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The *Exo*-Anomeric Effect Does not Govern the Conformation of Some 2,2'-*O*-Substituted α,α'-Trehalose Derivatives. Solid State and Solution Evidences.

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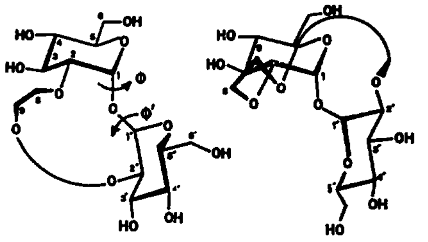
Abstract: *The crystal structure and solution conformation of the chiral mono-trehalo-15-crown 5 1 shows what is probably the first case of a disaccharidic structure where the anomenc effect does not dominate. This unexpected conformational change seems to be a general tendency in 2,2'-polyethylene glycol substituted trehalose derivatives.*

The anomeric effect is the most important factor influencing the conformation of carbohydrates around the glycosidic linkages[1]. During the synthesis of chiral crown ethers incorporating α,α-trehalose we have observed an interesting conformational change in the disaccharide moiety depending on the position of the polyethylene glycol linkage. While mono-*trehalo*-crowns with tetraethylene glycol linkage between positions 3 and 3' show the expected geometry around the glycosidic linkage (fig.1, Isomer A, Φ,Φ' 70°), a mono-*trehalo*-18-crown-6 **2** with the linkage between positions 2 and 2' shows, on the basis of NMR data[2], a structure which is not the expected in accordance with the anomeric effect (fig. 1, Isomer B, $\Phi,\Phi' \geq 100°$). This conformational change strongly contrasts with the usual lack of flexibility observed in the conformation around the glycosidic linkage of the trehalose disaccharide in solution[3].

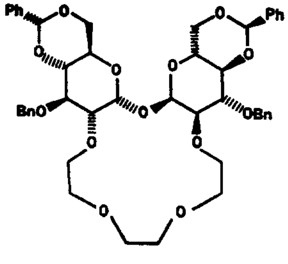


Isomer A ($\Phi,\Phi' \simeq 70°$) Isomer B ($\Phi,\Phi' \gg 100°$)

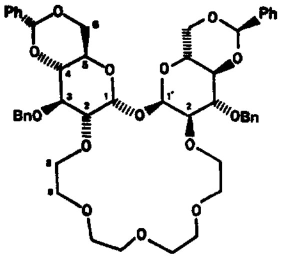
Fig. 1. Schematic representation of isomers A and B for macrocycles 1, 2, and 3.

In an attempt to establish the generality of this phenomenum when the polyethylene glycol chain is linked to positions 2,2' of trehalose, we now have synthesised the mono-*trehalo*-2,2' crowns **1** and **3** with variable lenght of the polyethylene glycol chain as well as the mono- and disubstituted derivatives **4** and **5**[4]. In this communication we report on the crystal structure of the mono-*trehalo*-2,2'-15-crown-5 **1** and on some n.m.r. spectroscopic studies of **1**,**3** and the acyclic derivatives **4** and **5** in solution, which confirm the previous results obtained for the crown ether **2**. The results indicate that there exists a tendency in these 2,2' substituted trehalose derivatives to adopt a different conformation around the glycosidic bond. Semiempirical calculations (PM3) for α,α-trehalose and its 2-*O*-ethylene glycol **10** and 2-*O*-ethyl **11** derivatives support these results.

The mono-*trehalo*-2,2'-15-crown-5 **1** was prepared in 55% yield by condensation of the diol precursor **6**[5] with triethylene glycol ditosylate in the presence of KOH as previously described by us for the mono-*trehalo*-2,2'-18-crown-6 **2**[2]. The mono-*trehalo*-2,2'-21-crown-7 (**3**) was synthesised, in a similar way, by condensation of the disubstituted derivative **5** with ethylene glycol. Crystallization by slow diffusion of hexane into an ethyl acetate solution of **1** resulted in the formation of crystals suitable for X-ray analysis[6]. A Pluto view[7] of the solid state conformation of **1** is shown in Figure 2. The molecule presents a pseudobinary axis. The geometrical parameters around the glycosidic linkage are given in Table I. The most striking features of this structure are the unprecedented values of the torsion angles Φ and Φ' (150° and 123°) around the glycosidic linkage. These values are different from those previously found for the mono-*trehalo*-3,3'-tetraethylene glycol **8** (Φ,Φ' 76°,70°, Table I)[2] and those for trehalose and trehalose derivatives[8]. Furthermore, the mean distance H1-H5' in **1** is 4.7Å, which is a much larger value than that found in the crystal structure of **8** (2.8 Å). The bond lengths C5-O5 and C1-O1 of **1** (Table I) are similar in value, and shorter than those found in normal C-O bonds, in accordance with the anomeric effect[1]. However, O5-C1 bonds are definitively shorter than the C1-O1 bonds, in contrast with the observed values for axial glycosides[9] indicating that the *exo*-anomeric effect does not dominate. The crystal structure of **1** is probably the first case of a disaccharidic structure where the *exo*-anomeric effect does not dominate



1



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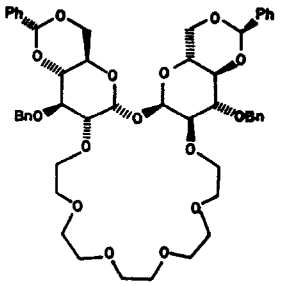

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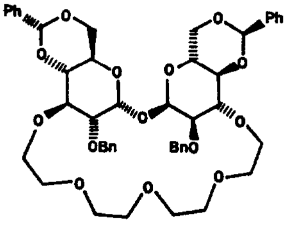

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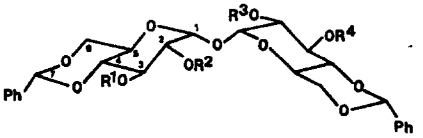


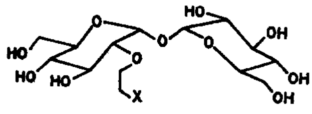
4: $R^1 = R^4 = Bn$, $R^2 = CH_2CH_2OH$, $R^3 = H$

5: $R^1 = R^4 = Bn$, $R^2 = R^3 = (CH_2CH_2O)_2Ts$

6: $R^1 = R^4 = Bn$, $R^2 = R^3 = H$

7: $R^1 = R^4 = H$, $R^2 = R^3 = Bn$

9: $R^1 = R^4 = Bn$, $R^2 = (CH_2CH_2O)_4Ts$, $R^3 = H$



10: X = OH

11: X = H

(the relative orientation of C-1 and O-5 of the opposite ring is not *gauche*) and presents a similar geometry to that the previously proposed[2] for the mono-*trehalo*-2,2'-18-crown-6 (**2**) in solution on the basis of NMR data and molecular mechanics calculations (fig.1, Isomer **B**). The origin of this conformational preference is not yet well understood but it seems to be a general tendency in 2,2'-polyethylene glycol substituted trehalose derivatives. Thus, monoalkylation of α,α-trehalose in position 2, or dialkylation in positions 2 and 2', to give **4** and **5** respectively, causes a conformational change similar to that observed in macrocycles **1**-**3**, as inferred from NOe experiments and semiempirical calculations.

Table II gives the ratio of NOe values[10] between H1-H5' and H1-H2 taken as reference. The calculated distance (Å) between H1 and H5' for macrocycles **1-3** and for the acyclic derivatives **4-7** are also given. Table III gives the chemical shift values for the anomeric protons and anomeric carbons of **1-8** in $CDCl_3$. The smaller NOe ratios involving H1 and H5' of macrocycles **1-3** and compounds **4** and **5** as compared with those of their diol precursor **6** and the 2,2'-di-*O*-benzyl derivative **7** indicate a different conformation in the former compounds. The calculated[11] mean distances H1-H5' from the NOe values are larger (>3Å) for **1-5** than those for **6** and **7** (<3Å). Furthermore, the existence of a NOe between H1 and the protons of the polyethylene glycol chain in compounds **2-5** supports the proximity between H1 and the ethylene glycol protons. Semiempirical calculations for α,α'-trehalose and the 2-*O*-ethylene glycol (**10**) and the 2-*O*-ethyl- (**11**) derivatives were performed at the PM3 level[12] using the MOPAC program[13]. The protocol consisted in fully geometry optimization in internal coordinates with no symmetry constraints for each conformer starting from the coordinates obtained by force field calculations (Φ = Φ' ≈ 70° for isomer A and Φ 147°, Φ'67° for isomer B).

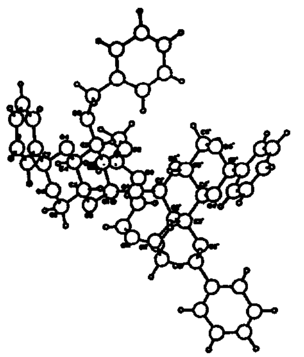


Fig. 2. Molecular structure of 1 in the crystalline phase.

For α,α'-trehalose two minima were obtained with similar interglycosidic angles (Φ,Φ' 88°, 90° and Φ,Φ' 82°,76°). When the position 2 of the α,α'-trehalose was substituted with an ethylene glycol moiety (compound **10**) two different minima were found, the coordinates provided by PM3 for α,α'-trehalose, corresponding to conformers A and B (fig.1). Conformer B showed a geometry with interglycosidic angles (Φ 86.4°, Φ'152.9°, Table I)[14] different from those expected according to the *exo*-anomeric effect and with the ethylene glycol chain in a similar conformation to that found for the crown ether **1** in the solid state

Table I. Selected Geometrical Parameters (°,Å) of the Crystal Structure of 1 and 8[a] and of the Calculated Minima for Compounds 10 and 11[b].

	Crystal Structure		PM3				
	1	8[a]	10		11		
			A	B	A	A'	B
Angles							
O5-C1-O1-C1' (Φ)	123.9(4)	76.3	83.0	86.4	82.2	69.0	87.0
O5'-C1'-O1-C1 (Φ)	150.4(3)	70.7	73.7	152.9	73.7	70.4	152.8
C1-C2-O2-C8	120.2(4)	-	135.6	136.6	132.4	105.4	138.0
C2-O2-C8-C9	-81.6(6)	-	-179.8	-81.2	-177.5	-78.5	-76.5
O2-C8-C9-O9	-36.3(12)	-	-75.0	-70.0	-	-	-
Bond lengths (Å).							
C5-O5	1.427(6)	1.439	1.432	1.435	1.432	1.432	1.435
C5'-O5'	1.418(6)	1.431	1.428	1.431	1.428	1.428	1.431
O5-C1	1.409(6)	1.414	1.404	1.415	1.404	1.404	1.416
O5'-C1'	1.409(6)	1.404	1.401	1.395	1.401	1.401	1.396
C1-O1	1.425(5)	1.415	1.413	1.405	1.413	1.413	1.405
C1'-O1	1.420(5)	1.419	1.417	1.414	1.417	1.417	1.414
-ΔHf			514.4	516.8	474.8	476.5	476.5
μ			2.55	4.09	2.00	1.69	3.47

[a] From reference 2.

[b] Calculated heats of formation (Hf kcal/mol) and dipole moments (μ, debye) are also given.

(Table I, fig.2). The calculated energy for this conformer was 2.4 kcal/mol lower than that for the corresponding A isomer (Φ 83.0°, Φ' 73.7°). This remarkable agreement between the calculated and X-ray conformation seems to indicate that PM3 is a reliable calculation method for this type of molecules.

The calculations for the 2-*O*-ethyl derivative **11** gave two minima with the same energy. One corresponding to isomer B (Φ,Φ' 87.0°, 152.8°), the other one corresponding to a new conformer A' (Φ,Φ' 70.4°, 69.0°) with interglycosidic angles similar to conformer A, but with the ethyl chain in the same conformation that conformer B. A third minimum corresponding to conformer A(Φ,Φ' 82.2°, 73.7°) had an energy 1.7 kcal/mol higher than isomers A' and B (Table I). This result indicates that the tendency of the 2-*O*-substituted trehalose to adopt an unusual conformation is mainly steric in origin. The molecule has two ways to alleviate the steric strain: a) changing the conformation around the glycosidic linkage from Φ,Φ' 70° to Φ,Φ' 100°; b) placing the substituent in position 2 far away from the opposite glucose moiety. According to the calculations these effects are more pronounced when the substituent is an ethylene glycol chain (ca. 0.7 kcal/mol) due to the additional strain originated by the *gauche* effect.

Table II. NOe Ratio Values and Calculated Distances (Å) between H1 and H5' of Macrocycles 1, 2 and 3 and Acyclic Precursors 4-7.

	1	2	3	4	5	6	7
$\frac{\text{NOE H1 H5'}}{\text{NOE H1 H2}}$	0.17	0.21	0.27	0.23	0.29	0.38	0.50
d (H1-H5')[a]	≈3.4[b]	≈3.2	≈3.1	≈3.2[c]	≈3.0	≈2.8	≈2.5
$\frac{\text{NOE H1 Hetgl}}{\text{NOE H1 H2}}$	-	0.4	0.24	0.38	0.11	-	-
$\frac{\text{NOE H1 Hetgl}}{\text{NOE H1 H2}}$	-	-	0.32	-	-	-	-

[a] Calculated from NOe values after reference 11. Error ± 10%.
[b] In crystal 4.76 Å. This NOE distance corresponds to the intraresidue H1-H5 pair.
[c] Calculated by PM3 4.6Å.

Table III. Chemical Shift Values (δ) of the Anomeric Protons and Anomeric Carbons of Macrocycles 1-3 and Precursors 4-7 in $CDCl_3$.

Compounds	H1	H1'	C1	C1'
1	5.63		97.9	
2[a]	6.05		100	
3	5.58		97.6	
4	5.21	5.18	95.9	94.5
5	5.20		94.5	
6[b]	5.20		95.2	
7[b]	5.11		93.5	
8[a]	5.11		94.2	

[a] From reference 2.
[b] From reference 5.

Conformers **A** and **B** can be considered as not interconvertible atropoisomers and all attempts to obtain macrocycle **2** in conformation **A** by a stepwise synthetic strategy were unsuccessful. Thus, intracyclization of the 2-*O*-tetraethylene glycol derivative **9**[4] in THF at 70°C in the presence of KOH resulted in the formation of the mono-*trehalo*-18-crown-6 (**2**) (isomer B) in four hours and almost quantitative yield. Similarly, condensation of the 2-*O*-ethylene glycol derivative **4** with triethylene glycol ditosylate gave after 15 h. compound **2** in 40% yield. Atropoisomer **A** was never detected.

The presence of potassium can probably help to maintain the preferred conformation of the polyethylene glycol chain favouring the cyclization reaction to give isomer **B**. Nevertheless, the potassium ions are not decisive to induce the observed conformational change. Thus, cyclization of diol **6** with tetraethylene glycol ditosylate in the presence of KOH yielded compound **2** in 80%[2]. However, the same reaction in the presence of tetrabutyl-ammonium hydroxyde gave **2** in only 12% yield, the mono-alkylated derivative **9** being also obtained in 20% yield. No traces of other cyclization products were detected. In conclusion, the results obtained indicate that 2-*O*-substitution of α,α-trehalose induces a conformational change around the glycosidic bond and causes the molecule to adopt a geometry different from that predicted by the *exo*-anomeric effect. This fact seems to be mainly steric in origin[15] and is specially pronounced in the case of ethylene glycol due to the *gauche* effect which restricts the conformational mobility of the chain. Although we do not think that the stereoelectronic effects simply disappear, in some cases they can be overwhelmed by the steric effects. A compromise between the two effects will define the conformational equilibrium of the disaccharides in solution. Thus, the conformation for the 2,2'-di-*O*-benzyl derivative **7** in solution seems to be, as deduced from the NOe's data, the one expected according to the *exo*-anomeric effect.

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Supplementary Material Available. Tables of atomic coordinates, isotropic thermal parameters for compound **1** (3 pages); observed and calculated structure factors (18 pages). ^{1}H-NMR and MS-FAB spectra of compounds **1**, **2** and **3**.

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reflections, Philips PW1100 diffractometer with Θ 65°. Direct methods. Refinement on F_0 with three blocks matrix and anisotropic thermal factors for the non-H atoms while the hydrogen ones were kept isotropic. R factor=0.051 for the 3296 observed reflections (I 3ϕ(I)).- Lists of atomic parameters and structure factors are available, on request, from the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Request should be accompanied by the full citation for this communication.

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