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Sensing or No Sensing: Can the Anomeric Effect Be Probed by a Sensing Molecule?

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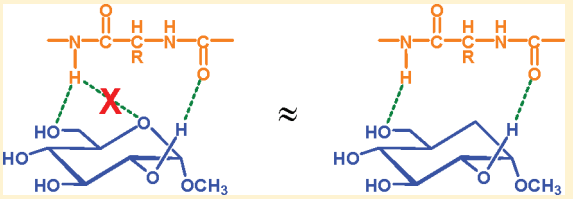
Supporting Information

ABSTRACT: The anomeric effect plays a central role in carbohydrate chemistry, but its origin is controversial, and both the hyperconjugation model and the electrostatic model have been proposed to explain this phenomenon. Recently, Cocinero et al. designed a peptide sensor, which can bind to a sugar molecule methyl D-galactose, and claimed that the anomeric effect can be sensed by the spectral changes from the β- to the α-complex, which are ultimately attributed to the lone pair electron density change on the endocyclic oxygen atom [*Nature* **2011**, *469*, 76; *J. Am. Chem. Soc.* **2011**, *133*, 4548]. Here, we provide strong computational evidence showing that the observed spectral changes simply come from the conformational differences between the α- and β-anomers, as the replacement of the endocyclic oxygen atom with a methylene group, which disables both the endo- and the exo-anomeric effects in methyl D-galactose, leads to similar spectral shifts. In other words, the "sensor" cannot probe the anomeric effect as claimed. We further conducted detailed energetic and structural analyses to support our arguments.



INTRODUCTION

The anomeric effect refers to the enhanced thermodynamic preference of the α-anomer over the β-anomer of a six-membered carbohydrate ring with an electronegative substituent Y at the anomeric carbon (C1).[1−9] Although it was initially found in carbohydrates and ubiquitously exists in monosaccharides and their derivatives, the concept has been extended to saturated heterocycles and acyclic systems containing heteroatoms and is broadly defined as the preference of a gauche conformation over an anti conformation for a R−X−C−Y moiety, where X is an atom with lone pairs such as O or S, and Y denotes an electronegative atom such as O, N, or halogen.[10−13] The magnitude of the anomeric effect ranges from a few to tens of kJ/mol and thus is comparable to the strength of conventional hydrogen bonds. It is generally believed that both steric and electronic interactions make contributions to the conformational preferences,[14] but their exact roles are controversial. The current popular theory for the anomeric effect is the hyperconjugation model, which centers on the electron delocalization from the oxygen lone pairs to the vacant antibonding orbital σ_{CY}^*.[15−18] This n$\rightarrow\sigma^*$ negative hyperconjugation explanation can well interpret the geometric variations in α- and β-anomers, although Perrin et al. have demonstrated that the geometrical variations can also be rationalized in terms of intramolecular electrostatic interactions at least in certain molecules.[19] In fact, the validity of the n$\rightarrow\sigma^*$ hyperconjugation model itself has been generally challenged.[19−25] An alternative explanation for the anomeric effect is the electrostatic model,[1,26] which suggests that the nearly antiparallel arraignment of the two local dipoles in the axial conformer stabilizes the molecule. This electrostatic model can well interpret the experimental observations that aqueous solvation effects stabilize β-anomers.[27−29] Recently, for the first time, we were able to theoretically derive the self-consistently optimized wave functions corresponding to the hypothetical electron-localized states (i.e., the classical Lewis structures) of α- and β-anomers, and we demonstrated that the conformational preferences persist when the hyperconjugative interactions are "turned off".[30] This is the strongest computational evidence so far to disprove the hyperconjugation explanation for the anomeric effect. However, we reiterate that this disproval does not mean the rejection of the existence of hyperconjugative interactions within molecules.[31,32]

Very recently, Cocinero et al. conducted an elaborate experiment in attempt to discern underlying factors leading to the anomeric effect. They designed a peptide sensor (*N*-acetyl-L-phenylalanine), which can bind to the archetypal carbohydrate, methyl D-galactose, in a solvent-free environment.[33,34] As the carbohydrate molecule has α- and β-anomeric forms that interact with the molecular probe via hydrogen bonds as shown in Figure 1, these authors claimed that the differences in the key N−H and O−H (indicated by the arrows in Figure 1) vibrational spectra of the two carbohydrate−peptide complexes reflect the anomeric effect. They found that the C-terminal N−H vibrational band in the peptide molecule red-shifts by ~40 cm^{-1} from the β- to the α-complex; meanwhile, the O2−H stretching frequency in the carbohydrate molecule blue-shifts by ~80 cm^{-1}.

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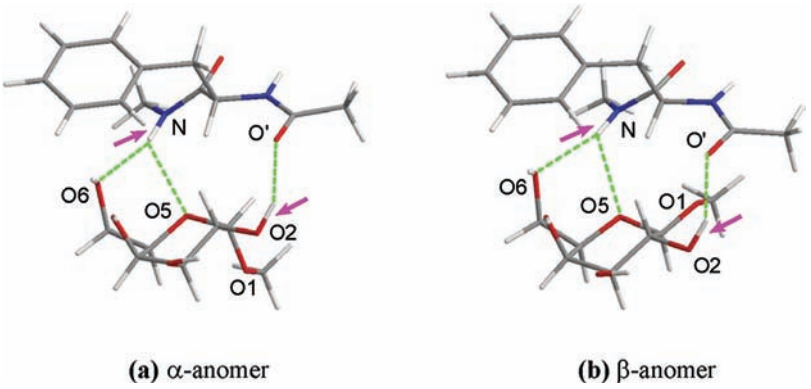

Figure 1. Hydrogen-bonding interactions between the sensing molecule (top) and two different carbohydrate anomers (below) for the carbohydrate−peptide complex **1**. Adapted from refs 33 and 34.

The experimental observation was further confirmed by DFT (MO5-2X/6-31+G**) computations and interpreted with the NBO analysis. However, we feel that the experimental results only delineated the different binding capability of the α- and β-sugars to the peptide sensor and could not provide any clue as to which isomer is more stable than the other, let alone the physical nature of the anomeric effect. The very long distances between the endocyclic O5 and the amide hydrogen (2.61 and 2.39 Å in the α- and β-anomeric complexes shown in Figure 1) also raise a serious question as to whether there is any meaningful hydrogen-bonding interactions between them. As such, we decided to further look into these two carbohydrate−peptide complexes with the intention to uncover the true origins of the experimentally observed vibrational frequency shifts by mutating the involved functional groups computationally.

COMPUTATIONAL STRATEGIES

We first followed the computational procedure identical to that of Cocinero et al.[33,34] and derived the optimal structures of the carbohydrate−peptide complex **1** and obtained the vibrational frequencies at the DFT(MO5-2X/6-31+G**) level with the Gaussian 03 program.[35] The harmonic wavenumbers were also similarly scaled by a factor of 0.9419.[36] Afterward, we mutated the functional groups one-by-one in methyl D-galactose, which participate in the hydrogen-bonding interactions with the peptide (see the three dashed lines in Figure 1), and reoptimized the subsequent geometries and examined the changes of the relevant vibrational frequencies.

To further probe the interactions between the carbohydrate and peptide molecules, we performed energy decomposition analysis based on the block-localized wave function method (BLW-ED in short) at the same theoretical level of MO5-2X/6-31+G**. The BLW method combines the concepts and advantages of both the valence bond (VB) and the molecular orbital (MO) theories and defines the intermediate and physically intuitive electron-localized states self-consistently.[37,38] This BLW method has been used to formulate the BLW-ED procedure where the total intermolecular binding energy (ΔE_b) is decomposed into a number of physically intuitive terms, including structural deformation (ΔE_{def}), steric (ΔE_s, which is a combination of the electrostatic and Pauli repulsive interactions), polarization (ΔE_{pol}), and charge transfer (ΔE_{CT}) energy terms as[39−41]

$$\Delta E_b = \Delta E_{def} + \Delta E_s + \Delta E_{pol} + \Delta E_{CT} \quad (1)$$

We note that the very same procedure was reintroduced and implemented to the Q-Chem software under the name of "absolutely localized molecular orbitals (ALMOs)" by Khaliullin et al.[42] In this work, we employed the BLW-ED approach, which has been implemented to our in-house version of GAMESS,[43] to conduct energy decomposition analysis to elucidate the physical origin of the sugar−peptide interactions.

Table 1. Key Bond Distances (Å) and Vibrational Frequencies (cm^{-1}) in the Optimal Carbohydrate−Peptide 1 and Mutated Complexes 2−4 at the MO5-2X/6-31+G Level[a]**

complex		R (O6···H)	R (O5···H)	R (H···O′)	ν (N−H)	ν (O2−H)
1	α	1.997	2.610	1.954	3328 (−45)	3569 (+91)
	β	2.098	2.444	1.900	3373	3478
2	α	2.018	2.546	1.935	3335 (−60)	3544 (+5)
	β	2.106	2.463	1.946	3395	3539
3	α	2.052		2.023	3365 (−67)	3568 (+53)
	β	2.192		1.956	3432	3515
4	α		2.038	1.949	3379 (−41)	3566 (+87)
	β		2.181	1.873	3420	3479

[a] Numbers in parentheses are the relative shifting from the β- to the α-anomeric complexes, and symbols "+" and "−" refer to the blue- and red-shiftings, respectively.

RESULTS AND DISCUSSION

The key optimal hydrogen-bond distances and vibrational frequencies of the C-terminal N−H bond in the peptide molecule and the O2−H bond in the sugar molecule were compiled in Table 1. Our geometries for the complex **1** are very close to those reported by Cocinero et al.,[33] and similar spectral differences between the α- and β-anomers are observed. For instance, from the β- to the α-anomeric complex, the N−H vibrational band is displaced by 45 cm^{-1} to a lower wavenumber, while the O2−H band shifts by 91 cm^{-1} to a higher wavenumber. These data reflect the relative strengthening and weakening of the concerned hydrogen bonds as evidenced by the changes of the hydrogen-bond distances and are in excellent agreement with the experimental findings (∼40 and ∼80 cm^{-1}, respectively) and the computational results in the literature.[33,34] Of particular, we note that the distance between (N−)H and O5 is 2.61 Å in the α-complex and 2.44 Å in the β-complex, both of which are considerably longer than the distances between (N−)H and O6 (2.00 and 2.10 Å, respectively), and, as a matter of fact, are beyond the range of hydrogen bonds. Cocinero et al., however,

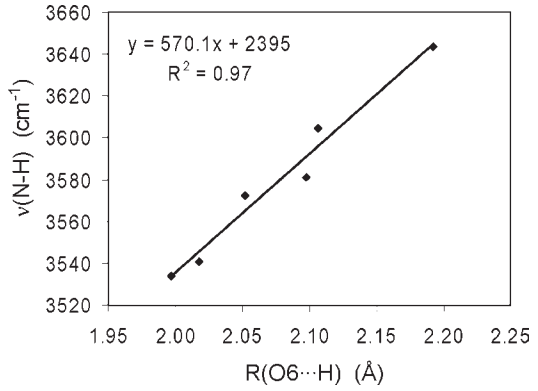

Figure 2. Correlation between the stretching vibrational frequency of the C-terminal N−H bond and the O6···HN hydrogen-bonding distance.

suggested that the spectral changes of the N−H and O2−H bond stretching vibrations are mediated by the electron density changes at O5, which is the core of the anomeric effect. In other words, the infrared spectroscopy is "an experimental signature of this single anomeric effect".[33]

To explore the exact causes of these experimentally observed and computationally confirmed spectral shifts, we alternatively disabled the hydrogen-bonding interactions as shown in Figure 1 by individually mutating the functional groups in methyl D-galactose including the OCH_3 group at the anomeric center C1, the endocyclic O5 atom, and the CH_2OH group at the C5 position. The substitution of the OCH_3 group by an ethyl group leads to complex **2**, whereas the replacements of the O5 atom by a methylene group and the CH_2OH group by a hydrogen atom result in complexes **3** and **4**, respectively. All mutants **2**−**4** were subject to geometry reoptimizations, and the subsequent key structural parameters and vibrational frequencies were also presented in Table 1.

Table 1 shows that on moving from the β- to the α-anomeric complex **2**, a similar structural change for the NH···O6/O5 hydrogen bonding to **1** is observed, as is the red-shifting (60 cm^{-1}) of the N−H bond vibrational frequency. The O2−H vibration changes little, but this is in accord with the negligible variation of the O2−H···O′=C distance. The most illuminating finding perhaps comes from the mutation of O5, which plays a central role in the anomeric effect (complex **3**). The previous NBO analysis showed that the exo-anomeric effect due to the n(O1)→σ^*(C1−O5) hyperconjugation is more pronounced than the endo-anomeric effect due to the n(O5)→σ^*(C1−O1) hyperconjugative interaction. Yet the replacement of this endocyclic O5 atom with a methylene group in complex **3** deactivates both the exo- and the endo-anomeric effects and thus completely shuts down the so-called "anomeric modulation". Strikingly, from the β- to the α-complex **3**, the N−H vibrational frequency red-shifts by 67 cm^{-1} to a lower wavenumber, and the O2−H vibrational frequency blue-shifts by 53 cm^{-1} to a higher wavenumber. The very same spectroscopic behaviors in complexes **1** with the anomeric effect and **3** without any anomeric effect impose a significant challenge on the claim that the spectral changes in the carbohydrate−peptide complex **1** correlate with "the relative reduction in the lone pair electron density at O5 in the α-anomer, caused by the hyperconjugative interaction".[33] If we remove the CH_2OH group at the C5 position completely (complex **4**), the C-terminal NH group will switch its hydrogen-bonding interaction to O5 as the NH···O5 distance shortens significantly as compared to the rest of the three complexes (see Table 1). There is a similar reduction of the N−H vibrational frequency (41 cm^{-1}) and an increase of the O2−H vibrational frequency (87 cm^{-1}) from the β- to the α-anomeric complex **4** as well. Nevertheless, even for **4** there is no convincing proof at all to associate the spectral changes with the anomeric effect. As a matter of fact, by comparing complexes **1**−**3** (note that O6 is removed in complex **4**), we can find a good correlation between the N−H vibration and the O6···H distance (Figure 2), which shows that the N−H vibrational frequency red-shifts along with the shortening of the hydrogen-bond distance related to O6···H−N. Whereas this can be well explained in terms of the n(O6)→σ^*(N−H) electron transfer, Figure 2 clearly indicates that O5 does not play a detectable let alone modulating role in the N−H spectral band, as O5 is 2.4−2.6 Å away from the nearest hydrogen atom, which is beyond any legitimate hydrogen-bond distances. At the most, the spectral changes signal the differences of the hydrogen-bonding interactions, mostly due to the conformational (steric) changes and local dipole−dipole interactions in the α- and β-anomers, whose overall dipole moments are 3.514 and 3.762 D, respectively, for methyl D-galactose.

Table 2. Computed Energy Components (kJ/mol) at the Optimal Molecular Geometries at the MO5-2X/6-31+G Level with the BLW-ED Approach**

complex		ΔE_{def}	ΔE_s	ΔE_{pol}	ΔE_{CT}	ΔE_b
1	α	24.8	−53.8	−23.3	−20.5	−72.8
	β	19.2	−53.9	−22.8	−23.5	−81.0
2	α	10.5	−55.0	−24.3	−20.8	−89.5
	β	16.1	−54.5	−22.8	−20.7	−81.9
3	α	31.2	−42.7	−17.6	−17.5	−46.7
	β	22.2	−41.4	−16.1	−20.8	−56.0
4	α	26.5	−44.2	−20.0	−17.4	−55.1
	β	18.2	−42.4	−19.8	−19.5	−63.5

Although the definitions of energy terms are far from stringent, energy decomposition analysis (EDA) can provide a deeper understanding of intermolecular interactions and explore chemical bonding features within a molecule, and a variety of EDA schemes thus have been designed and developed.[44−54] Here, we employed the BLW-ED approach[39−41] to conduct energy decomposition analyses to elucidate the physical origin of the sugar−peptide interactions. Table 2 lists the results for complexes **1**−**4**. It is obvious that for all of these hydrogen-bonding systems, electrostatic attraction is the driving force, but both the polarization and the charge transfer make considerable contributions to the stability of the complexes as well.[55] It is interesting to note that for the carbohydrate−peptide complex **1**, there are comparable steric and polarization interactions in the α- and β-anomers, and the major difference lies in the structural deformation energy cost, which is 5.6 kJ less, and the charge transfer energy, which is 3.0 kJ/mol more in the β-anomeric complex than in the α-anomeric complex. The latter seems a support for the claim by Cocinero et al.[33] that the reduction of the electron density at O5 in the α-anomer results in a weakening of the interaction between the carbohydrate and the sensor. Yet the structural data in Table 1 strongly suggest that the difference in charge transfer energy comes from the enhanced hydrogen bonding between the hydroxyl group O2−H and the carbonyl group O′=C, whose distance reduces from

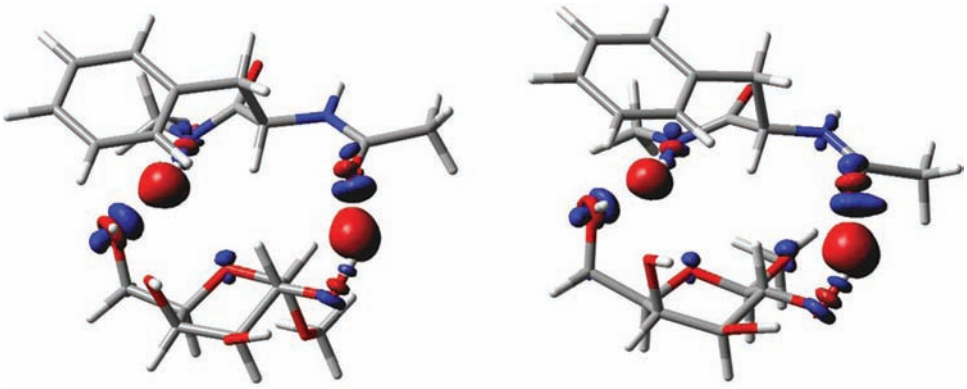

Figure 3. EDD maps showing the electron transfers in hydrogen-bonding interactions between methyl D-galactose and *N*-acetyl-L-phenylalanine (isodensity 5.0×10^{-4} au). Red and blue surfaces refer to the increasing and decreasing of the electron density, respectively.

1.95 Å in the α-anomeric complex to 1.90 Å in the β-anomeric complex. This suggestion can be verified by the electron density difference (EDD) maps in the carbohydrate−peptide complex. Figure 3 clearly shows that the charge transfer overwhelmingly occurs in the two hydrogen bonds (O2−H···O′=C and NH···O6), and the role of O5 is negligible and consistent in both α- and β-anomeric complexes.

The charge transfer energy listed in Table 2 measures the two (or three if O5 is counted as a hydrogen-bond acceptor as shown in Figure 1) hydrogen-bonding interactions in sugar−peptide complexes. These numbers are much lower than the NBO data listed in the paper by Cocinero et al.,[33] where the total charge transfer energy amounts to 80.42 and 66.09 kJ/mol in the α- and β-anomeric complexes (note here that there are stronger electron transfer interactions in the α- than in the β-anomeric complexes, in contrast to our data in Table 2). We remind that the magnitude of "normal" (like the ones here) hydrogen-bonding interaction energies ranges from a few to tens of kilojoules per mole, and the NBO computations tend to significantly overestimate the hyperconjugation (charge transfer) energy due to the use of nonoptimal orbitals, as was clearly exhibited in the ethane case where the NBO analysis concludes that the steric repulsion favors the eclipsed conformer instead of the staggered conformer.[56] The total NBO charge transfer energies in the sugar−peptide complexes obtained by Cocinero et al. are close to the total binding energies and thus obviously out of the question. Regarding the use of nonorthogonal orbitals in the BLW-ED approach as in all ab initio VB methods, we note that molecular properties can be fully determined by the electron density alone after all, and there is no theoretical ground showing that the use of nonorthogonal orbitals would underestimate the hyperconjugation energy by exaggerating the role of steric effects. As all computational methods must be justified by viable experimental evidence, studies with the BLW method, which is the simplest variant of ab initio VB theory, on conjugated systems where a large body of experimental data has been accumulated, have provided convincing structural and energetic results consistent with experimental findings.[57−60] The negligible n(O5)→σ^*(N−H) electron transfer can be further justified by the fact that charge transfer is short-range and decays exponentially.[61]

Interestingly, Table 2 also shows that the peptide has a higher binding energy with the β-anomer than with the α-anomer of the carbohydrate molecule by 8.2 kJ/mol, largely due to the lower deformation cost and higher charge transfer stabilization energy in the former. The preference of the α-anomer to the β-anomer (10.1 kJ/mol) is thus greatly diminished in the sugar−peptide complex **1**, although the α-form is still slightly favored over the β-form. The substitution of the exo-anomeric oxygen O1 with CH_2 (complex **2**) turns off both the endo- and the exo-anomeric effects, yet BLW-ED analysis shows that all of the energy terms are comparable to those in complex **1**, except the deformation penalty. The low deformation energy in complex **2** eventually results in higher binding energies than in **1**, and for both the monomer and the complex, α-anomers are preferred. The mutation of the endo-anomeric oxygen O5 (**3**) or the O6 (**4**), however, significantly reduces the electrostatic attraction, ultimately weakening the binding interaction between the sugar molecules and the peptide. This implies the significance of the local dipoles around O5 and O6 in methyl D-galactose.

Table 3. Energy Differences ($\Delta E_{\alpha\rightarrow\beta}$, kJ/mol) between α- and β-Anomers with Decomposed Contributions from Steric Effect (ΔE_s), Electron Delocalization (ΔE_{del}), and Dispersion Effect (ΔE_{disp})

molecule	$E_{\alpha\rightarrow\beta}$	E_s	ΔE_{del}	ΔE_{disp}
2-methoxytetrahydropyran	7.5	10.4	−6.6	3.7
cyclohexyl methyl ether	0.1	−4.5	1.5	3.2
2-tetrahydropyranol	5.5	9.2	−5.9	2.3
cyclohexanol	−1.7	−2.5	−0.4	1.2

At the final stage, we studied the endo- and exo-anomeric effects in methyl D-galactose with the model of 2-methoxytetrahydropyran.[62] Following the earlier procedure[30] for the sake of comparison, we first performed geometry optimizations at the MP2/6-31+G(d) level, followed by the generalized BLW computations, which quench the geminal and hyperconjugative interactions from the lone pairs of both oxygen atoms (O5 and O6) by strictly localizing the electrons within functional groups and the lone pairs on oxygen atoms with our ab initio VB software XMVB.[63,64] The energy difference between the α- and β-anomers ($\Delta E_{\alpha\rightarrow\beta}$) at the MP2 level is subsequently decomposed into three contributions, electron delocalization (ΔE_{del}), steric effect (ΔE_s), and dispersion

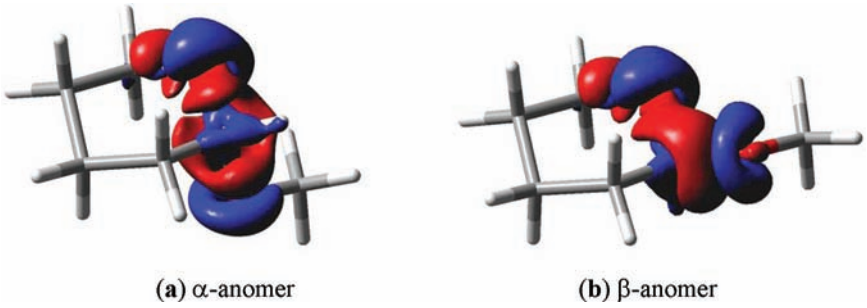

Figure 4. EDD maps showing the electron delocalization within 2- methoxytetrahydropyran displaying the endo- and exo-anomeric effects (isodensity 0.002 au). Red and blue surfaces refer to the increasing and decreasing of the electron density, respectively.

(ΔE_{disp}), as

$$\Delta E_{\alpha\rightarrow\beta} = E_{\beta}(\mathrm{MP2}) - E_{\alpha}(\mathrm{MP2}) = E_{\beta}(\mathrm{HF}) - E_{\alpha}(\mathrm{HF}) + \Delta E_{disp}$$
$$= E_{\beta}(\mathrm{BLW}) - E_{\alpha}(\mathrm{BLW}) + \Delta E_{del} + \Delta E_{disp}$$
$$= \Delta E_{s} + \Delta E_{del} + E_{disp} \quad (2)$$

Similar to the BLW-ED approach, here the steric energy term (ΔE_s) is composed of both the electrostatic interaction (stabilizing or destabilizing) and the Pauli repulsion. Table 3 compiled the energy terms for 2-methoxytetrahydropyran and its reference molecule of no anomeric effect, cyclohexyl methyl ether. For comparison, results for 2-tetrahydropyranol and cyclohexanol were also listed. As expected, 2-methoxytetrahydropyran and 2-tetrahydropyranol exhibit similar energy contributions and conformational preferences, which are dominated by the steric effect. Furthermore, there are stronger hyperconjugative interactions in the equatorial conformers than in the axial conformers. This seems different from the hyperconjugation model, but we note that in our calculations the delocalization energy includes not only the vicinal n→σ^* hyperconjugative interactions, but also the geminal interactions among the bonds sharing common apex atoms.[65] Figure 4 shows the electron density variations due to the electron delocalization in 2-methoxytetrahydropyran.

CONCLUSION

In summary, Cocinero et al. claimed that the changes of the lone pair electron density on the endocyclic O5 in the sugar molecule methyl D-galactose can be directly "sensed" by the peptide *N*-acetyl-L-phenylalanine as the stretching frequency changes are caused by the anomeric effect.[33] However, our calculations demonstrated that the replacement of O5 with a methylene group, which disables both the endo- and the exo-anomeric effects in methyl D-galactose, results in a similar red-shifting of the C-terminal N−H vibrational band and a similar blue-shifting of the O2−H stretching vibrational frequency on moving from the β- to the α-complex. On the basis of our detailed energy analyses and structural examination, we conclude that the claim of "sensing the anomeric effect" is premature and an overinterpretation of the experimental data, as the changes are simply due to the variations of hydrogen-bonding distances in the two carbohydrate−peptide complexes, which do not necessarily involve the anomeric effect in a sensible way.[66] In other words, Cocinero et al.'s delicate experiment showed only the structural differences of the two anomers of methyl D-galactose as expected, but failed to address the relative stability as well as the cause of the different stabilities of these two anomers.

ASSOCIATED CONTENT

Supporting Information. Optimal geometries of the carbohydrate−peptide complex **1** and its mutated complexes **2**−**4** with absolute energies (in hartrees) at the MO5-2X/6-31+G** theoretical level by the Gaussian 03 program. Complete ref 35. This material is available free of charge via the Internet at http://pubs.acs.org.

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