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Sugar Thioureas as Anion Receptors. Effect of Intramolecular Hydrogen Bonding in the Carboxylate Binding Properties of Symmetric Sugar Thioureas

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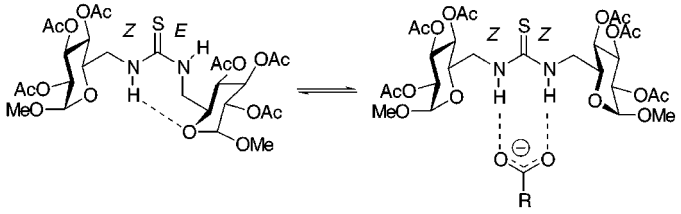
ABSTRACT



The conformational behavior of sugar thiourea receptors in chloroform-*d* solution and their binding properties toward carboxylate ligands have been examined. The association constants were found to be largely independent of the initial proportion of the bound conformation. In contrast, the existence of competitive intramolecular hydrogen-bonding strongly decreased the K_{as} values, whereas the existence of a lipophilic microenvironment at the vicinity of the binding site favored the association process.

Hydrogen bonds are known to be largely responsible for the inter- and intramolecular order in nucleic acids and proteins, and there is little doubt that they are structurally as important in carbohydrates.[1] However, of the many artificial receptors that employ hydrogen-bond centers as key recognition and binding elements, only a few are related to sugars.[2] As a part of a project aimed at the understanding of molecular recognition processes involving carbohydrates, we sought to construct saccharide-embodying receptors for which hydrogen bonding would be the primary driving force for complex formation. Toward this end, sugar thioureas offer many interesting features.[3] The relatively high acidity of the NH thiourea protons is correlated with a strong hydrogen-bonding donor capability already exploited in the design of efficient anion receptors.[4] Thiourea segments embedded into a

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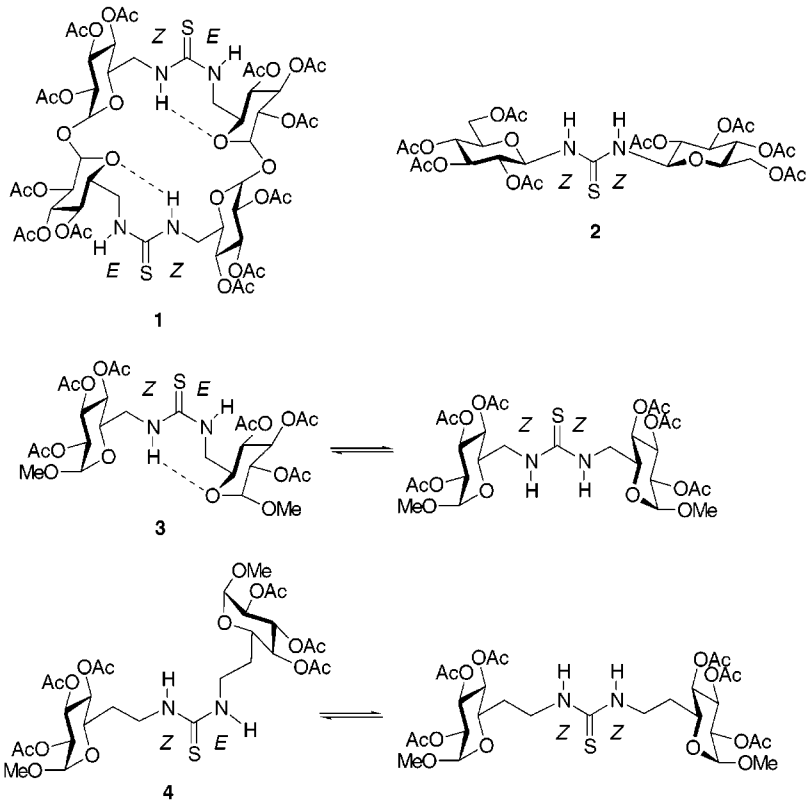

Figure 1. Rotameric equilibria for compounds **1**−**4** in chloroform-*d* solution.

pseudooligosaccharide structure may, thus, provide efficient anchoring points for hydrogen-bonding recognition of complementary functional groups, such as carboxylate, phosphate or sulfonate, in a specific and predictable fashion. Alternatively, intramolecular hydrogen bonds may act as key stabilizing interactions in the host structure itself, inducing secondary structures. Since the *E*−*Z* rotameric interconversion rates at the pseudoamide N−C(═S) bonds in thioureas fall in the range of the chemical shift time scale, variable-temperature NMR spectroscopy offers a good opportunity for structural characterization of preferred folding patterns and identification of the structural requirements for efficient complexation.

We have considered in our study a series of symmetric structures possessing different degrees of conformational flexibility at the thiourea segments, including the macrocyclic pseudotetrasaccharide **1**[5] and the linear pseudodisaccharides **2**,[6] **3**, and **4** (Figure 1).

The known hybrid trehalose−thiourea macrocycle **1** has been shown to exist in chloroform-*d* solution exclusively in the *Z*,*E*/*E*,*Z* alternate conformation. The thiourea NH protons in the anti disposition with respect to the thiocarbonyl sulfur atoms are directed to the inside of the cavity and involved in seven-membered intramolecular hydrogen bonds, with the opposite pyranoid oxygen atoms acting as acceptors.[7] Albeit a dynamic degenerated equilibrium resulting from conrotatory rotations at the pseudoamide bonds occurs (coalescence temperature, T_c 295 K), the conformational constrains imposed by the macrocyclic structure prevents *Z*,*Z* arrangements at any of the thiourea functionalities. Conversely, the thiourea group in the per-*O*-acetylated bis(*β*-D-glucopyranosyl)thiourea **2** adopts the *Z*,*Z* configuration as the only rotameric form in chloroform-*d* solution with both NH

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(7) The stabilization of *Z*,*E* rotamers in sugar thioureas by seven-membered hydrogen bonds was supported by chemical shift temperature coefficient measurements, rotational barrier calculations and molecular modeling. It seems to be a main structural feature of this class of compounds, as seen from specifically designed models. See: (a) Ortiz Mellet, C.; Moreno Marín, A.; Jiménez Blanco, J. L.; García Fernández, J. M.; Fuentes, J. *Tetrahedron: Asymmetry* **1994**, *5*, 2325−2334. (b) García Fernández, J. M.; Ortiz Mellet, C.; Jiménez Blanco, J. L.; Fuentes, J.; Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S. *Carbohydr. Res.* **1996**, *286*, 55−65.

protons, in syn 1,3-parallel disposition, pointing toward the β-face of the pyranose ring.[8]

The new podant-like sugar thioureas **3** and **4** were conceived to represent intermediate conformational situations at the thiourea region as compared with **1** and **2**. They were obtained by the coupling reaction of the corresponding amino sugar hydrochlorides with the sugar isothiocyanate counterparts following previously reported methodologies.[9]

Compound **3** may be seen as a monomeric analogue of the macrocyclic dimer **1**. The low-temperature range ^{1}H NMR spectra recorded in chloroform-*d* solution showed a 4:1 *E*,*Z*-to-*Z*,*Z* relative population, coalescence occurring at 285 K. At 313 K the chemical exchange processes became fast and the NMR spectra displayed signals for a single methyl α-D-glucopyranoside subunit, in agreement with the expected C_{2v} symmetry. The temperature dependence of the thiourea protons NMR chemical shifts below coalescence at 5 mM concentration in $CDCl_3$ revealed some interesting features (Figure 2). First, the *trans*-NH proton in the *E*,*Z* rotamer resonated at a significant lower field than the *cis*-NH proton and then the corresponding *trans*-NH protons in the (*Z*,*Z*) conformation. Moreover, the temperature-independent character of $\delta_{trans-NH}$ is in agreement with the behavior generally observed for completely intramolecularly hydrogen-bonded amide protons.[10] The structural relationship between **3** and **1** joined to the above-discussed data strongly suggest that the *E*,*Z* rotamer of **3** is likewise stabilized by a seven-membered NH···$O_{endocyclic}$ intramolecular hydrogen bond[7] (Figure 1).

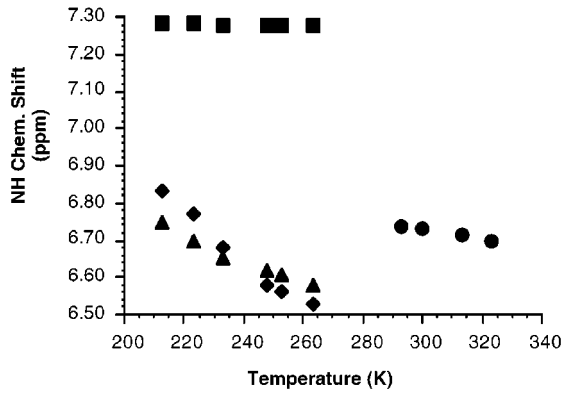

Figure 2. Thiourea proton chemical shifts as a function of temperature for compound **3**. Data are collected in $CDCl_3$ at 5 mM concentration. Above coalescence: fast exchanging NH (●). (*Z*,*E*) Rotamer: *trans*-NH (■) and *cis*-NH (◆). (*Z*,*Z*) Rotamer: *trans*-NH (▲).

Variable-temperature ^{1}H NMR spectra of compound **4** in $CDCl_3$ likewise evidenced the presence of relatively slow-rotating bonds. At temperatures below 263 K, signals for the *E*,*Z* (asymmetric) and *Z*,*Z* rotamer (symmetric), in a 9:1 relative proportion, were observed. Even though both NH protons in **4** have several hydrogen-bonding options available to them in any of the configurational arrangements, their chemical shifts and temperature-coefficient values were rather consistent with the data for non-hydrogen-bonded thiourea protons (Figure 3).

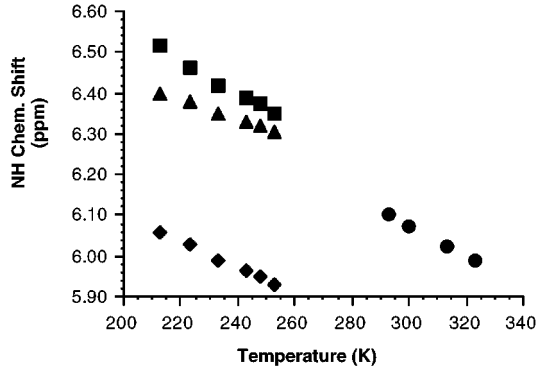

Figure 3. Thiourea proton chemical shifts as a function of temperature for compound **4**. Data are collected in $CDCl_3$ at 5 mM concentration. Above coalescence: fast exchanging NH (●). (*Z*,*E*) Rotamer: *trans*-NH (■) and *cis*-NH (◆). (*Z*,*Z*) Rotamer: *trans*-NH (▲).

The present evidence for strong binding of thioureas to carboxylates can be rationalized in terms of the formation of trans-bidentated four-center hydrogen bonds, although a fast equilibrium between monodentated complexes is also possible (Figure 4).[11] In any case, strong binding involves necessarily the *Z*,*Z* rotameric form of the thiourea group.

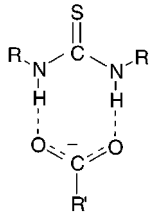

Figure 4. Proposed four-center bidentated hydrogen bonds between thiourea and carboxylate groups.

In principle, folding patterns of sugar thioureas favoring the *E*,*Z* configurational arrangement must disfavor the

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intermolecular association process. Thus, the experimental ^{1}H NMR and K_{as} data (Table 1) evidenced that the hydrogen-bond interaction of **1**, for which a 1,3-parallel disposition of the NH protons is prevented, with benzoate is weaker than any of the interactions of the NH protons of **2**−**4** in their complexes with benzoate or acetate. Notwithstanding, the measured K_{as} values for the (7→7)-thiourea-linked heptose derivative **4** are about three times higher than for the *Z*,*Z* monoconfigurational receptor **2**. They are also 7-fold greater than the corresponding values for the (6→6)-linked hexose analogue **3**, even though the relative population of the active *Z*,*Z* conformation is about twice lower.

Table 1. Thermodynamic Data for **1**−**4** and Their Benzoate and Acetate Complexes

receptor	rotameric populations[a]	T_c (K)	K_{as}[b] (OBz, M^{-1})	K_{as}[b] (OAc, M^{-1})
1	100% *(Z,E:E,Z)*	295	13	n.d.
2	100% *(Z,Z)*		210	197
3	4:1 *(Z,E)*/*(Z,Z)*	285	102	95
4	9:1 *(Z,E)*/*(Z,Z)*	268	590	630

[a] Obtained by digital integration of the NH signals at temperatures below coalescence. [b] At 300 K. Average values from at least two separate experiments. Errors are estimated to be ±10%. [c] Not determined.

The above evidence suggests that the ability for recognition and binding between receptor and ligand is, to some extent, independent of the initial proportion of the bound conformation found in the complex. Most likely, the discrepancy in carboxylate binding affinity for **3** and **4** stems from the differences in the molecular order of the receptors themselves in chloroform-*d* solution. Thus, binding to carboxylate anion through intermolecular bidentated hydrogen-bonding has an additional energetic cost in the case of **3** (i.e,. breaking the preexisting intramolecular hydrogen bond in the *E*,*Z* configuration) as compared to **4**. This becomes even more evident when comparing the complexing behavior of **2** and **4**. Despite the expected higher acidity of the anomeric pseudoamide protons and the complementary preorganization of the thiourea binding site in **2**, carboxylate binding is more efficient in the case of the flexible receptor **4**. The differences in K_{as} values for **2** and **4** are possibly due to the higher lipophilicity at the proximity of the hydrogen bond donor centers in the later, which must facilitate the desolvation processes of the incoming carboxylate guest.[12]

The conformational properties of a given molecule almost certainly play a major role in specifying its ability to form stable supramolecular complexes. However, our results indicate that a simple quantification of the "active" conformation in the conformational equilibrium prior to complex formation is not a reliable data to anticipate association efficiency, a situation already encountered in natural systems.[13] The existence of specific intramolecular interactions that can oppose intermolecular hydrogen-bond and the nature of the substituents at the vicinity of the binding site may exert a dramatic influence in the complexing properties. Identification of preferred folding patterns and intramolecular interactions in carbohydrate conjugates should assist, then, in the efficient design of artificial sugar-based receptors, an aspect currently under development in our group.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **3** and **4** and their precursors and experimental conditions for binding studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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