Pergamon

Tetrahedron Letters, Vol. 37, No. 3, pp. 287-290, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02151-5

Diastereoselective Recognition of β Anomers of Phenyl Glucosides by a Cyclobis(paraquat-*p*-phenylene) Receptor: A Computational Study

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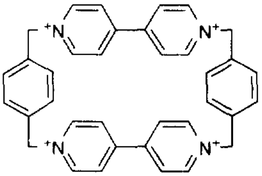
Abstract: *The preference of a cyclobis(paraquat-*p*-phenylene) receptor for binding phenyl β-glucopyranoside over the α- anomer was investigated by constant temperature molecular dynamics simulations conducted using the AMBER* force field and the GB/SA continuum solvation model. The energy difference between the complexes of the β- and α- anomers in water was found to be 0.3 ± 0.1 kcal·mol^{-1} using a stochastic dynamics algorithm and 0.1 ± 0.1 kcal·mol^{-1} for a mixed mode Monte Carlo/stochastic dynamics method. This same trend was found in gas phase simulations, in which the complex with the β anomer was more stable by 0.4±0.1 kcal·mol^{-1}. In all cases the complex of the β anomer was shown to be more stable, indicating a possible steric origin for the diastereoselectivity of binding.*

Staley and Smith have recently found that the tetrachloride salt of cyclobis(paraquat-*p*-phenylene) receptor **1**, originally studied by Stoddart,[1] complexes phenyl glycosides in aqueous solution.[2] Among their findings was the intriguing observation that **1** bound phenyl β-glucopyranoside (**2**) more strongly than its α- anomer (**3**); this proved to be a general trend among the glycosides studied. Since the receptor is achiral, the question arises as to what factors favor the complexation of β-glycosides by a consistent 0.7 kcal·mol^{-1}.



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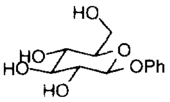

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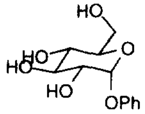

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From the studies of Stoddart, it is known that **1** binds electron-rich aromatic rings in aqueous solution.[1] The factors likely to influence the binding of phenyl glycosides to **1** can therefore be enumerated as: steric interactions between glycoside and receptor in the complex, differential solvation of the two anomers (leading to different desolvation energies upon binding), and electron density on the phenyl rings of the glycosides. Smith has studied the ^{13}C chemical shifts of the phenyl C_4 and, by doing so, shown that electron density appears to be unchanged between **2** and **3**. In addition, Smith found that **1** bound **2** more tightly in acetonitrile, by 0.7 kcal·mol^{-1}, strongly suggesting that the difference does not result from hydrophobic desolvation. Thus, by elimination, steric factors would seem to be the likely source of the preference for **2**. In this paper, the role played by steric factors is examined using molecular dynamics simulations.

Although the relative binding energies of the two stereoisomers can in principle be calculated from a thermodynamic cycle, this approach was abandoned due to the inability of molecular mechanics force fields to adequately reproduce the relative energies of anomers. This problem is underscored by the numerous computational approaches to reproducing phenomena such as the anomeric equilibria in D-glucose[3] and 2-methoxytetrahydropyran.[4] These recent studies have emphasized the need for detailed, explicit solvation models to correctly estimate the solvation differences using molecular mechanics force fields.[3a, 4] As a consequence, it was decided to focus only on the energy difference between the complexes **1•2** and **1•3** as a probe of whether steric interactions between the glycosides and the receptor favor the binding of **2** over **3**.

The MacroModel[5] V4.5 molecular modeling package was used for all the computations performed. To simulate the binding of **2** and **3** to **1** in aqueous medium, a series of constant temperature MD simulations were conducted using the AMBER* force field[6] in conjunction with the GB/SA continuum solvent model for water.[7] The "stochastic dynamics" algorithm (SD) of Berendsen[8] was used for temperature control. The protocols employed in this study were 400 ps equilibration and 1000 ps data collection for the complexes. To ensure proper sampling, each simulation consisted of multiple trajectories generated from different starting points; the energy values reported herein represent averages obtained from the multiple trajectories. The **1•2** complex was found to be more stable than **1•3** by 0.4 ± 0.1 kcal·mol^{-1}. The results of these simulations, along with the other simulations performed in this study (*vide infra*), are presented in Table 1.

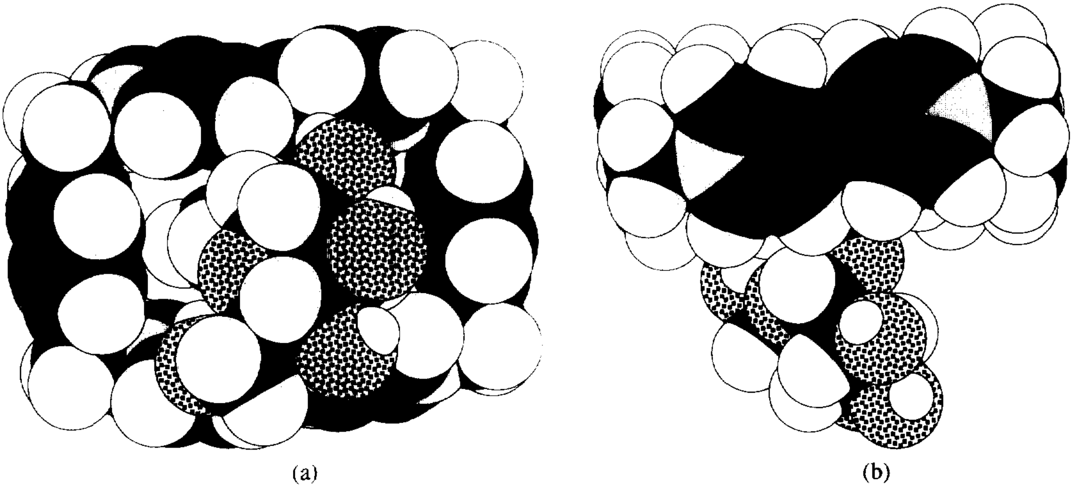
Table 1. Average enthalpies obtained from constant temperature simulations.

method	solvent	**1•2** (kcal)	**1•3** (kcal)	$\Delta H(\alpha-\beta)$ (kcal)
SD	H_2O	-45.37	-45.09	0.3
SD	H_2O	-45.42	-44.94	0.5
SD	H_2O	-45.48	-44.99	0.5
MC/SD	H_2O	-28.13	-28.10	0.0
MC/SD	H_2O	-28.55	-28.37	0.2
MC/SD	H_2O	-28.51	-28.28	0.2
SD	none	150.88	151.33	0.5
SD	none	150.80	151.14	0.3

Lingering concern over the completeness of sampling in these simulations stimulated the use of the recently developed, mixed mode torsional Monte Carlo/stochastic dynamics (MC/SD) algorithm of Still.[9] Rotations about the glycosidic bonds as well as the C-O bonds of the glucose hydroxyls were randomly perturbed during the MC/SD simulation to stimulate conformational interconversion. Owing to the increased rate of sampling, as well as the increased computational cost, MC/SD simulations were run for a 300 ps equilibration period followed by 500 ps of data collection. Simulations conducted using this protocol gave significantly different answers than the stochastic dynamics simulations: the steric energies obtained from the MCSD simulations were roughly 17 kcal·mol^{-1} higher for both complexes and the **1•2** complex was found to be more stable than **1•3** by 0.15±0.08 kcal·mol^{-1}, as shown in Table 1.

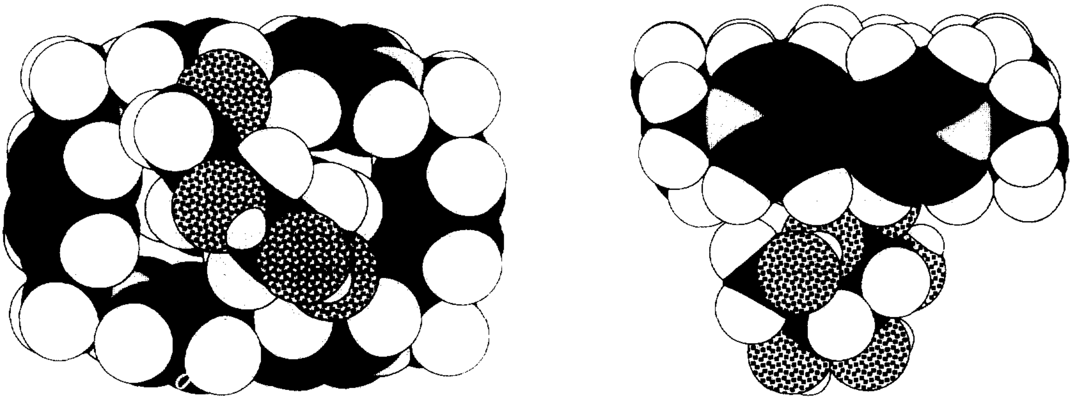
To see whether the preference of **1** for **2** was insensitive to solvent, the simulations were also run in the gas phase. Again, a stochastic dynamics simulation of the two complexes was run using the AMBER* force field using the protocol previously discussed. The results of these simulations were qualitatively similar to those obtained from the simulations in aqueous medium. Again, the **1•2** complex proved to be more stable than **1•3** by 0.4 ± 0.1 kcal·mol^{-1}. Since this preference is virtually identical to that found using a solvation model, it can be viewed as strong computational evidence for the lack of a hydrophobic component to the preference for binding **2**.

On the basis of these results, one can conclude that the preference of **1** for **2** is most likely steric in nature. The empirical force field used considers the phenyl rings of **2** and **3** as electronically equivalent, thereby suggesting that the differences in binding observed do not arise from an electronic preference. Additionally, the results are consistent regardless of solvent, both experimentally and computationally, strongly disfavoring an explanation based on solvophobic effects. Indeed, as illustrated by the structures displayed in Figures 1 and 2, this steric preference may be viewed as arising from more favorable situation of the glycosyl portion of the β-anomer or, conversely, the placement of the glycosyl unit of the α-anomer closer to the binder. Several structural differences between the equilibrium structures of **1•2** and **1•3** support this view. First, the aromatic ring of the phenyl glycoside in **1•3** (Fig. 1) has been displaced from the aromatic cavity of **1** by roughly 0.5Å compared to that of **1•2** (Fig. 2) averaged over the duration of the simulations. This difference most likely arises from a steric impediment to burying the phenyl glycoside of **3** more deeply within **1**. One can also rationalize the steric preference for the β-anomer from the perspective of the glucose ring: complexing the phenyl glycoside to **1** results in a profound increase in the effective size of the phenyl. A bulkier substituent such as the complexed glycoside should exhibit a stronger preference for the equatorial position, resulting in the relative stabilization of the β-anomer when complexed.



(a) (b)

Figure 1. Front (a) and top (b) views of the lowest energy complex of **1** with phenyl α-glucopyranoside (**3**).



(a) (b)

Figure 2. Front (a) and top (b) views of the lowest energy complex of **1** with phenyl β-glucopyranoside (**2**).

The consistent underestimation of the energy difference between **1•2** and **1•3** can probably be attributed to the lack of representation of the eletronic interactions between the phenyl glycosides and the paraquat units in **1**. Our observation that the phenyl ring of **3** is less well encapsulated by **1** suggests that the electronic attraction between the **1** and **3** should be somewhat diminished relative to that present in **1•3**. A more accurate representation of the charges on the phenyl rings of **2** and **3** would potentially provide a more realistic estimation of the energy difference between **1•2** and **1•3**.

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(*Received in USA* 28 *August* 1995; *revised* 6 *November* 1995; *accepted* 8 *November* 1995)