Vapor Pressure Studies of Benzene–Cyclodextrin Inclusion Complexes in Aqueous Solution

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Abstract: Precise vapor pressure–solubility measurements have been made for aqueous solutions of benzene with α-, β-, and γ-cyclodextrins (CD) at temperatures in the range 15–45 °C. From the inferred values of benzene fugacity and solubility at known concentrations of the CD's, equilibrium constants, enthalpy changes, and heat capacity changes have been determined for formation of 1:1 complexes of each of the three CD's. Thermodynamic results have also been obtained for higher-order complexes (2:1 and 1:2) of benzene and α-CD and for the complex of 2 benzenes with 1 β-CD. The thermodynamic data indicate that hydrophobic effects become increasingly important in stabilizing the benzene–CD complexes as the cavity size of the CD's increases. The 1:1 complex of β-CD is considerably more stable than the 1:1 complexes of α- and γ-CD. Heat capacity changes are quite negative for formation of all the 1:1 benzene–CD complexes.

The host–guest chemistry of inclusion compounds of the α- and β-cyclodextrins (cycloamyloses containing 6 and 7 glucose units, respectively) has been widely studied in relation to the general problem of understanding structural and ligand binding effects.[1-5] There has been considerable interest in the extent to which alkyl- and aryl-hydrocarbon groups of various sizes and geometry can penetrate into the torus-shaped central cavity of the cyclodextrins.[1-8] X-ray crystallographic results provide clear evidence that organic substrates can be incorporated in channel- or cage-type complexes, sometimes with significant rearrangement of the cyclodextrin structure.[1,2,9-12] NMR, calorimetry, and various optical spectral methods have produced important information about the binding of guest molecules, including some evidence that hydrophobic effects are involved in stabilizing adducts in aqueous solution.[1-5,7]

Although many investigations have been made with use of polar derivatives of hydrocarbons as guest molecules, there appear to have been relatively few thermodynamic studies of the interactions of unsubstituted hydrocarbon solutes with aqueous solutions of the cyclodextrins. Vapor pressure/solubility studies of the formation of hydrocarbon inclusion compounds with α- and β-cyclodextrins and several derivatives of these compounds have been reported by Lammers and co-workers.[6] Wishnia and Lappi used vapor pressure and ultracentrifuge results to obtain the stoichiometry and thermodynamic properties of hydrocarbon complexes with α- and β-cyclodextrins.[7] Recently, Hoshino et al. obtained a value for the equilibrium constant for the formation of the inclusion compound of benzene with β-cyclodextrin.[8]

Particularly in relation to the problem of understanding the extent to which hydrophobic effects promote binding, it would seem important to obtain accurate results for the formation of a variety of hydrocarbon-cyclodextrin complexes. Unfortunately, the usual optical and NMR spectral methods and calorimetry are difficult to apply with sufficient accuracy to obtain thermodynamic results for interactions between the very slightly soluble hydrocarbons and the cyclodextrins in aqueous solution. Of the methods which have been used for studying the complexation of hydrocarbons by aqueous solutes, vapor pressure–solubility experiments appear to be the most promising for inferring accurate values of binding constants and other thermodynamic constants for known complexes.

Recently we have reported several thermodynamic studies of volatile solutes in aqueous solutions, using a completely automated vapor pressure apparatus developed in this laboratory.[13-18] The method yields extremely precise vapor pressure–composition data in the very low concentration region. Considering the utility of the vapor pressure method in studies of the solubilization of hydrocarbons by aqueous solutions of polar organic compounds, including surfactants, we thought it would be worthwhile making a careful study of the formation of complexes of a single hydrocarbon (benzene) with cyclohexaamylose (α-CD), cycloheptaamylose (β-CD), and cyclooctaamylose (γ-CD). Vapor pressure–composition results are reported here for these three systems at temperatures ranging from 15 to 45 °C.

Experimental Section

Recent publications from this laboratory describe our automated vapor pressure apparatus and results obtained for aqueous solutions of hydrocarbons.[13-18] Highly reproducible increments of benzene are added to previously evacuated solutions of cyclodextrin in water by means of a 6-port HPLC valve with external sample loop. Pressures are monitored continuously by a pressure transducer interfaced with a microcomputer. The microcomputer tests for pressure equilibrium, stores values of the measured equilibrium pressure, and activates the valve to add successive increments of benzene. Approximately 30 to 45 min are required from the time a new increment of benzene is added until equilibrium is attained. At the higher benzene concentrations, crystalline adducts of the hydrocarbon with cyclodextrin begin to form, but the data reported here apply only to homogeneous aqueous solutions.

α- and β-cyclodextrins were purchased from Aldrich Chemical Co.; samples were carefully dried prior to use. γ-Cyclodextrin was kindly provided by Dr. Donald M. Sand of the Hormel Institute in the form of the *n*-propanol inclusion compound. Aqueous solutions of this material were boiled to remove the propanol and treated with bromobenzene to

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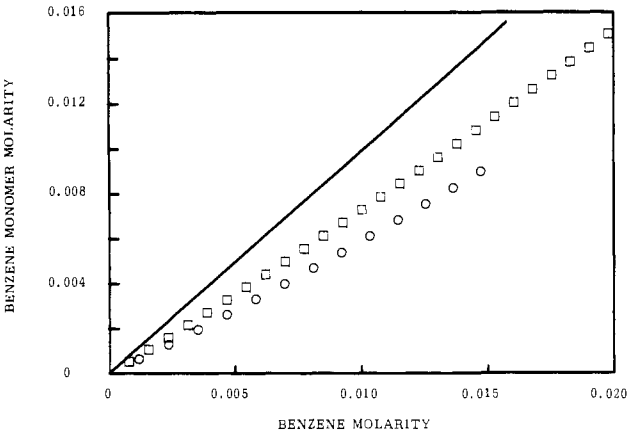

Figure 1. Dependence of benzene monomer concentration on total benzene concentration for aqueous solutions of α-cyclodextrin containing 0.01269 M (□) and 0.02240 M (○) cyclodextrin at 25 °C. The solid line indicates the results for benzene in pure water (from ref 15). Symbol diameters are approximately 25 times the experimental uncertainties.

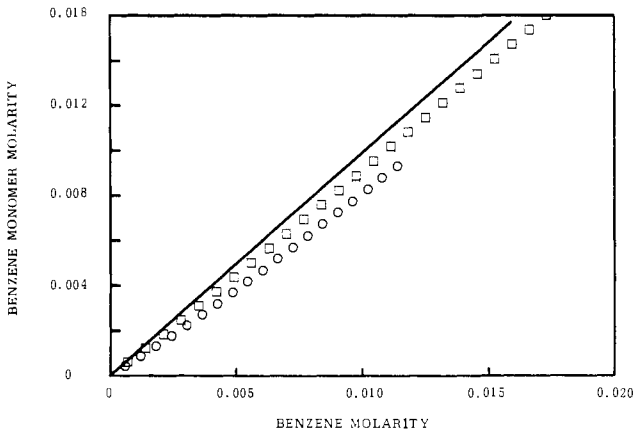

Figure 2. Dependence of benzene monomer concentration on total benzene concentration for aqueous solutions of β-cyclodextrin containing 0.001131 M (□) and 0.002813 M (○) cyclodextrin at 25 °C. The solid line represents data for benzene in pure water.

precipitate γ-cyclodextrin (leaving any α- and β-cyclodextrin in solution). The precipitate was recrystallized several times with propanol.

The initial treatment of data involved converting measured total pressure data into benzene fugacities, using second virial coefficient values reported previously.[15] With use of known values of the solubility and Henry's law constant of benzene in water,[15] it was possible to calculate the concentration of uncomplexed (monomeric) benzene in the aqueous solution (c_B) corresponding to the known total benzene concentration [B] and cyclodextrin concentration [CD]. The results for each system consisted of 180 to 370 sets of values of [CD], [B], and c_B at known temperatures in the range 15 to 45 °C.

Results and Discussion

Figures 1–3 show typical data for the solubilization of benzene by α-, β-, and γ-cyclodextrin. Each plot indicates the dependence of the concentration of benzene monomer in the aqueous phase (c_Be on the total benzene concentration [B] at specific total concentrations of cyclodextrin [CD]. Included in the figures are solid lines indicating the dependence of c_B on [B] in pure water; these curves have been calculated from results in ref 15. Using the assumptions of the mass action model, we may equate the concentration of benzene in adducts containing both benzene and cyclodextrin to the difference between the total concentration of benzene in solution at a given cyclodextrin concentration and the concentration of benzene in pure water at the same value of c_B. In analyzing the present results, nonlinear least-squares methods described previously[15,19] have been used to correlate the vapor

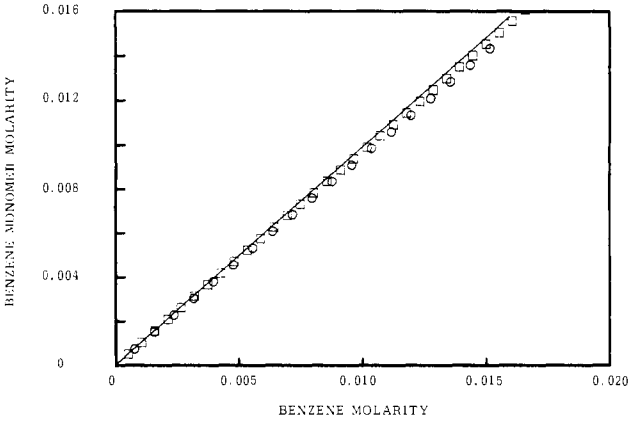

Figure 3. Dependence of benzene monomer concentration on total benzene concentration for aqueous solutions γ-cyclodextrin containing 0.002566 M (□) and 0.005056 M (○) cyclodextrin at 25 °C. The solid line indicates the results for benzene in pure water.

pressure–solubility results and to obtain values of equilibrium constants for forming specific complexes in the aqueous solution phase.

Previous results,[6,7] as well as a preliminary analysis of the present data, suggest that not only the 1:1 complex but also the 2:1 and 1:2 benzene–cyclodextrin adducts may have to be considered when activities of the interacting species are allowed to vary over relatively wide ranges. Our least-squares analysis of the results for the β-cyclodextrin system indicates that a relatively strong 1:1 complex forms between the cyclodextrin and benzene and that the 2 benzene:1 cyclodextrin species also contributes significantly to the total concentration of complexed benzene in solutions at the higher benzene activities. In the case of the α-cyclodextrin system, the 1:1, 1:2, and 2:1 complexes all need to be accounted for to obtain a quantitative fit of the vapor pressure–composition data. With γ-cyclodextrin, the solubility of the benzene–cyclodextrin adducts is quite small, and the 1:1 complex is comparatively weak. Therefore, for this system it is only possible to report reliable values for the thermodynamic properties of the 1:1 complex, although at the higher benzene activities, there is some evidence for formation of the 2:1 benzene–cyclodextrin complex.

Table I lists values for the formation constant, ΔH, and ΔC_p values for 1:1, 2:1, and 1:2 benzene–cyclodextrin complexes, calculated by applying the mass action model[15] to vapor pressure–solubility data taken in the temperature range 15–45 °C. An excellent fit of the vapor pressure–solubility data at varying concentrations and temperatures is achieved for each system. The root-mean-square deviation (RMSD) in benzene solubility is in the range 1.2 to 1.8 × 10^{-5} M in each case.

The thermodynamic constants characterizing the formation of the three 1:1 complexes are strikingly different. A moderately strong 1:1 complex forms between benzene and α-cyclodextrin, with an equilibrium constant of 31.6 L mol^{-1} at 25 °C and a relatively large exothermic value of ΔH (−3.2 kcal mol^{-1}). The negative value of ΔC_p (−65 cal mol^{-1} K^{-1}) probably indicates that some of the region of "highly ordered" water that ordinarily surrounds benzene molecules in dilute aqueous solution is lost on formation of the complex.[17] The fact that the enthalpy of formation of the 1:1 complex is quite negative suggests that strong dipole–induced dipole interactions help stabilize that adduct;[17] it is probable, therefore, that the bound benzene resides in the polar region at the mouth of the α-cyclodextrin cavity.

The value of the formation constant for the 1:1 complex of benzene with β-cyclodextrin (169 L mol^{-1} at 25 °C) is considerably greater than that for either the α- or the γ-cyclodextrin 1:1 complex. Considering the sizes of the torus-shaped cavities of the three cycloamyloses as determined from crystal structures,[11,12] we infer that benzene penetrates deeply into the cavity of β-cyclodextrin in forming the 1:1 complex, although the fit must be rather tight. In the γ-cyclodextrin 1:1 complex, the benzene molecule is probably free to rotate and move about the cavity.

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Table I. Thermodynamic Constants for Formation of Complexes between Benzene and Cyclodextrins in Dilute Aqueous Solution[a]

cyclodextrin[b]	complex	K (25 °C)[c]	ΔH°, kcal mol^{-1} (25 °C)	ΔC_p°, cal mol^{-1} K^{-1}	RMSD, M
α	1:1	31.6 ± 0.1 L mol^{-1}	−3.14 ± 0.06	−65 ± 2	
	2:1	97 ± 4 L^2 mol^{-2}	0.6 ± 0.5		1.8×10^{-5} [d]
	1:2	325 ± 11 L^2 mol^{-2}	−3.9 ± 0.5		
β	1:1	169 ± 1 L mol^{-1}	−0.45 ± 0.08	−119 ± 10	
	2:1	2270 ± 30 L^2 mol^{-2}	−4.0 ± 0.8	−133 ± 84	1.2×10^{-5} [e]
γ	1:1	9.1 ± 0.1 L mol^{-1}	3.4 ± 0.2	−320 ± 30	1.8×10^{-5} [f]

[a] Standard states: unit molarity, ideal dilute solution. Enthalpy and heat capacity values corrected for thermal expansion of solvent. Errors in constants represent standard deviations. [b] α-Cyclodextrin is cyclohexaamylose; β-cyclodextrin is cycloheptaamylose; γ-cyclodextrin is cyclooctaamylose. [c] Equilibrium constants for formation of 1 benzene to 1 cyclodextrin (1:1); 2 benzenes to 1 cyclodextrin (2:1); and 1 benzene to 2 cyclodextrin (1:2) complexes from the monomers at 25 °C. [d] Root-mean-square deviation for fitting 290 data sets at 15, 25, 35, and 45 °C to the mass action model. Cyclodextrin concentrations of 0.023, 0.0128, and 0.0087 M at benzene fugacities up to 70% of saturation. [e] Root-mean-square deviation for fitting 370 data sets at 15, 20, 25, 30, 35, 40, and 45 °C. Cyclodextrin concentrations of 0.00293 and 0.00124 M at benzene fugacities up to 70% of saturation. [f] Root-mean-square deviation for fitting 180 data sets at 15, 25, 35, and 45 °C at cyclodextrin concentrations of 0.0053, 0.0026, and 0.0011 M at benzene fugacities up to 60% of saturation.

In the case of the 1:1 β-cyclodextrin complex, ΔH of formation is practically zero (−0.45 kcal mol^{-1}), consistent with the view that the interior of the cavity is rather hydrophobic; the large negative value of ΔC_p probably reflects the loss of some of the structured water that is originally present around benzene and possibly also within the cavity before the benzene is introduced. In the case of the 1:1 γ-cyclodextrin complex, ΔH has actually become positive (+3.4 kcal mol^{-1}), and ΔC_p is quite large and negative. (The value −320 cal mol^{-1} K^{-1} is unreasonably large in magnitude, probably owing to the neglect of higher-order benzene–γ-cyclodextrin complexes in the mass action model.)

Taken together, the thermodynamic results for the 1:1 benzene–cyclodextrin complexes show the importance of hydrophobic effects in stabilizing the β- and γ-cyclodextrin adducts. In this connection, it is useful to consider the transfer reactions (at 25 °C)

$$\beta\text{-CD} + \text{benzene}\cdot\alpha\text{-CD} = \alpha\text{-CD} + \text{benzene}\cdot\beta\text{-CD} \quad (1)$$

and

$$\gamma\text{-CD} + \text{benzene}\cdot\alpha\text{-CD} = \alpha\text{-CD} + \text{benzene}\cdot\gamma\text{-CD} \quad (2)$$

where CD denotes a cyclodextrin molecule. Equation 1 represents the removal of a benzene molecule from its 1:1 complex with α-CD and the simultaneous formation of a 1:1 complex with β-CD. For reaction 1, the dimensionless equilibrium constant is 5.3, ΔH = +2.7 kcal mol^{-1}, and ΔS = 12.4 cal mol^{-1} K^{-1}. At 25 °C, reaction 2 has an equilibrium constant equal to 0.29, a value of ΔH equal to +7 kcal mol^{-1}, and ΔS = 21 cal mol^{-1} K^{-1}. Thus, the thermodynamic constants for transferring benzene from the 1:1 complex with α-CD into the β-CD and γ-CD cavities clearly indicate the increasingly hydrophobic nature of the benzene–cyclodextrin interaction as the cavity size increases. To summarize, benzene in the 1:1 complex with α-cyclodextrin appears to reside in a polar, low-energy environment, and it moves into the β-CD and γ-CD cavities with quite large positive enthalpies and entropies of transfer. The greater rotational and translation freedom of benzene in the γ-cyclodextrin (as compared with β-CD) is probably responsible for the larger ΔS of formation of the γ-CD complex. However, this favorable entropy change is more than offset by an unfavorable energy change, so that the γ-CD–benzene complex is the weakest of the three 1:1 adducts.

Information about the 2:1 and 1:2 complexes in Table I tends to support the views advanced in the preceding paragraphs. By combining results for the 1:1 and 2:1 benzene–α-CD complexes, one can obtain thermodynamic constants at 25 °C for the reactions

$$\text{benzene} + \text{benzene}\cdot\alpha\text{-CD} = (\text{benzene})_2\cdot\alpha\text{-CD} \quad (3)$$

and

$$\alpha\text{-CD} + \text{benzene}\cdot\alpha\text{-CD} = \text{benzene}\cdot(\alpha\text{-CD})_2 \quad (4)$$

The equilibrium constant for reaction 3 is about 3 L mol^{-1}, and the reaction is endothermic by 3.8 kcal mol^{-1}; these results may be compared directly with the thermodynamic results recently reported for the formation of the benzene dimer in dilute aqueous solution.[15] Although the equilibrium constant for reaction 3 is several times larger than the dimerization constant for benzene in aqueous solution, the enthalpy change for adding a benzene molecule to the 1:1 complex is the same within experimental error as the enthalpy of dimerization of benzene. It seems probable, therefore, that the 2:1 complex forms by attaching a benzene molecule to the benzene side of the 1:1 adduct, although the isomer having benzenes on both ends of the α-cyclodextrin torus may also contribute to the stability of the 2:1 aggregate. Thermodynamic constants for reaction 4 indicate that the addition of an α-CD to the 1:1 benzene–α-CD complex occurs slightly exothermically and with an equilibrium constant equal to about 10 L mol^{-1}. These results are consistent with the formation of a 1:2 species in which benzene is simultaneously capped by two α-CD molecules, oriented with their secondary hydroxyl sides facing each other.

There have been relatively few studies of the formation of hydrocarbon complexes with α and β-cyclodextrin[6-8] and apparently no previous reports of complexes of hydrocarbons with γ-cyclodextrin. A recent article[8] reports a value of 196 L mol^{-1} for the formation constant of the 1:1 complex of benzene with β-cyclodextrin at 28 °C (determined by a fluorescence spectrophotometric method), in reasonable agreement with the results given here. Several articles by Lammers and co-workers[6] provide formation constants for hydrocarbon–cyclodextrin complexes, pertaining to dilute solution standard states for the cyclodextrin and the complex and gaseous states for the hydrocarbon. In the absence of accurate information about the transfer of the hydrocarbons from the gas phase into dilute aqueous solutions, it is difficult to compare these data with the present results.

The most closely related previous study of hydrocarbon–cyclodextrin complexes is that by Wishnia and Lappi,[7] who obtained thermodynamic information about the 1:1 complexes of cyclohexane and *n*-heptane with both α- and β-cyclodextrin, as well as results for the 2:1 hydrocarbon–α-cyclodextrin complexes. These complexes have considerably larger formation constants than those of benzene, reflecting the much smaller solubilities of heptane and cyclohexane in water (as compared with benzene). A similar effect has been observed in the formation of solubilizates of hydrocarbons by micellar solutions of aqueous surfactants; cyclohexane–surfactant complexes are more stable than the corresponding benzene complexes.[16,18] The enthalpies of formation of the 1:1 complexes of cyclohexane with α- and β-cyclodextrin, reported by Wishnia and Lappi, are approximately 1 kcal mol^{-1} more exothermic than values determined here for the analogous benzene complexes, and the heat capacities for formation of these complexes are also quite comparable. However, Wishnia and Lappi report an enthalpy of formation of approximately −11 kcal mol^{-1} for the 1:2 cyclohexane–α-cyclodextrin complex at 25 °C, a value much more negative than the value −3.9 kcal mol^{-1} obtained here for the 1:2 benzene–α-cyclodextrin complex.

Attempts to estimate the contributions of hydrophobic effects to the stability of various cyclodextrin complexes have been

complicated by the presence of groups other than hydrocarbons in the guest molecules. Small changes in the geometry or polarity of hydrocarbon derivatives can greatly change the energy and free energy of cyclodextrin inclusion complexes;[1-5] therefore, additional studies like the present one will be needed to determine the role of the hydrocarbon moiety in stabilizing these adducts. The vapor pressure method is practically the only technique capable of yielding reliable thermodynamic results for complexes of the slightly soluble hydrocarbons.

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Registry No. α-Cyclodextrin benzene complex (1:1), 30915-12-9; α-cyclodextrin benzene complex (2:1), 88945-47-5; α-cyclodextrin benzene complex (1:2), 88932-63-2; β-cyclodextrin benzene complex (1:1), 88932-64-3; β-cyclodextrin benzene complex (2:1), 88932-65-4; γ-cyclodextrin benzene complex (1:1), 88932-66-5.

Conformational Energy of Glycine in Aqueous Solutions and Relative Stability of the Zwitterionic and Neutral Forms. An ab Initio Study

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Abstract: A recently developed method permits one to evaluate with ab initio LCAO–MO–SCF procedures the free energy and the enthalpy of solution of molecular species as well as the change in energy arising from changes in molecular structure and conformation. The method is here applied to study the conformational surface of the two forms of glycine, NT and ZW, with the STO-3G and 4-31G basis sets. The influence of the basis set and other computational parameters on the conformational surface is systematically examined in order to assess the reliability of the results. The differences in energy (internal energy, free energy, enthalpy) between NT and ZW in vacuo as well as in solution are also determined. The ΔH value for the passage $NT_{gas} \rightarrow ZW_{sol}$ is equal to −19.5 kcal/mol at 298 K, while the experimental value is −19.2 kcal/mol. An analysis of the whole energy cycle involving both forms of glycine indicates that the aforementioned good agreement between experimental and computed values takes advantage of some compensation of errors but that the magnitude of these errors could be greatly reduced within the context of the present computational method.

1. Introduction

A procedure recently elaborated in our group[1,2] makes possible, with a reasonable computational effort, the ab initio evaluation of physicochemical properties of solutes in dilute solutions. The basic procedure may be adapted to several specific problems, a part of which has been considered in previous papers (solvent shift of electronic spectra,[2,3] changes in the free energy of solutions produced by light absorption or emission,[4] solvent effect on chemical reaction energy profile and mechanism[5]). We shall consider here the application of this method to the evaluation of conformational energies of solutes. As a test case, we have chosen the aqueous solution of glycine. This molecule can be found in a zwitterionic form (ZW), stable in solution and in crystals, and in a neutral form (NT) which is stable in the gas phase. Consequently, the investigation will be extended to the evaluation of the relative stability of these two forms. Some attention will be paid to the assessment of the computational procedure, and an appropriate analysis of the degree of confidence of the results having a direct physicochemical interest will be done.

Glycine, being one of the simplest molecules of biochemical interest, has been the object of numerous theoretical investigations. We dispense with a rather long list of papers which should include in vacuo calculations performed at different levels of accuracy as well as calculations involving also the solvent, the references more pertinent to the discussion being quoted at the appropriate places. A few years ago we published a comparison of conformational maps of ZW and NT glycine obtained with empirical, semiempirical, and ab initio procedures[6] (hereafter called paper 1). In most calculations reported in this paper, we have employed the same set of computational parameters as in the ab initio SCF STO-3G computations of paper 1 (internal geometry, basis set, selections of points in the conformational space, fitting procedure, ecc.) to make an immediate comparison of the two sets of results. Actually, the only difference is due to the introduction in the molecular hamiltonian of a one-electron operator taking into account the interaction of the solvent. Extension of the basis set and changes in internal geometry will be also considered in order to shed more light on the dependence of the results on these parameters.

2. Outline of the Computational Method

The basic documentation of the method has been done in a preceding paper[1] to which reference is made for a more detailed description. The solvent is represented by a continuous dielectric with a cavity accurately modeled on the solute; in conformational calculations the shape of the cavity will depend on the considered conformation. The electrostatic solute–solvent interaction is represented by an operator $\hat{V}_\sigma(r)$ added to the Hamiltonian $\hat{H}_M^0$ of the solute M in vacuo

$$\hat{H}_M = \hat{H}_M^0 + \hat{V}_\sigma \quad (1)$$

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