Synthesis, Conformational Flexibility and Preliminary Complexation Behaviour of α,α′-Trehalose-based Macrocycles Containing Thiourea Spacers

José M. García Fernández,* José L. Jiménez Blanco, Carmen Ortiz Mellet and José Fuentes*

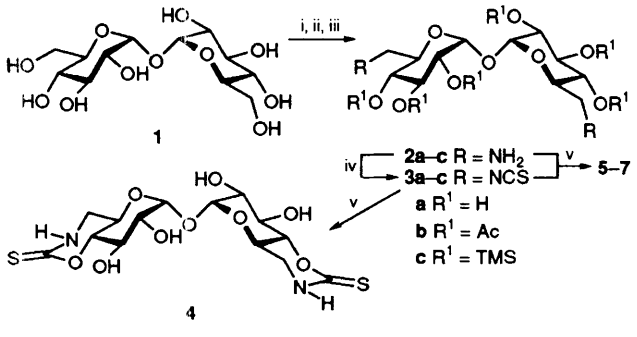
Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain

An efficient synthesis of macrocyclic ligands incorporating two α,α′-trehalose subunits linked through the primary C-6,6′ positions by means of 1,3-thiourea spacers is reported; the *Z*/*E* configuration of the N–C(=S) bonds is governed by intramolecular hydrogen bonding as well as steric factors.

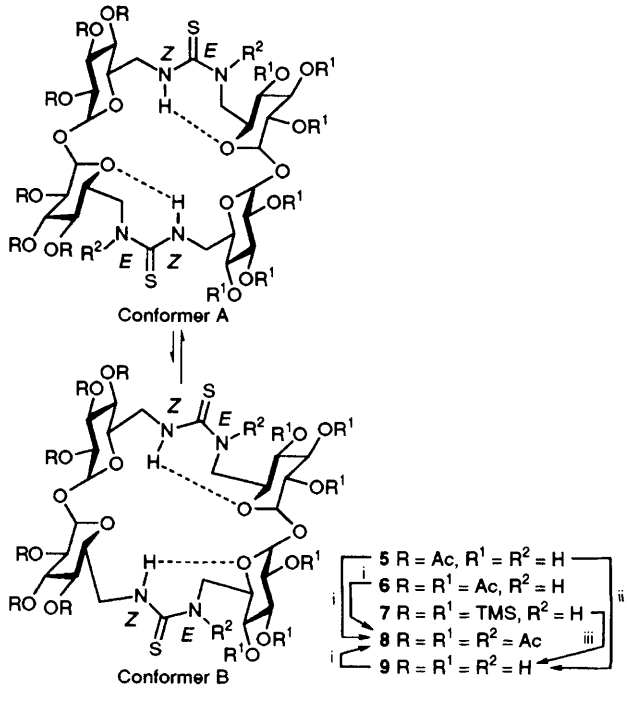
Macrocyclic polyamides, from which cyclopeptides are paradigmatic examples,[1] possess a restrained flexibility where each planar amide framework can adopt either the *Z* or *E* configuration above the carbonyl–nitrogen partial double bond.[2] The resulting global conformation is dependent on the environment, thus making this type of macrocycle a unique class of compounds. Thioureas also conform to this structural feature, with the *a priori* advantage that the possibility of designing symmetric macrocyclic derivatives may facilitate structural analysis by means of dynamic NMR techniques. Hitherto, only a few examples of cyclic poly(thioureas) have been reported,[3] and there appear to be no reports on their conformational behaviour in solution. In connection with our previous studies on sugar thioureas,[4] we have now undertaken the synthesis and conformational study of macrocyclic poly(thioureylene)oligosaccharides.[5] Our interest is in the development of a novel class of chiral receptors combining the well-known complexing abilities of cyclic oligosaccharides, typically cyclodextrins,[6] and the conformational adaptability of cyclopeptides. On the other hand, these sugar–thiourea coronands may be considered as conformationally restricted glycopeptide analogues, useful as model compounds for the study of specific carbohydrate–peptide interactions, *e.g.* interactions involving the pseudoamide NH protons and the carbohydrate oxygen atoms.

Here we describe a short and efficient synthesis of new cyclic pseudooligosaccharides **5–9** incorporating two α,α′-trehalose subunits connected by thiourea bridges. In a first approach, the synthetic strategy adopted was to convert the commercial disaccharide **1** into the 6,6′-diamino derivative **2a** (3 steps, 70% overall yield) and subsequently to transform the diamine into the corresponding diisothiocyanate **3a** by reaction with thiophosgene (90%, Scheme 1), following the synthetic pathway previously used in the preparation of monosaccharide derivatives.[7] Attempts at the direct condensation of **2a** with **3a** failed, the intramolecular bis(cyclic thionocarbamate) **4** being the only isolated product. Thus, protection of the hydroxy groups in **3a** becomes a prerequisite, whereas the diamine precursor **2a** can be used either fully unprotected or selectively *O*-protected. Per-*O*-acetyl (**2b**, **3b**) and per-*O*-trimethylsilyl derivatives (**2c**, **3c**) of **2a** and **3a** have been synthesized and used in condensation reactions to give the cyclic bis(thioureylene)pseudotetrasaccharides **5–7** in 40–65% isolated product yields (Scheme 2). These unusually high yields for bimolecular cyclisation reactions are probably due to the favourable geometric characteristics of the α,α′-trehalose molecule, a rigid disaccharide having C_2 symmetry and concave shape already exploited in the preparation of macrocyclic derivatives,[8] and to the high mutual affinity of the funtional groups put into the reaction. Conventional acetylation of **5** or **6** afforded the di-*N*-acetate **8** in virtually quantitative yield, whereas removal of the protecting groups in **6** or **7** gave the fully unprotected, water soluble derivative **9** (40 or 98% yield, respectively; Scheme 2).

The ^1H and ^{13}C NMR spectra of **6** and **7**, recorded at room temperature in $CDCl_3$ showed broad signals indicative of relatively slow chemical exchange processes. Temperature variable (−50 to +50 °C) spectra evidenced the presence of conformer A exclusively (**6**), or a conformational equilibrium between conformers A and B (**7**). Both conformations present two NH protons directed to the inside of the cavity which are probably involved in hydrogen bonding, as seen from temper-



Scheme 1 *Reagents and conditions*: i, Ph_3P, I_2, DMF, 80 °C; ii, NaN_3, DMF, 80 °C; iii, Ph_3P, dioxane–MeOH (5 : 1), then aq. NH_3, room temp.; iv, $CSCl_2$, $CaCO_3$, acetone–H_2O, room temp.; v, pyridine, 40 °C; **2a** → **2b**, diethyl ethoxymethylenemalonate, MeOH, 40 °C, then Ac_2O–pyridine (1 : 1) and subsequent treatment of the peracetate with Cl_2 in $CHCl_3$ (70% overall yield, isolated as dihydrochloride); **1** → **2c**, i, ii, then BSA, DMF, TBAF and then iii; DMF = *N*,*N*-dimethylformamide; BSA = *N*,*O*-bis(trimethylsilyl)acetamide; TBAF = tetra-*n*-butylammonium fluoride



Scheme 2 Conformational equilibria of macrocycles **5–9** (degenerated equilibria resulting from concerted rotations around the appropriate N–C(S) bonds are omitted): conformer A was the only rotamer detected in the cases of compounds **5**, **6**, **8** ($CDCl_3$) and **9** (D_2O) by low-temperature ^1H NMR experiments and/or acetylation (→ **8**); compound **7** existed as a 1 : 0.75 mixture of conformers A and B.

Reagents and conditions: i, Ac_2O–pyridine (1 : 1); ii, NaMeO, MeOH; iii, 60% AcOH–H_2O, 40 °C.

ature coefficient measurements for the corresponding chemical shifts (<0.001 ppm K^{-1}). The existence of seven-membered NH···O hydrogen bonds has been unequivocally proved in monosaccharide 6-deoxy-6-thioureido aldopyranoses by rotational barrier calculations,[4] the stabilization energy being *ca.* 2 kcal mol^{-1} (1 cal = 4.184 J). It is noteworthy that seven-membered NH···O hydrogen bonds also play an important role in the conformational behaviour of cyclopeptides,[1a,9] and they could also be a key structural feature of glycopeptides.

The fully unprotected derivative **9** displays satisfactorily narrow ^1H and ^{13}C signals for a single type of α-D-glucopyranosyl subunit only after heating at 90 °C in D_2O, indicative of a higher activation energy for rotameric interconversion as compared with **6** or **7**. Previous results on the influence of solvent polarity on the height of the *Z*/*E* rotational barriers of sugar thioureas suggest that exchange should be faster if the intramolecular hydrogen bonds are broken by solvation. The present result probably means that in compound **9** the seven-membered NH···O hydrogen bonds remain effective in water, the increase in the activation energy being a consequence of solvation of the NH protons directed outside the ring.

Preliminary cation-binding studies in water, using thin-layer ligand-exchange chromatography,[10] show that **9** binds Cs^+ preferentially amongst univalent cations ($Cs^+ > K^+ > Na^+$) and forms a strong complex with Cu^{2+} ($Cu^{2+} \gg Zn^{2+}$, Ba^{2+} and Ca^{2+}) amongst divalent cations. Nevertheless, the R_f values (>0.5) are indicative of low complexation coefficients, excepting the Cu^{2+} complex (R_f *ca.* 0). Stable complexes of macrocyclic thioureas with soft ions such as Au^+ and Ag^+ have already been reported,[4] the chelating interaction being restricted to outside-directed sulfur atoms. In our case, the absence of strong complexation by coordination with carbohydrate oxygen atoms is probably due to the rather lipophilic character of the cavity, as seen from a Corey–Pauling–Koltun (CPK) model of **9**, and is in agreement with reported data for α,α′-trehalose-based glycophanes.[8]

Additional evidence for these conclusions by comparison of the conformational behaviour of cyclic and linear thioureyl-enepseudooligosaccharides as well as the conformational response of these new cyclic receptors towards potential guest molecules is currently being sought in our laboratory.†

We thank the Dirección General de Investigación Científica y Técnica for financial support (grant no. PB 91/0617), the Junta de Andalucía for a doctoral fellowship (J. L. J. B.) and the Ministerio de Educación y Ciencia of Spain for a postdoctoral fellowship (J. M. G. F.). We are also grateful to Dr S. Penadés (C. S. I. C., Madrid) for fruitful discussions.

Received, 28th September 1994; Com. 4/05951D

Footnote

† All new compounds, with the exception of **5** which was transformed *in situ* into the tetradecaacetate **8**, gave satisfactory microanalytical, mass spectral and NMR (COSY, HETCOR and ROESY) data in accord with the proposed structures.

Selected data for **6**: δ_H (300 MHz, $CDCl_3$, 323 K), 6.46 (t, 1 H, NH, *J* 6.2 Hz), 5.51 (t, 1 H, H-3, *J* 9.8 Hz), 5.38 (d, 1 H, H-1, *J* 3.5 Hz), 5.11 (dd, 1 H, H-2), 5.01 (t, 1 H, H-4, *J* 9.8 Hz), 3.78 (m, 2 H, H-5,6), 3.31 (m, 1 H, H-6′); 248 K, 6.91 (d, 1 H, NH_z, *J* 7.9 Hz), 6.65 (t, 1 H, NH_E, *J* 6.1 Hz), 5.74 (d, 1 H, H-1_E, *J* 3.9 Hz), 5.39 (d, 1 H, H-1_Z, *J* 4.0 Hz). For **7**: δ_H (500 MHz, $CDCl_3$, 328 K), 6.51 (br s, 1 H, NH), 4.86 (d, 1 H, H-1, *J* 2.7 Hz), 3.97 (dt, 1 H, H-5, $J_{4,5}$ 9.5, $J_{5,6}$, $J_{5,6'}$ 3.3 Hz), 3.87 (t, 1 H, H-3, *J* 9.0 Hz), 3.55 (br s, 2 H, H-6,6′), 3.44 (dd, 1 H, H-2), 3.36 (br t, 1 H, H-4); 248 K, 7.11 (d, 1 H, NH_Z conformer A, *J* 9.1 Hz), 7.01 (br s, 0.75 H, NH_Z conformer B), 6.12 (t, 1 H, NH_E A, *J* 7.0 Hz), 6.04 (t, 0.75 H, NH_E B, *J* 7.0 Hz), 4.83 (d, 1 H, H-1_E A, *J* 3.9 Hz), 4.72 (d, 0.75 H, H-1_E B, *J* 2.9 Hz), 4.65 (d, 1.75 H, H-1_Z A and B, *J* 2.8 Hz. For **8**: δ_H (500 MHz, $CDCl_3$, 328 K), 8.46 (br s, 1 H, NH), 5.53 (d, 1 H, H-1_E, *J* 3.4 Hz), 5.28 (d, 1 H, H-1_Z, *J* 3.8 Hz). For **9**: δ_H (500 MHz, D_2O, 363 K), 5.61 (d, 1 H, H-1, *J* 3.9 Hz), 4.50 (dt, 1 H, H-5, $J_{4,5}$ 9.8, $J_{5,6}$, $J_{5,6'}$ 4.4 Hz), 4.36 (t, 1 H, H-3, *J* 9.8 Hz), 4.26 (br s, 2 H, H-6,6′), 4.20 (dd, 1 H, H-2), 3.92 (t, 1 H, H-4).

References

1 For leading references, see: (*a*) B. Sarkar, in *Progress in Macrocyclic Chemistry*, vol. 2, ed. R. M. Izatt and J. J. Christensen, Wiley, New York, 1981, ch. 5; (*b*) G. R. Marshall, *Tetrahedron*, 1993, **49**, 3547; (*c*) S. Jackson, W. DeGrado, A. Dwivedi, A. Parthasarathy, A. Higley, J. Krywko, A. Rockwell, J. Markwalder, G. Wells, R. Wexler, S. Mousa and R. Harlow, *J. Am. Chem. Soc.*, 1994, **116**, 3220.

2 For a review on the conformational behaviour of amides and related compounds, see: W. E. Steward and T. H. Siddal, *Chem. Rev.*, 1970, **70**, 517.

3 M. Rosser, D. Parker, G. Ferguson, J. F. Gallagher, J. A. K. Howard and D. S. Yufit, *J. Chem. Soc., Chem. Commun.*, 1993, 1267; A. V. Bogatsky, N. G. Lukyanenko and T. I. Kirichenko, *Tetrahedron Lett.*, 1980, **21**, 313; A. V. Bogatsky, N. G. Lukyanenko and T. I. Kirichenko, *Zh. Org. Khim.*, 1981, **17**, 1279; *Chem. Abstr.*, 1982, **96**, 6997m.

4 C. Ortiz Mellet, A. Moreno Marín, J. L. Jiménez Blanco, J. M. García Fernández and J. Fuentes, *Tetrahedron Asymmetry*, in the press.

5 J. M. García Fernández, J. L. Jiménez Blanco, C. Ortiz Mellet and J. Fuentes, preliminary results presented at the XVIIth International Carbohydrate Symposium, Ottawa, Canada, 1994, abstr. B2.109.

6 M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag, Berlin, 1978; *Cyclodextrins and Their Industrial Uses*, ed. D. Duchêne, Editions de Santé, Paris, 1987; *New Trends in Cyclodextrin Chemistry*, ed. D. Duchêne, Editions de Santé, Paris, 1991.

7 J. M. García Fernández, C. Ortiz Mellet and J. Fuentes, *Tetrahedron Lett.*, 1992, **33**, 3931; J. M. García Fernández, C. Ortiz Mellet and J. Fuentes, *J. Org. Chem.*, 1993, **58**, 5192; J. M. García Fernández, C. Ortiz Mellet, J. L. Jiménez Blanco and J. Fuentes, *J. Org. Chem.*, 1994, **59**, 5565.

8 J. M. Coterón, C. Vicent, C. Bosso and S. Penadés, *J. Am. Chem. Soc.*, 1993, **115**, 10066; S. Penadés and J. M. Coterón, *J. Chem. Soc., Chem. Commun.*, 1992, 683; C. Vicent, C. Bosso, F. H. Cano, J. L. G. de Paz, C. Foces-Foces, J. Jiménez-Barbero, M. Martín-Lomas and S. Penadés, *J. Org. Chem.*, 1991, **56**, 3614.

9 L. G. Pease, C. H. Niu and G. Zimmermann, *J. Am. Chem. Soc.*, 1979, **101**, 184.

10 J. Briggs, P. Finch, M. C. Matulewicz and H. Weigel, *Carbohydr. Res.*, 1981, **97**, 181.