Structural Effects on the Binding of Amine Drugs with the Diphenylmethyl Functionality to Cyclodextrins. II. A Molecular Modeling Study

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Molecular modeling has been used to study the complexation between α-, β-, or γ-cyclodextrin (CD) and a group of amine compounds having the diphenylmethyl functionality. The computer program SYBYL 5.3 and the Tripos force field (version 5.2) were used for all the calculations. Three-dimensional structures of 13 amine compounds were built individually from their atoms, and CDs were built based on the X-ray crystallographic coordinates. The diphenylmethyl derivative–CD complexes were constructed and optimized. Based on the calculated binding energies accompanying the inclusion process, the preferred method of approach of the compounds to the cavities of the CD molecules, and the structural effects on the binding between amine compounds and three CDs were explored. The calculated binding energies exhibited a good correlation with the stability constants obtained from solution calorimetric titrations. The present study shows that for similar ligand molecules, the molecular modeling technique should enable us to visualize the structure of the inclusion complexes and will also assist us in determining the ability of a potential drug molecule to form a stable complex with CDs.

KEY WORDS: molecular modeling; computer graphics; molecular mechanics; SYBYL; inclusion complex; diphenylmethyl derivatives; cyclodextrins (CDs).

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six (α-CD), seven (β-CD), or eight (γ-CD) glucopyranose units (1). A CD ring is externally hydrophilic and relatively apolar internally. Many drug molecules are capable of residing within the central cavity of a CD molecule, thus forming an inclusion complex. The inclusion complexes formed display interesting properties and may increase the stability and solubility of the guest molecules (2,3).

A number of amine compounds used medicinally bear the diphenylmethyl functionality. Complexation with CDs may increase the aqueous solubility and enhance the stability of some of these diphenylmethyl derivatives.

Studies of complexes of these amine compounds with CDs are very limited. In our previous paper, the titration microcalorimetric results for the binding of some amine drugs with the diphenylmethyl functionality to α-, β-, and γ-cyclodextrins in aqueous solution at 25°C were presented (4). Structural effects on the stability constants, thermodynamics, and inclusion complex geometry were explored based on the solution calorimetric results.

In order to support our explanation and to elucidate further the binding mechanism, the determination of the geometries of inclusion complexes is essential. X-ray crystallography requires the synthesis, isolation, and crystallization of the complex (5). Corey–Pauling–Koltun (CPK) models provide a rapid assessment of the relative space-filling properties of ligand and substrate but cannot provide quantitative information about interatomic forces. For the purpose of our analysis, the application of computational methods to problems in molecular structure seems to offer the best combination of speed and accuracy (6–12).

We present herein the results of the molecular modeling studies on the same series of amine drugs and their complexes with α-, β-, and γ-CDs using the Tripos force field (13). Preliminary results have been reported in the preceding paper in this series.

MATERIALS AND METHODS

General Considerations

Molecular mechanical calculations were performed with the program, SYBYL 5.3 (13), using the Tripos force field (version 5.2), and executed on a Silicon Graphics 4D120GTX Graphics workstation. Energy minimizations were carried out using the MAXIMIN 2 energy minimizer with its default values (13). All structures were optimized until the energy change from one iteration to the next was less than 0.05 kcal/mol.

There is one important limitation to the accuracy of our computations. The calculations do not take into account water molecules. Ignoring the solvent could, among other consequences, cause the complexes to appear more flexible than they are in reality. This is because complexation is driven partly by hydrophobic forces that are not incorporated into our calculations. This omission of solvent, unfortunately, is a traditional limitation of computational chemistry. The addition of water molecules to the calculations will increase the computation time dramatically and is not practical for large molecules such as our complexes at the present time.

The principle goal of our research is to compare the energy gain on the formation of the inclusion complexes for a series of compounds with α-CD, β-CD, or γ-CD. Considering the structural similarity between the ligand compounds, it is reasonable to assume that these compounds bind to CD by a similar mechanism. Therefore, the relative magnitudes of energy gain for the series on complex formation should not be critically dependent upon the presence of water molecules. The inclusion of water molecules in the calculation, however, would change the absolute values of total energy.

The potential energy function, $E$, of the molecule used in the force field includes stretching, bending, torsion, van der Waals, electrostatic interaction, and constraint (including distance, angle, torsion angle and range constraints)
terms (14). The charge calculations were performed using the Gast–Hück method, which is a combination of two other charge computation methods: the Gasteiger–Marsili method to calculate the $\sigma$ component of the atomic charge (15–17) and the Hückel method to calculate the $\pi$ component of the atomic charge (18,19). $E$ is a measure of intramolecular strain relative to a hypothetical situation. By itself $E$ has no physical meaning.

Fig. 1. Computer-generated minimal energy structures. A, cyclizine · 2HCl−α-CD complex; B, cyclizine · 2HCl−β-CD complex; C, chlorcyclizine · 2HCl−β-CD complex; D, hydroxyzine · 2HCl−β-CD complex. Color is coded by atom type: red, O; white, C; cyan, H; blue, N; purple, Cl. Parts of the guest molecules are shown in yellow color for clarity.

Fig. 2. Computer-generated minimal energy structures. A, adiphenine · HCl−β-CD complex; B, proadifen · HCl−γ-CD complex; C, proadifen · HCl−β-CD complex; D, terfenadine · HCl−β-CD complex (1:2 stoichiometry). Color is coded by atom type: red, O; white, C; cyan, H; blue, N. Parts of the guest molecules are shown in yellow color for clarity.