of ln K_a as well as the residuals and cross-validation residuals for the complexation of α- and β-cyclodextrin with benzene derivatives are given in Tables 2 and 3, respectively. Plots of observed versus calculated ln K_a for both sets of compounds are illustrated in Figure 1.

Both models explain more than 85% of the variance in the experimental values of the association constants. Correlation coefficients of 0.92 were obtained by Liu and Guo for these data sets of benzene derivatives complexed with α- and β-cyclodextrin using steric, electronic, and hydrophobic constants in a nonlinear regression model.[32] In such models the number of coefficients to be determined in the regression analysis is 10, while here the number of such coefficients are 8 and 9 for models (10) and (11), respectively.

Table 3. Experimental and Calculated Values of the Association Constant (ln K_a) for the Complexation of β-Cyclodextrin with Mono- and 1,4-Disubstituted Benzene Derivatives as Well as Residuals of the Regression and Cross-Validation

X	Y	ln K_a (obsd)	ln K_a(calc)	residual	CV-residual
H	H	4.79	4.46	0.33	0.40
CH_3	H	4.94	5.06	−0.12	−0.14
Et	H	5.80	5.86	−0.06	−0.08
C═CH	H	5.44	5.23	0.21	0.22
H	OH	4.77	4.73	0.04	0.05
OCH_3	H	5.34	5.03	0.31	0.34
OEt	H	5.66	5.35	0.31	0.39
CH_2OH	H	4.96	5.17	−0.21	−0.23
CH_2Cl	H	5.63	5.88	−0.25	−0.31
CHO	H	5.01	4.93	0.08	0.09
COMe	H	5.24	5.13	0.11	0.14
CO_2Me	H	5.76	5.73	0.03	0.04
CO_2Et	H	6.29	5.96	0.33	0.44
CN	H	5.14	5.09	0.05	0.06
H	NH_2	4.83	4.89	−0.06	−0.07
H	NHMe	4.87	5.27	−0.40	−0.44
NHC_2H_5	H	5.38	5.68	−0.30	−0.45
NMe_2	H	5.38	5.47	−0.09	−0.29
NHCOMe	H	5.06	5.27	−0.21	−0.32
NO_2	H	5.63	5.57	0.06	0.07
F	H	4.51	4.64	−0.13	−0.14
Cl	H	5.17	5.32	−0.15	−0.16
Br	H	5.77	5.99	−0.22	−0.24
I	H	6.74	6.50	0.24	0.31
COOH	H	5.88	5.68	0.20	0.25
CH_3	CH_3	5.48	5.60	−0.12	−0.16
Cl	Cl	5.77	5.89	−0.12	−0.13
Br	Br	6.85	6.72	0.13	0.17
I	I	7.31	7.36	−0.05	−0.17
CH_2OH	OH	4.98	5.10	−0.12	−0.13
C_2H_5	OH	6.20	5.78	0.42	0.71
NO_2	OH	5.50	5.43	0.07	0.08
I	OH	6.86	6.60	0.26	0.34
I	F	6.23	6.45	−0.22	−0.28
NO_2	NH_2	5.72	5.38	0.34	0.39
CH_3CO	OH	5.02	4.96	0.06	0.08
Br	OH	6.10	6.12	−0.02	−0.02
CH_3O	OH	5.09	4.91	0.18	0.21
OH	OH	4.73	4.95	−0.22	−0.25
Cl	OH	5.55	5.50	0.05	0.05
CH_3	OH	5.34	5.27	0.07	0.08
COOH	OH	5.06	5.45	−0.39	−0.45
Cl	NO_2	5.04	5.10	−0.06	−0.09
NO_2	COOH	5.39	5.39	0.00	−0.01
CHO	OH	4.96	4.91	0.05	0.06
COOH	NH_2	5.21	5.63	−0.42	−0.53

The main difference in models (10) and (11) is given by the fact that the model describing the complexation of α-cyclodextrin includes four electronic parameters, while that for the complexation of β-cyclodextrin with benzene derivatives does not included any of such parameter. This model includes five topographic descriptors and three topological indices but no one quantum chemical descriptor. The interpretation of these differences on the basis of the driving forces for cyclodextrin inclusion complexation is given in a following section. However, before making this interpretation we need to orthogonalize the molecular descriptors included in such models due to the high intercorrelation existing between some of them.

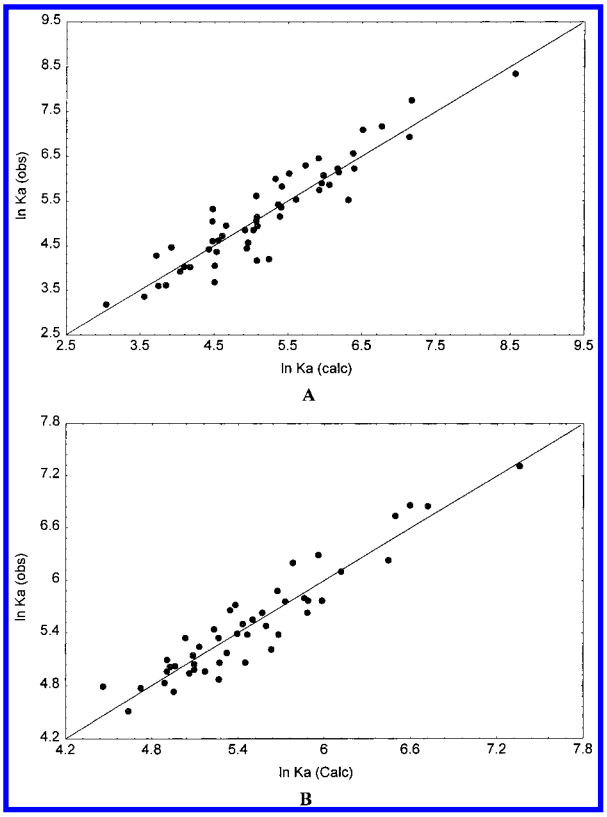

Figure 1. Observed versus predicted association constants (ln K_a) for the complexation of α- (A) and β-cyclodextrin (B) with mono- and 1,4-disubstituted benzene derivatives.

ORTHOGONALIZATION OF DESCRIPTORS

The orthogonalization process of molecular descriptors was introduced by Randić 10 years ago as a way to improve the statistical interpretation of the models built by using interrelated indices.[37−41] The main philosophy of this approach is to avoid the exclusion of descriptors on the basis of its collinearity with other variables previously included in the model. It is known that the interrelatedness among the different descriptors can result in highly unstable regression coefficients, which makes impossible to know the relative importance of an index and underestimates the utility of the regression coefficients in a model. However, in some cases strongly interrelated descriptors can enhance the quality of a model because the small fraction of a descriptor which is not reproduced by its strongly interrelated pair can provide positive contributions to the modeling. This is the case of pairs of topological and topographic descriptors based on the same graph-theoretical invariant. For instance, in model (10) the indices ${}^3\chi_C^{\upsilon}$ and ${}^3\Omega_C^c(q)$ are based on the same graph-invariant, i.e., on multiplication of vertex degrees in a cluster of order three. Consequently, they are strongly interrelated, containing a duplication of 99% of information. However, there is 1% of structural information based on electron charge densities of the atoms which is contained in the topographic index ${}^3\Omega_C^c(q)$ that can be useful for describing the complexation constant in α-cyclodextrin. A more critical situation is observed in the model (11) where all the descriptors included are 2D and 3D connectivity indices, many of them showing strong interrelation.

The Randić method of orthogonalization has been described in detail in several publications.[37−41] Thus, we will give only a general overview here. The first step in orthogonalizing the molecular descriptors in models (10) and (11) is to select the appropriate order of orthogonalization, which in this case is the order in which the variables were selected in the forward stepwise search procedure of the linear regression analysis. The first variable ($\upsilon 1$) is taken as the first orthogonal descriptors ${}^1O(\upsilon 1)$, and the second one is orthogonalized with respect to it by taking the residual of its correlation with ${}^1O(\upsilon 1)$. The process is repeated until all variables are completely orthogonalized, and the orthogonal variables are then used to obtain the new model. In Tables 4 and 5 we resume the results of the orthogonalization of molecular descriptors included in models (10) and (11). In this case, the last row corresponds to the final model with the orthogonalized molecular descriptors. In the orthogonalization process of variables in model (11) there was an orthogonal variable that resulted statistically not significant, and it was excluded in the final model. This variable ${}^5\chi_C^{\upsilon}$ is very strongly correlated to ${}^5\Omega_C(q)$ containing 99.84% of duplication, which is probably the main cause for the lack of significance of the 2D descriptor to the description of the complexation process in β-cyclodextrin.

In Tables 4 and 5 we can observe the great stability of the regression coefficients after the orthogonalization of molecular descriptors. This stability influences the relative importance of each descriptor to the property studied. In Table 6 we give the values of the mean effect of each variable in models (10) and (11) to the complexation constants in α- and in β-cyclodextrin, respectively, before and after the orthogonalization of variables.

INTERPRETATION OF QSPR MODELS

At present it is known that the cyclodextrin inclusion complexation is influenced by a different kind of interactions. An overwhelming role is played by the van der Waals forces, primarily consisting of induction and dispersion forces.[42,43] The hydrophobic interaction is another factor influencing the complexation due to the hydrophobic nature of the cavity of cyclodextrins.[44,45] Another factor is related to the electrostatic force, mainly due to dipole−dipole interactions as consequence of the highly polar character of cyclodextrin.[46,47] However, most of these factors are interrelated to each other, and it is difficult to determine the contribution of each by separate. For instance, hydrophobic interaction is intimately related to van der Waals forces, and the electrostatic interactions are also related to dispersion interactions, which are part of the van der Waals forces.

When molecular descriptors based on physicochemical properties, such as substituent constants, are used in QSPR, it is possible to determine the nature of the driving forces of the complexation, e.g., hydrophobic, steric, or electronic. For instance, Liu and Guo have determined that "in α-cyclodextrin complexes, the electronic effect is more important that the hydrophobic effect" and in β-cyclodextrin "the hydrophobic effect contributes more than the electronic effect".[32] However, as these factors are interrelated to each other it is difficult to obtain definitive conclusion on the nature of the driving forces and Cai et al. have recently concluded that "the van der Waals interaction should be the main driving force for the inclusion complexes between α-cyclodextrin with mono- and 1,4-disubstituted benzenes,

Table 4. Regression Coefficients in Model (10) for Orthogonal Molecular Descriptors

${}^1O[{}^3\Omega_C^c(q)]$	${}^2O[B(3-4)]$	${}^3O[E_{HOMO}]$	${}^4O[{}^4\epsilon_p]$	${}^5O[E_{LUMO}]$	${}^6O[{}^3\chi_C^v]$	${}^7O[ES_\sigma(1)]$	intercept	R	s
5.0771							4.1447	0.6616	0.855
5.0771	7.1418						4.1447	0.7626	0.745
5.0771	7.1418	−0.6304					4.1447	0.8370	0.636
5.0771	7.1418	−0.6304	0.8225				4.1447	0.8774	0.563
5.0771	7.1418	−0.6304	0.8225	0.9500			4.1447	0.8956	0.527
5.0771	7.1418	−0.6304	0.8225	0.9500	−21.1820		4.1447	0.9250	0.455
5.0771	7.1418	−0.6304	0.8225	0.9500	−21.1820	29.0541	4.1447	0.9332	0.435

Table 5. Regression Coefficients in Model (11) for Orthogonal Molecular Descriptors

${}^1O[{}^3\chi_p^v]$	${}^2O[{}^6\chi_p^v]$	${}^3O[{}^4\Omega_p^c(q)]$	${}^4O[{}^6\Omega_{pC}^c(q)]$	${}^5O[{}^5\Omega_C(q)]$	${}^6O[{}^6\Omega_p(q)]$	${}^7O[{}^4\Omega_p(q)]$	intercept	R	s
1.8367							3.3532	0.8390	0.342
1.8367	−5.8902						3.3532	0.8617	0.322
1.8367	−5.8902	3.9075					3.3532	0.8768	0.309
1.8367	−5.8902	3.9075	−0.8210				3.3532	0.8866	0.301
1.8367	−5.8902	3.9076	−0.8211	261.7926			3.3532	0.9051	0.280
1.8367	−5.8902	3.9076	−0.8211	261.7926	−25.8547		3.3532	0.9127	0.273
1.8367	−5.8902	3.9076	−0.8211	261.7926	−25.8547	−37.0161	3.3532	0.9353	0.239

Table 6. Mean Effect of Each Variable Included in Models (10) and (11) before and after Orthogonalization

model (10)			model (11)		
index	no-orthog	orthog	index	no-orthog	orthog
${}^3\Omega_C^c(q)$	7.02	1.08	${}^3\chi_p^v$	2.78	2.13
$B(3-4)$	0.91	0.50	${}^6\chi_p^c$	9.20	−0.68
E_{HOMO}	13.50	5.78	${}^4\Omega_p^c(q)$	24.88	2.15
${}^4\epsilon_p$	2.52	1.58	${}^6\Omega_{pC}^c(q)$	−0.38	−0.19
E_{LUMO}	0.09	0.05	${}^5\Omega_C(q)$	3.27	1.56
${}^3\chi_C^v$	−5.33	−5.06	${}^6\Omega_p(q)$	−10.58	−2.67
$ES_\sigma(1)$	−2.27	−2.27	${}^4\Omega_p(q)$	−22.07	−22.07

rather than the electrostatic force".[48] Thus, it could be preferable to find the structural more than the physicochemical factors responsible for the complexation of cyclodextrins and benzene derivatives. With this objective we will use the orthogonalized variables for interpreting the QSPR models previously developed with topological, topographic, and quantum-chemical descriptors.

The preponderance of electronic effects in model (10) over other types of molecular descriptors clearly indicates the importance of the electrostatic factor in the complexation of α-cyclodextrin. The greatest mean effect of an orthogonalized descriptor, the average contribution of each orthogonal variable on the complexation, is that of the energy of the highest occupied molecular orbital (E_{HOMO}). The negative sign of the coefficient of this variable (and the positive sign in E_{LUMO}) indicates that electron repulsion in frontier orbitals is probably a decisive factor in the complexation of benzene derivatives in α-cyclodextrin. Two other electronic parameters appear in this model that are also related to the frontier orbitals (electrophilic superdelocalizability σ of the atom number 1) and to dipole−dipole interactions (local dipole character of the bond 3−4). This model included only two topological and one topographic descriptor, which do not account for differentiation between mono- and 1,4-disubstituted benzene derivatives. However, the topological index ${}^3\chi_C^v$ has the second greatest mean effect on the complexation (see Table 6), which indicates that after electronic effects topological factors are of relative importance to the complexation of benzenes in α-cyclodextrin.

In contrast, model (11) does not include any quantum chemical descriptor indicating the lack of importance of the "pure" electrostatic interactions in the complexation of benzene derivatives in β-cyclodextrin. In this case the molecular descriptors included are topographic and topological indices of higher orders describing paths, clusters, and path-clusters of orders 4−6. We can see in Table 5 that the model including only one topological descriptor (${}^3\chi_p^v$) has a correlation coefficient of 0.8390, that explains 70% of the variance in the complexation of benzene derivatives in β-cyclodextrin.

The greatest mean effect of an orthogonalized variable corresponds to a 3D-connectivity index based on charge density weighted graphs of order 4: ${}^4\Omega_p(q)$ (observe the difference with that of nonorthogonal descriptors). The second and third mean contributions are also of 3D-connectivity indices. Another 3D-connectivity index, ${}^6\Omega_{pC}^c(q)$, accounts for differentiation between mono- and 1,4-disubstituted benzene derivatives. The 3D-connectivity indices are derived by using electron charge density as vertex weights in the calculations.[18] Thus, these descriptors contain some electronic information on the benzene derivatives. However, it has been clear in previous works with these descriptors that they can be considered as "corrected" connectivity indices and that their main structural information is that of the connectivity indices.[18,23] Consequently, all the descriptors included in model (11) account for the "molecular shape" of the benzene derivatives.[28,29,49−52]

The main reason of the differences between complexation of α- and β-cyclodextrin with benzene derivatives is that in the firsts the guest molecule is not completely inside the cavity of the host. In this case only the substituent in the benzene ring is inside the cavity of α-cyclodextrin as a consequence of the smaller size of this cavity compared to that of the β-cyclodextrin. Consequently, the complexation of these derivatives with the α-cyclodextrin do not depend on their "molecular shape". In this case the repulsive electronic interactions of the benzene derivatives and the host molecule determine the association constant of the complexation. On the contrary, in the complexation of β-cyclodextrin the benzene derivatives are completely inside the cavity of the host because this cavity is sufficiently larger as to accommodate the guest inside. This deeper inclusion of the guest in the apolar cavity of β-cyclodextrin is more influenced by topological and topographic molecular features that

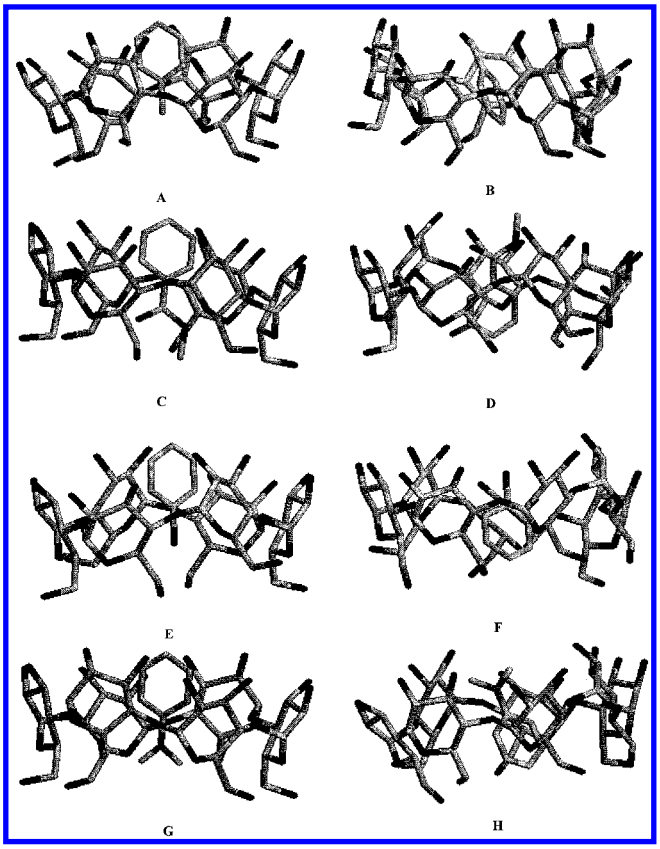

Figure 2. Molecular diagrams of the inclusion complexes of α- and *β*-cyclodextrin with four monosubstituted benzene derivatives calculated by molecular mechanic MM2 force field. Toluene in α- (A) and *β*-cyclodextrin (B); methylbenzoate in α- (C) and *β*-cyclodextrin (D); chlorobenzene in α- (E) and *β*-cyclodextrin (F); *N*,*N*-dimethylaniline in α- (G) and *β*-cyclodextrin (H).

determine the van der Waals and hydrophobic interactions of host−guest complexes. In closing, we conclude that stronger electronic interactions result from the noncomplete penetration of the guest molecule in the cavity of the host. However, a deep penetration of the guest in the cavity of the host results in topologic/topographic-controlled interactions, such as van der Waals and hydrophobic interactions.

To show the orientation of the benzene derivatives in the cavities of α- and *β*-cyclodextrin we have calculated the energy of four complexes by using molecular mechanics MM2 force field. The host molecules selected are as follows: toluene, chlorobenzene, methylbenzoate, and *N*,*N*-dimethylaniline. These substituents were selected because they account for different steric, hydrophobic, and electronic features as they are situated in different quadrants of a substituent diagram. This diagram was obtained by plotting 35 aromatic substituent in the space spanned by the first two principal components extracted from intraclass correlation matrix based on hydrophobic, electronic, and steric constants.[53] The computational procedure followed has been explained in a previous section. In Figure 2 we illustrate the stick diagrams of the complexes of these four benzene derivatives with both α- and *β*-cyclodextrin. As can be seen, in all cases the benzene derivative does not penetrate the cavity of the α-cyclodextrin, but it is kept with the substituent inside and the phenyl ring outside the cavity. On the contrary, deeper penetrations are observed for the benzene derivatives in *β*-cyclodextrin. In these cases the benzene derivative is completely inside the apolar cavity of the cyclodextrin as expected from our predictions based on QSPR models. The inclination observed in the benzene derivatives complexed in *β*-cyclodextrin has been observed experimentally. For instance, Kamiya et al. have observed that monosubstituted benzene guests have an inclination angle of the molecular long axis in the range of 19°−27°.[54] This reproduction of the observed inclination angle of the guest in the host molecule by molecular mechanics calculations is indicative that this theoretical approach reproduces well enough the stereochemistry of the inclusion complexes in agreement with previous reports in this direction.[55,56]

CONCLUSION

The models found to describe the complexation of α- and *β*-cyclodextrin with benzene derivatives include molecular descriptors accounting for topological (2D-connectivity), topographic (3D-connectivity), and electronic (quantum chemical) features of the studied molecules. These model using such combination of molecular descriptors are better than any other model that can be found by using only one type of the studied descriptors. Thus, we have proved that the combined use of 2D-, 3D-connectivity and quantum chemical descriptors is an appropriate approach to QSPR studies. These models not only are good enough to predict the association constants of the benzene derivatives in cyclodextrins but also permit the interpretation of the driving forces of such complexation processes after the orthogonalization of variables is carried out.

We have proved with the combined use of topological, topographic, and quantum chemical descriptors that the main driving force for the complexation of α-cyclodextrin with benzene derivatives are the electronic repulsion, mainly between frontier orbitals, of the host and guest molecules. The other factors, van der Waals and hydrophobic interactions, are mainly nonsignificant in this complexation. It is due to the fact that the benzene derivatives do not penetrate into the cavity of the cyclodextrin as has been proved by our molecular modeling calculations. On the contrary, the complexation process of *β*-cyclodextrin with benzene derivatives is controlled by topological and topographic parameters indicating the relevance of the van der Waals and hydrophobic interactions that are mainly dependent on such structural features. In this case the electronic interaction is not a driving force of the process of complexation as it is proved by the lack of any quantum chemical descriptor in the QSPR model. The main cause of the behavior is the deep penetration of benzene derivatives into the cavity of the cyclodextrin that is mainly apolar and hydrophobic.

ACKNOWLEDGMENT

E.E. thanks the Ministero de Educacion y Cultura for a contract as Foreign Young Researcher in Spain. I.P.-L. acknowledges the University of Santiago de Compostela for a foreign research grant. Thanks are given to the Xunta de Galicia (projects PGIDT00PX120317PR and PGIDT99-PXI20305B) and Ministerio de Educaci*σσ*n y Cultura, Spain (project PM99-0125) for partial financial support.

REFERENCES AND NOTES

(1) Katritzky, A. R.; Lobanov, V. S.; Karelson, M. QSPR: The correlation and quantitative prediction of chemical and physical properties from structure. *Chem. Soc. Rev.* **1995**, 279−287.

(2) *Advances in Quantitative Structure−Property Relationships*; Charton, M., Ed.; JAI Press: Amsterdam, 1996; Vol. 1.
(3) Katritzky, A. R.; Maran, U.; Lobanov, V. S.; Karelson, M. Structurally diverse quantitative structure−property relationship correlations of technologically relevant physical properties. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1−18.
(4) Katritzky, A. R.; Petrukhin, R.; Tatham, D.; Basak, S.; Benfenati, E.; Karelson, M.; Maran, U. Interpretation of quantitative structure−property and -activity relationships. *J. Chem. Inf. Comput. Sci.* **2001**, 41, in press.
(5) Karelson, M. *Molecular Descriptors in QSAR/QSPR*; John Wiley & Sons: New York, 2000.
(6) Kubinyi, H. Parameters. In *Methods and Principles in Medicinal Chemistry Vol. 1, QSAR: Hansch Analysis and related Approaches*; Mannhold, R., Krogsgaard-Larsen, P., Timmerman, H., Eds.; VCH: Weinheim, 1993; pp 21−36.
(7) *Topological Indices and Related Descriptors in QSAR and QSPR*; Devillers, J., Balaban, A. T., Eds.; Gordon and Breach: Amsterdam, The Netherlands, 1999.
(8) Estrada, E.; Uriarte, E. Recent advances on the role of topological indices in drug discovery research. *Curr. Med. Chem.* **2001**, *8*, 1699−1714.
(9) Karelson, M.; Lobanov, V. S.; Katritzky, A. R. Quantum-chemical descriptors in QSAR/QSPR studies. *Chem. Rev.* **1996**, *96*, 1027−1043.
(10) Rappé, A. K.; Casewit, C. J. *Molecular Mechanics Across Chemistry*; University Sci. Books: Herndon, VA, 1997.
(11) Balaban, A. T. Topological and stereochemical molecular descriptors for dastabases useful in QSAR, similarity/dissimilarity and drug design. *SAR QSAR Environ. Res.* **1998**, *8*, 1−21.
(12) Randić, M. Molecular topographic descriptors. In MATCH/CHEM/COMP 1987. *Proceedings of an International Course and Conference on the Interfaces between Mathematics, Chemistry and Computer Science, Dubrovnik, Yugoslavia, 22−26 June 1987*; Lacher, R. C., Ed.; Elsevier: Amsterdam; pp 101−108.
(13) Randić, M. On characterization of three-dimensional structures. *Int. J. Quantum Chem.: Quantum Biol. Symp.* **1988**, *15*, 201−208.
(14) Randić, M.; Jerman-Blazić, B.; Trinajstić, N. Development of 3-dimensional molecular descriptors. *Comput. Chem.* **1990**, *14*, 237−246.
(15) Bogdanov, B.; Nikolić, S.; Trinajstić, N. On the three-dimensional Wiener number. *J. Math. Chem.* **1989**, *3*, 299−309.
(16) Estrada, E.; Montero, L. A. Bond order weighted graphs in molecules as structure−property indices. *Mol. Eng.* **1993**, *2*, 363−373.
(17) Estrada, E.; Ramirez, A. Edge adjacency relationships and molecular topographic descriptors. Definition and QSAR applications. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 837−843.
(18) Estrada, E. Three-dimensional molecular descriptors based on electron charge density weighted graphs. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 708−713.
(19) Randić, M.; Razinger, M. Molecular topographic indices. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 140−147.
(20) Diudea, M. V.; Horvath, D.; Graovac, A. Molecular topology. 15. 3D distance matrices and related topological indices. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 129−135.
(21) Schultz, H. P.; Shultz, E. S.; Schultz, T. P. Topological organic chemistry. 9. Graph theory and molecular topological indices of stereoisomeric organic compounds. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 864−870.
(22) Estrada, E. Characterization of 3D molecular structure. *Chem. Phys. Lett.* **2000**, *319*, 713−718.
(23) Estrada, E.; Molina, E. 3D connectivity indices in QSPR/QSAR studies. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 791−797.
(24) Randić, M. On characterization of molecular branching. *J. Am. Chem. Soc.* **1975**, *97*, 6609−6615.
(25) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976.
(26) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Structure−Activity Analysis*; Research Studies Press: Letchworth, 1986.
(27) Estrada, E. Edge adjacency relationships and a novel topological index related to molecular volume. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 31−33.
(28) Estrada, E.; Guevara, N.; Gutman, I. Extension of edge connectivity index. Relationships to line graph indices and QSPR applications. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 428−431.
(29) Estrada, E.; Rodriguez, L. Edge-connectivity indices in QSPR/QSAR studies. 1. Comparison to other topological indices in QSPR studies. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 1037−1041.
(30) Estrada, E. Edge-connectivity indices in QSPR/QSAR studies. 2. Accounting for long-range bond contributions. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 1042−1048.
(31) Kikuchi, O. Systematic QSAR procedures with quantum chemical descriptors. *Quant. Struct.-Act. Relat.* **1987**, *6*, 179−184.
(32) Liu, L.; Guo, Q.-X. Novel prediction for the driving force and guest orientation in the complexation of α- and β-cyclodextrin with benzene derivatives. *J. Phys. Chem. B* **1999**, *103*, 3461−3467.
(33) Rodriguez, L.; Estrada, E. *MODEST (MOlecular DESign Tool) for Windows, Version 3.0*; 1999−2000. This software is distributed free under request to E. Estrada: estrada66@yahoo.com.
(34) Dewar, M. J. S.; Zoebish, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: a new general purpose quantum mechanical molecular model. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.
(35) Stewart, J. J. P. *MOPAC 6.0, Quantum Chemistry Program Exchange*; Indiana University: Bloomington, IN, Program 455, 1990.
(36) *Hyperchem 3.0 for Windows*; Hypercube, Inc.: 1993.
(37) Randić, M. Resolution of ambiguities in structure−property studies by us of orthogonal descriptors. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 311−320.
(38) Randić, M. Orthogonal molecular descriptors. *New J. Chem.* **1991**, *15*, 517−525.
(39) Randić, M. Correlation of enthalpy of octanes with orthogonal connectivity indices. *J. Mol. Struct.* (*Theochem*) **1991**, *233*, 45−59.
(40) Lučić, B.; Nikolić, S.; Trinajstić, N.; Jurić, D. The structure−property models can be improved using the orthogonalized descriptors. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 532−538.
(41) Klein, D. J.; Randić, M.; Babić, D.; Lučić, B.; Nikolić, S.; Trinajstić, N. Hierarchical orthogonalization of descriptors. *Int. J. Quantum Chem.* **1997**, *63*, 215−222.
(42) Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. Approach to the aspects of driving force of inclusion by α-cyclodextrins. *J. Am. Chem. Soc.* **1978**, *100*, 916−919.
(43) Tabushi, I. Cyclodextrin catalysis as a model for enzyme action. *Acc. Chem. Res.* **1982**, 66−72.
(44) Eftink, M. R.; Andy, M. L.; Bystrom, K.; Perlmutter, H. D.; Kristol, D. S. Cyclodextrin inclusion complexes: studies of the variation in the size of alicyclic guests. *J. Am. Chem. Soc.* **1989**, *111*, 6665−6772.
(45) Ross, P. D.; Rekharsky, M. V. Thermodynamics of hydrogen bond and hydrophobic interactions in cyclodextrin complexes. *Biophys. J.* **1996**, *71*, 2144−2154.
(46) Sakurai, M.; Kitagawa, M.; Hoshi, H. Inoue, Y.; Chujo, R. A molecular orbital study of cyclodextrin inclusion complexes. III. Dipole moments of cyclodextrins in various types of inclusion complexes. *Carbohydr. Res.* **1990**, *198*, 181−191.
(47) Connors, K. A.; Pendergast, D. D. Microscopic binding constants in cyclodextrin systems: complexation of α-cyclodextrin of sym-1,4-disubstituted benzenes. *J. Am. Chem. Soc.* **1984**, *106*, 7607−7614.
(48) Cai, W.; Xia, B.; Shao, X.; Guo, Q.; Maigret, B.; Pan, Z. Molecular interactions of α-cyclodextrin inclusion complexes using a genetic algorithm. *J. Mol. Struct.* (*Theochem*) **2001**, *535*, 115−119.
(49) Kier, L. B.; Hall, L. H. Derivation and significance of valence molecular connectivity. *J. Pharm. Sci.* **1981**, *70*, 583−589.
(50) Altenburg, K. Eine bemerkung zu dem Randicshen "Molekularen Bindungs-Index (Molecular Connectivity Index)". *Z. Phys. Chem. Leipzig* **1980**, *261*, 389−393.
(51) Estrada, E. Connectivity polynomial and long-range contributions in the molecular connectivity model. *Chem. Phys. Lett.* **1999**, *312*, 556−560.
(52) Kier, L. B.; Hall, L. H. Intermolecular accessibility: the meaning of molecular connectivity. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 784−791.
(53) Wootton, R.; Cranfield, R.; Sheppey, G. C.; Goodford, P. J. Physicochemical-activity relations in practice. 2. Rational selection of benzenoid substituents. *J. Med. Chem.* **1975**, *18*, 607−613.
(54) Kamiya, M.; Mitsuhashi, S.; Makino, M.; Yoshioka, H. Analysis of the induced rotational strength of mono- and disubstituted benzenes included in β-cyclodextrin. *J. Phys. Chem.* **1992**, *96*, 95−99.
(55) Lipkowitz, K. B. Application of computational chemistry to the study of cyclodextrins. *Chem. Rev.* **1998**, *98*, 1829−1873.
(56) Estrada, E.; Perdomo-López, I.; Torres-Labandeira, J. J. Molecular modeling (MM2 and PM3) and experimental (NMR and thermal analysis) studies on the inclusion complex of salbutamol and β-cyclodextrin. *J. Org. Chem.* **2000**, *65*, 8510−8517.

CI0100402