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Stereoselective glycosylation reactions with 2-deoxyglucose: A computational study of some catalysts

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ABSTRACT

2-Deoxy glycosides are important components of many oligosaccharides with antibiotic and anti-cancer activity, but their synthesis can be very challenging. Phenanthrolines and substituted pyridines promote stereoselective glycosylation of 1-bromo sugars via a double S_N2 mechanism. Pyridine reacting with α-bromo, 2-deoxyglucose was chosen to model this reaction. The first step involves displacement of bromide by pyridine which can be rate limiting because bromide ion is poorly solvated in the non-polar solvents used for these reactions. We examined a series of small molecules to bind bromide and stabilize this transition state. Geometry optimization and vibrational frequencies were calculated using M06-2X/6-31+G(d,p) and SMD implicit solvation for diethyl ether. More accurate energies were obtained with M06-2X/aug-cc-pVTZ and implicit solvation. Urea, thiourea, guanidine and cyanoguanidine bind bromide more strongly than alkylamines, $(NH_2CH_2CH_2)_nNH_{3-n}$. Compared to the uncatalyzed reaction, urea, thiourea and cyanoguanidine lower the free energy of the transition state by 3 kcal/mol while guanidine lowers the barrier by 2 kcal/mol.

1. Introduction

The α- and β-2-deoxy glycosides (Scheme 1) are constituents of many bacterial antibiotic and anti-cancer oligosaccharides.[1] Altering the composition of these sugars affects their biological activity (for examples, see [2–4]). Efforts to study their therapeutics are hindered by their synthetic access. Although α- and β-2-deoxy glycosides are structurally diverse, they all lack a C2-oxygen functionality adjacent to the C1-anomeric center. In addition, many bacterial 2-deoxy-sugars often contain a number of modifications, including further deoxygenation at the C3– and/or C6-position.

The oligosaccharides are constructed using glycosylation reactions, in which a hydroxyl nucleophile (ROH) displaces a leaving group from an activated sugar electrophile (Scheme 1) (for recent reviews and advances, see [5–9]). This reaction creates a new stereocenter at the C1-anomeric carbon where the α- and β-2-deoxy glycosides are formed. Lack of C2-oxygen functionality precludes the use of well-established strategies to control the anomeric selectivity in the glycosylation reactions for the assembly of 2-deoxy-sugars.[10–12] In addition, many bacterial sugars lack a C6-oxygen, preventing conformational biases to control the anomeric selectivity. The stereoselective synthesis of 2-deoxy glycosides can rely on a direct strategy, an indirect strategy or addition to a glycal.[12] The indirect strategy requires a temporary group at C2 in the electrophilic donor. Although glycosylation reactions with the indirect approach are high selectivity, it is necessary to remove the temporary C2 group. Addition to glycans requires the use of specific protecting groups and the stereochemical configuration of the C4-substituent in the glycal donor for controlling 2-deoxy selectivity. The direct strategy requires proper selection of the promoter, solvent, protecting groups, and coupling partners to obtain high selectivity. Although substrate-controlled glycosylation methods have been successful in providing solutions to a number of challenging oligosaccharide syntheses, subtle changes to the sugar structures have pronounced effects on reaction selectivity and reactivity.

The ability of phenanthrolines to catalyze the stereoselective formation of α-glycosidic bonds has recently been discovered by the Nguyen group [13–16]. The glycosylation proceeds through a double S_N2 mechanism. The first step involves a phenanthroline or substituted pyridine displacing a bromide (Scheme 2). In the second step, this group is displaced by the HO of the nucleophile to complete the glycosylation reaction. In the present work, we focus on the first step and, to simplify the calculations, examine pyridine reacting with α-bromo, 2-

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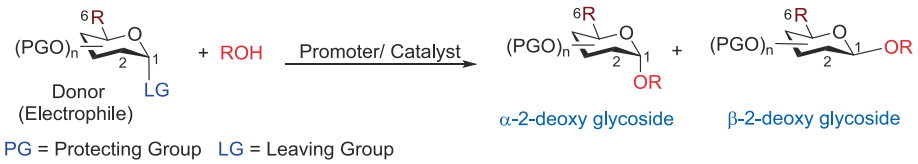
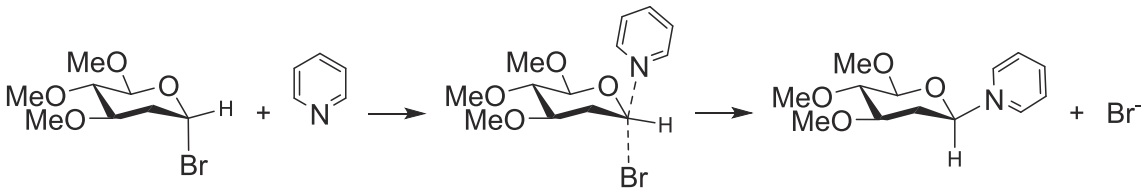


Scheme 1. Glycosylation reactions to form α- and β-2-deoxy glycosides.



Scheme 2. First step in the glycosylation of α-bromo, 2-deoxyglucose catalyzed by pyridine. The glycosylation is completed in a second S_N2 reaction, in which the ROH nucleophile displaces the pyridine.

deoxyglucose protected by methyl groups. This step can be rate limiting because the bromide ion is poorly solvated in the nonpolar solvents needed for the glycosylation reaction. Hydrogen bond donors can be effective catalysts by stabilizing ionic intermediates and products [17–19], with urea and thiourea being particularly effective. Thiourea derivatives are significantly better than ureas at catalyzing glycosylation reactions [20,21]. Specifically, macrocyclic bis-thiourea are excellent catalysts yielding β-glycosides with high stereoselectivity via a direct S_N2 mechanism.[21–24].

In previous studies, we have employed density functional theory (DFT) calculations to investigate stereoselective α-glycosylation and 1,2-cis furanosylation reactions catalyzed by phenanthroline in a double S_N2 mechanism [13–15]. In the present study, we use DFT calculations to examine the binding of bromide ion by a selection of small molecule hydrogen bond donors: 1,2-diaminoethane, bis(2-aminoethyl)amine, tris(2-aminoethyl)amine, urea, thiourea, guanidine and cyanoguanidine. We then test the ability of the best ligands to lower the energy of the transition state (TS) for the first S_N2 reaction of the glycosylation (Scheme 2) and thereby catalyze the overall reaction. The calculations in this short study have paved the way for an extensive experimental investigation supported by density functional calculations of catalysis of α-glycosylation reactions by protonated hydrogen bond donors.

The present exploratory study is dedicated to the memory of Professor Imre G. Csizmadia. HBS has known IGC since his graduate student days 50 years ago. Throughout his career, IGC championed the scientific education of students of diverse backgrounds through the hands-on experience of quantum chemical calculations. In keeping with this spirit, the present study began as a senior undergraduate research project for a student in biology (SH).

2. Computational methods

Calculations were carried out with the Gaussian series of programs [25] using the M06-2X functional [26,27]. In our previous studies on catalysis of glycosylation reactions [13–15], the mechanism for stereoselective glycosylation calculated with M06-2X functional was in better agreement with experiment than calculations with other functionals such as B3LYP. The SMD implicit solvation method [28] was used to model solvation in diethyl ether. Geometry optimization and frequency calculations employed the 6-31+G(d,p) basis set and included SMD solvation. The zero point energies and thermal corrections for enthalpy and free energy (298.15 K, 1 atm) computed with the M06-2X/6-31+G (d,p) level of theory were combined with single point energy calculations at the M06-2X/aug-cc-pVTZ level of theory and SMD solvation to obtain more accurate estimates of the energies. Because there are difficulties in estimating the solvation of ions in non-polar solutions using implicit solvation methods, the energies for the ligands binding to bromide are calculated relative to a solvent molecule binding to bromide. Likewise, the energies for the ligands binding to the transition state and to the post-transition state complex are calculated relative to the energies of the ligands binding to a solvent molecule. This results in a partial cancelation of the errors arising from the implicit solvation model and from the electronic structure method as well as contributions arising from translational entropy in solution.

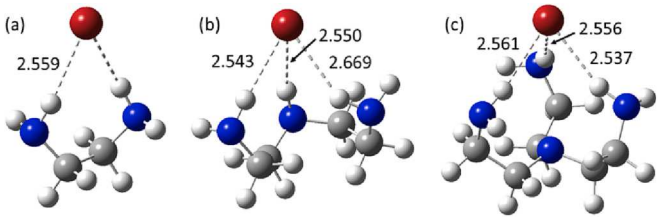


Fig. 1. Complexes of Br^- with (a) 1,2-diaminoethane, (b) bis(2-aminoethyl) amine and (c) tris(2-aminoethyl)amine (H-Br^- distances in Å).

3. Results and discussion

The first step in the stereoselective glycosylation reaction developed by the Nguyen group involves a phenanthroline or a related substituted pyridine displacing a bromide (Scheme 2).[13–16] Since bromide ion is poorly solvated in the non-polar solvents used for these reactions, a hydrogen bond donor ligand that can bind bromide should lower the barrier for this step and the catalytic effect should be proportional bromide binding strength. A series of simple ligands with N-H bonds was selected for their potential to form hydrogen bonds with Br^-. Fig. 1 shows Br^- complexed with a set of alkyl amines with increasing numbers of NH_2 groups. These ligands are often used in transition metal complexes. Since urea and thiourea derivatives have been shown to catalyze stereoselective glycosylations [20–24], a second set of simple urea derivatives was chosen to complex with Br^-. Complexes of Br^- with urea, thiourea, guanidine and cyanoguanidine are shown in Fig. 2.

The relative binding energies for Br^- in the complexes in Figs. 1 and 2 are summarized in Table 1. Some caution is needed in calculating these binding energies since implicit solvation methods have difficulties in modeling bare anions in non-polar solvents. These difficulties can be circumvented by calculating the binding energy of Br^- in a complex relative to the binding energy of Br^- to a solvent molecule. For bromide complexed with diethyl ether (Eq. (1)), the Br^- interacts with the hydrogens of one of the CH_3CH_2 groups and is stabilized by the C-O bond dipole. Bromide interacts more strongly with the N-H bonds in the

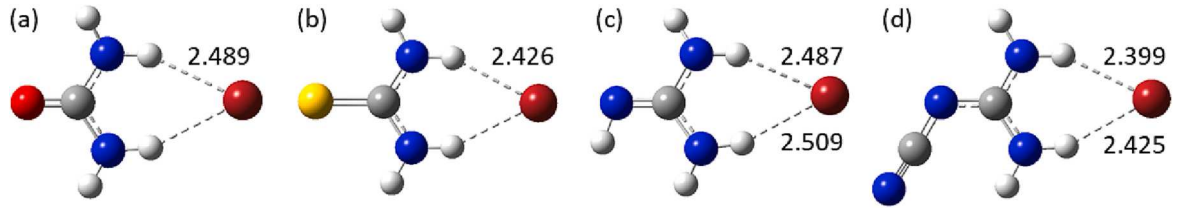


Fig. 2. Complexes of Br^- with (a) urea, (b) thiourea, (c) guanidine and (d) cyanoguanidine (H-Br^- distances in Å).

Table 1
Calculated relative binding energies for bromide with selected ligands (kcal/mol, using Eq. (3)).

Ligand	ΔH	ΔG
$H_2NCH_2CH_2NH_2$	−5.1	−3.9
$(NH_2CH_2CH_2)_2NH$	−7.4	−5.6
$(NH_2CH_2CH_2)_3N$	−8.1	−4.1
urea	−10.6	−8.9
thiourea	−12.9	−10.6
guanidine	−9.5	−8.6
cyanoguanidine	−15.1	−14.0

complexes with the ligands (Eq. (2)) than to the solvent (Eq. (1)). The relative binding energies are obtained by subtracting Eq. (1) from Eq. (2), which eliminates the need for calculating the energy of an isolated Br^- ion in solution.

$$EtOEt + Br^- \rightarrow EtOEt\text{-}Br^- \quad (1)$$

$$L + Br^- \rightarrow L\text{–}Br^- \quad (2)$$

$$L + EtOEt\text{–}Br^- \rightarrow L\text{–}Br^- + EtOEt \quad (3) = (2) - (1)$$

The alkyl amines have binding enthalpies of 5.1 – 8.1 kcal/mol and the values increase with the number of hydrogen bonds to Br^-, as expected. For the free energies of binding, there is a greater change in vibrational entropy on binding Br^- for the larger alkylamines with more

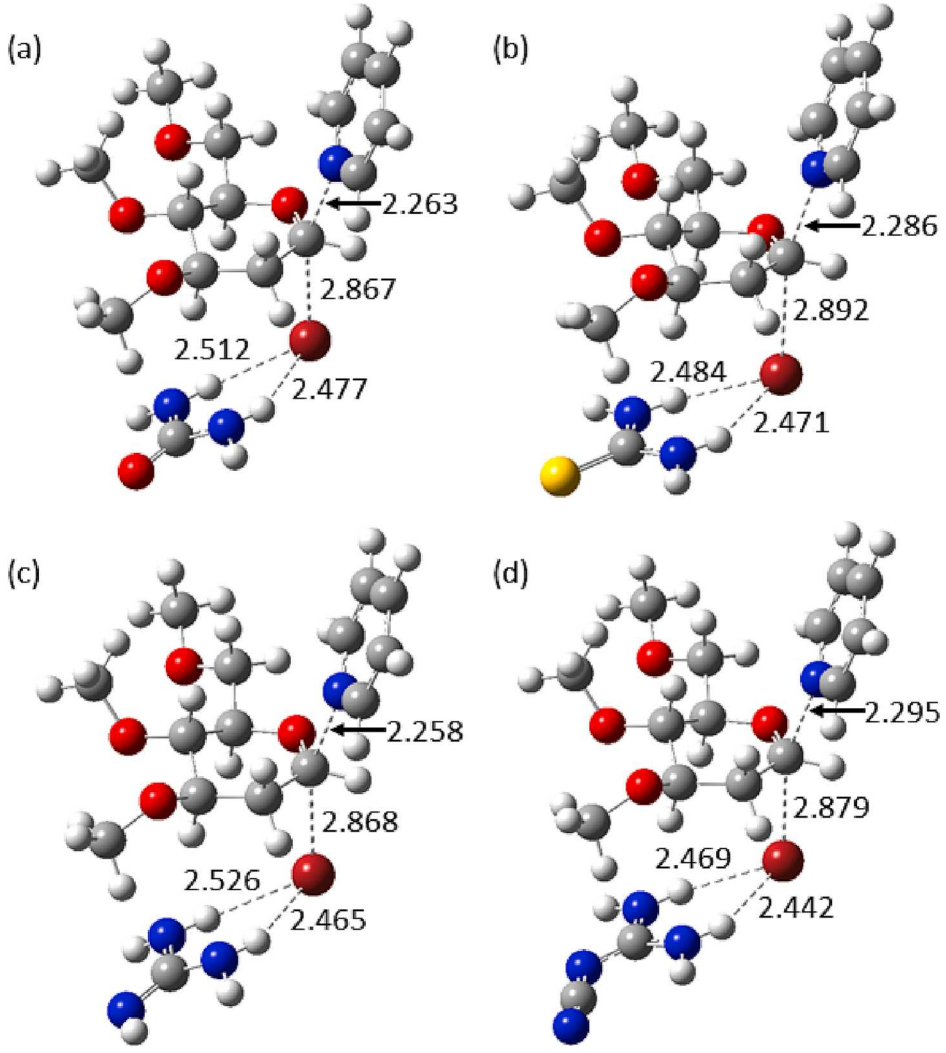


Fig. 3. Transition structures for the S_N2 reaction of pyridine 1-bromo, 2-deoxyglucose catalyzed by (a) urea, (b) thiourea, (c) guanidine and (d) cyanoguanidine (distances in Å). For the uncatalyzed reaction R(C1-N) = 2.163 Å and R(C1-Br) = 2.815 Å.

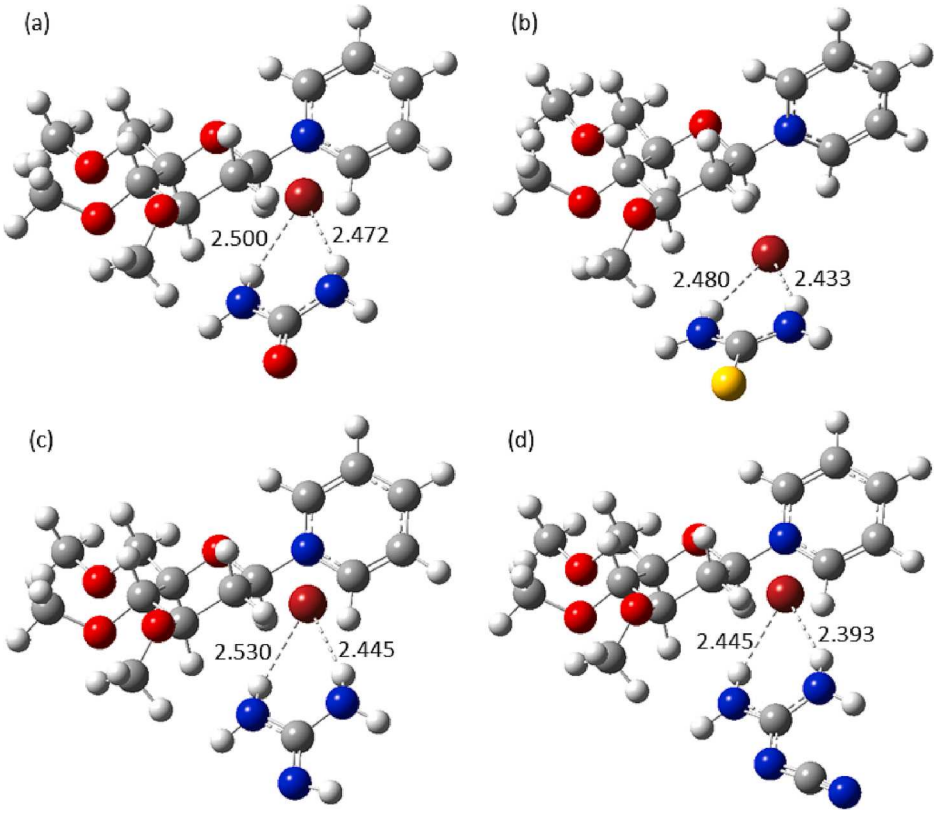


Fig. 4. Post-transition state minima for pyridine displacing Br^- in 1-bromo, 2-deoxyglucose complexed with (a) urea, (b) thiourea, (c) guanidine and (d) cyanoguanidine (H-Br^- distances in Å).

rotatable bonds than for the smaller alkylamines with fewer rotatable bonds. This counters the trend in the free energies of binding with the number of hydrogen bonds to Br^- and also leads to a smaller range in binding free energies (3.9 – 5.6 kcal/mol). Urea has a significantly larger binding enthalpy than $(NH_2CH_2CH_2)_3N$ even though it has only 2 hydrogen bonds to Br^-. This is due to a larger dipole moment and larger partial charges on the hydrogens of urea compared to the alkylamines. Replacing the O in urea with S yields thiourea and increases the binding enthalpy by 2.5 kcal/mol. This is in accord with the better catalytic activity for glycosylation found for thiourea derivatives than for urea derivatives [20,21]. Switching O in urea to NH yields guanidine and decreases the binding enthalpy by 1 kcal/mol. Adding CN as an electron withdrawing group to guanidine gives cyanoguanidine and increases the binding energy by 5 kcal/mol. The bromide binding energies in the urea, thiourea, guanidine and cyanoguanidine derivatives parallel the trends in the partial charges on the hydrogens (0.34, 0.36, 0.34 and 0.37, resp.) and the dipole moments (5.4, 7.4, 4.1 and 10.2 Debye, resp. by M06-2X/6-31+G(d,p)). The increase in binding energy is accompanied by a shortening of the NH – Br^- distances by 0.06 A for thiourea compared to urea and 0.08 Å for cyanoguanidine compared to guanidine. Since the alkyl amines bind Br^- more weakly than urea, thiourea, guanidine and cyanoguanidine, only the latter are considered for catalyzing the S_N2 reaction of pyridine with α-bromo glucose.

In the uncatalyzed reaction, the transition state for pyridine displacing the bromide is a simple S_N2 reaction with C-N and C-Br distances of 2.163 Å and 2.815 Å, respectively. The transition states with the ligands complexed to the bromide are shown in Fig. 3. The C-N distances are 0.10 – 0.13 Å longer and the C-Br distances are 0.05 – 0.07 Å longer than in the uncatalyzed transition state, with the more strongly bound ligands producing the larger shifts. The ligands are bound to the Br^- in the transition state with geometries similar to the complexes with Br^- shown in Fig. 2. The ligands interact with the Br π-type lone pairs and are approximately perpendicular to the C-Br σ bond that is being broken in the S_N2 transition state.

Table 2
Calculated relative binding energies of the ligands with the transition structure (kcal/mol, using Eq. (6)).

Ligand	ΔH	ΔG
urea	−4.0	−3.2
thiourea	−4.8	−3.2
guanidine	−3.1	−1.9
cyanoguanidine	−3.8	−3.3

Table 3
Calculated relative binding energies of the ligands with the post-transition state minimum (kcal/mol, using Eq. (6)).

Ligand	ΔH	ΔG
urea	−5.6	−3.8
thiourea	−5.3	−4.7
guanidine	−5.4	−3.7
cyanoguanidine	−5.8	−4.3

Along the reaction path after the transition state, there is a complex with the negatively charged bromide bound to the positively charged pyridyl sugar. The Br^- sits beneath C1-N bond at a distance of about 3.3 Å and interacts with the hydrogen on C1 (2.5 – 2.7 Å) in both the uncatalyzed case and when complexed with the ligands. Like in the transition states, the ligands are approximately perpendicular to the pyridyl sugar–Br^- interaction (Fig. 4). The ligand NH – Br^- distances are similar to the complexes in Figs. 2 and 3.

The relative binding energies for the ligands with the transition structure and with the post-transition state complex are listed in Tables 2 and 3, respectively. Since the ligands also bind fairly strongly with diethyl ether (enthalpies of −4.5 to −6.5 kcal/mol), the binding energies

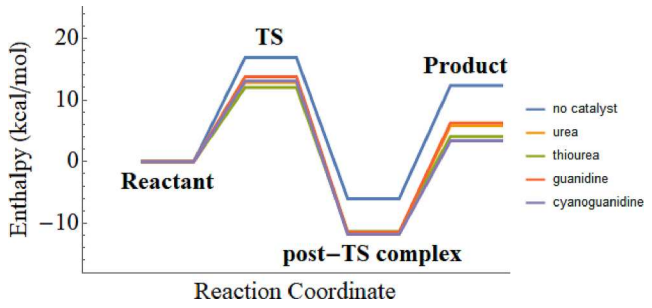


Fig. 5. Enthalpy profile for the reaction with and without the catalyzing ligands.

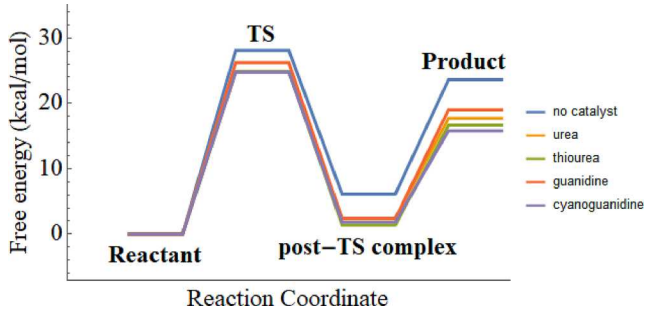


Fig. 6. Free energy profile for the reaction with and without the catalyzing ligands.

of the ligands in the transition state complex are computed relative to the binding of the ligands with the solvent. The energies for binding to the post-transition state minimum and to the EtOEt–Br^- complex in the product are calculated in an analogous fashion. There is also a pre-transition state minimum, but most of the ligands bind more strongly to the diethyl ether solvent than to the pre-transition state complex.

$$L + EtOEt \rightarrow L\text{–}EtOEt \quad (4)$$

$$L + X \rightarrow L\text{–}X \quad (5)$$

X = TS, post-TS complex, EtOEt–Br^-

$$L\text{–}EtOEt + X \rightarrow L\text{–}X + EtOEt \quad (6) = (5) - (4)$$

The calculated binding energies show that all of the ligands lower the energy of the transition state. Guanidine is the least effective, in accord with the lower ligand–Br^- binding energies listed in Table 1. However, the relative binding energies for the transition state fall in a narrower range than in Table 1, primarily because the binding energies of the ligand with the solvent (Eq. (4)) vary in a parallel fashion to the binding energies of the ligand with Br^- (Eq. (5)). The ligands stabilize the post-transition state complex and the product by a little more than the transition state because the charge on the Br^- is fully developed.

The binding energies in Tables 1–3 can be combined with the energy profile for the uncatalyzed glycosylation reaction to obtain the enthalpy and free energy profiles for the catalyzed reactions shown in Figs. 5 and 6, respectively. The final step from the post-TS complex to the product is endothermic because it involves the separation of the post-TS complexes into a positively charged pyridyl sugar and the negatively charged ligand-bromide complexes shown in Fig. 2.

The uncatalyzed reaction has a substantial enthalpy barrier in part because the Br^- leaving group is poorly solvated by diethyl ether. Furthermore, the free energy barrier is higher than enthalpy barrier because of loss of translational entropy as the pyridine nucleophile approaches the α-bromo, 2-deoxyglucose to form the transition state. For the catalyzed reactions, the calculations show that the ligands bind more strongly to the transition state than to the solvent, thereby lowering the reaction barrier. Urea, thiourea and cyanoguanidine lower the free energy of the transition state by a similar amount but guanidine is less effective. The post-transition state complex is strongly stabilized by the electrostatic attraction between the negatively charged Br^- leaving group and the positively charged pyridyl sugar. The four ligands considered in the present study are nearly equally effective in stabilizing the post-transition state complex. The electrostatic attraction in the post-transition state complex must be overcome when the leaving group is separated from the pyridyl sugar to form the separated products and results in a large increase in energy. In practice, this increase in energy is avoided by scavenging the Br^- by an agent such as isobutylene oxide (IBO).

4. Conclusions

Relatively few methods are available for the selective synthesis of α-2-deoxy glycosides. Substituted pyridines and phenanthrolines are highly effective in promoting the stereoselective glycosylation of 1-bromo 2-deoxy sugars via a double S_N2 mechanism. The first step, displacement of bromide by a substituted pyridine or phenanthroline, can be rate limiting because bromide is poorly solvated in the non-polar solvents used for these reactions. Pyridine reacting with α-bromo, 2-deoxyglucose was chosen as a representative reaction. A set of small molecules was selected to bind bromide in order to lower the energy of the transition state and accelerate the reaction. A series of alkylamines, $(NH_2CH_2CH_2)_nNH_{3-n}$, showed increasing binding enthalpy with the number of H – Br hydrogen bonds. However, urea, thiourea, guanidine and cyanoguanidine were found to bind bromide more strongly because of a larger dipole moment and larger partial positive charges on the hydrogens that interact with the bromide. Urea, thiourea and cyanoguanidine lowered the free energy of the transition state by 3 kcal/mol while guanidine lowered the barrier by 2 kcal/mol, potentially accelerating the first step of the overall reaction by 2 orders of magnitude. Even better catalysis may be achieved with ligands that bind Br^- more strongly, but not so strongly as to favor an S_N1 mechanism with concomitant loss of stereoselectivity. One possibility is to use protonated ligands since these will bind Br^- more strongly in the TS and will form a neutral complex with Br^-, reducing the electrostatic barrier to forming separated products. This approach is currently being explored experimentally and computationally, and computationally and will be reported in due course.

CRediT authorship contribution statement

Spencer Haisha: Investigation. **Hien M. Nguyen:** Conceptualization. **H. Bernhard Schlegel:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comptc.2023.114122.

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