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Two Interconverting Glycophanes from Maltose

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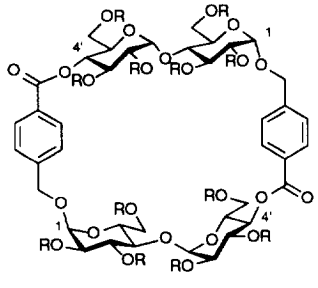
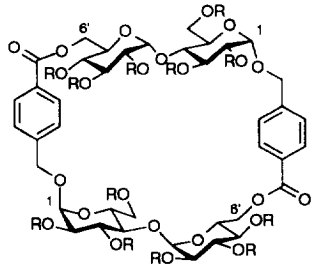
Abstract: *Two new glycophanes, **1** and **3**, that interconvert through transesterification in water at room temperature are presented. The synthesis, properties of interconvertion and preliminary binding and conformational studies of these macrocycles are also described.* Copyright © 1996 Elsevier Science Ltd

Preorganisation is essential in the design of artificial receptors. However, flexibility and reorganisation can often be as important as preorganisation to achieve complementarity for molecular recognition and catalysis. In biological receptors reorganisation is associated to conformational changes that can "turn on" or "turn off" an enzyme.[1] Recently, we have synthesised a new type of cyclodextrin-cyclophane hybrid receptors (glycophanes), which are endowed with the properties of both cyclodextrins (chirality, neutrality, lipophilic cavity and water solubility) and cyclophanes (additional aromatic interactions), to study the intermolecular forces involved in carbohydrate recognition.[2] These receptors have allowed us to study the binding of aminoacid and carbohydrates derivatives in aqueous media and to show the existence of lipophilic interactions between carbohydrates in water.[3]

We present here two new interconverting glycophanes **1** and **3**, made up of maltose, the constituent disaccharide in cyclodextrins, and (4-hydroxymethyl)benzoic acid as the aromatic segment, that rearrange into each other by transacylation in water at room temperature.



1, R=H
2, R=PMB

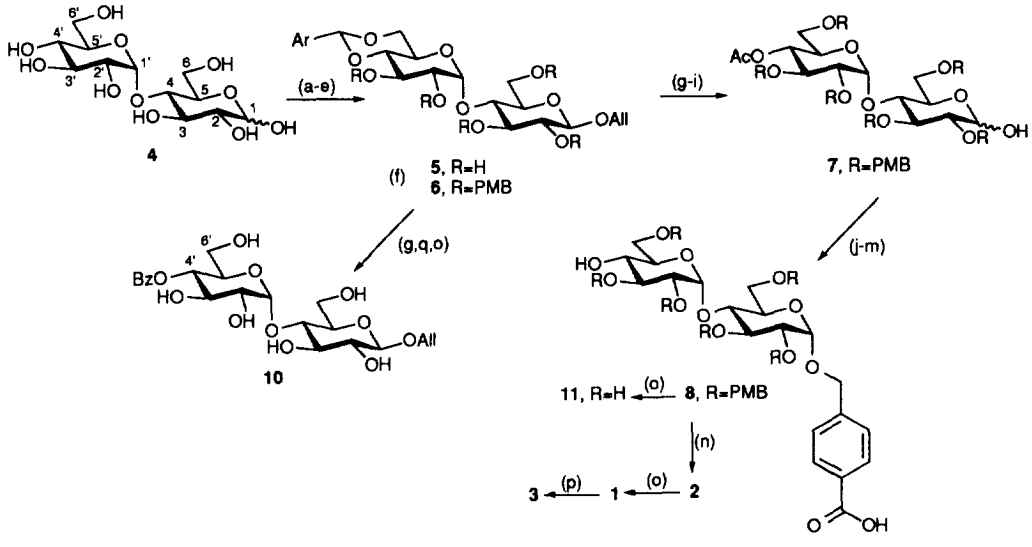


3, R=H

For the synthesis of glycophane **1** (Scheme 1), maltose **4** was selectively protected with an allyl group at the anomeric center, a *p*-methoxybenzylidene group at 4' and 6' positions and the rest of hydroxyl groups with *p*-methoxybenzyl (PMB) groups to give the intermediate **6**. This compound was transformed by reductive opening of the acetal, acetylation and deallylation into alcohol **7**. Hydroxy alcohol **8** was obtained by glycosidation of **7** with 4-(hydroxymethyl)methyl benzoate using the 'trichloroacetimidate' methodology[4], and subsequent deacetylation and hydrolysis of the ester. Cyclodimerization of **8** with DCC, DMAP, DMAP·HCl in

refluxing chloroform[5] gave the protected glycophane **2** in 28% yield (FAB-MS: m/z=2419.6 [M+guanidinium]$^+$, the matrix was doped with guanidinium ion). [6] Deprotection of **2** with trifluoroacetic acid yielded the water soluble glycophane **1** (90%).

Scheme 1



Reagents and conditions: (a) AcONa, Ac_2O, 68%; (b) HBr, AcOH, 92%; (c) AllOH, $Hg(AcO)_2$, 71%; (d) MeONa 1M, MeOH, 99%; (e) anisaldehyde dimethyl acetal, *p*-TsOH, DMF, 67%; (f) NaH, PMBCl, DMF, 89%; (g) $NaCNBH_3$, CF_3COOH, DMF, 74%; (h)Ac_2O, Pyridine, 89%; (i) $RhCl(PPh_3)_3$, $EtOH/H_2O$ (9:1) / HgO, $HgCl_2$, 75%; (j) CCl_3CN, K_2CO_3, 86%; (k) methyl 4-hydroxymethylbenzoate, TMSOTf, CH_2Cl_2, 80%, ratio α/β (2:1); (l) MeONa 1M, CH_2Cl_2/MeOH (1:1), 97%; (m) KOH aq. 6M, THF, MeOH, 99%; (n) DCC, DMAP, DMAP·HCl, $CHCl_3$, Δ, 28%; (o) CF_3COOH 5%, CH_2Cl_2, 85-90%; (p) aqueous solution; (q) BzCl, Pyridine, DMAP, 76%; Ar=*p*-methoxyphenyl; PMB=*p*-methoxybenzyl.

Compound **1** reorganised into a new isomeric glycophane **3** in aqueous solution by double transesterification from 4' to 6' positions. The structure of glycophanes **1** and **3** were elucidated using NMR spectroscopy. Assignment of the H4', H6' and H6b' in both compounds was unequivocal by homo-decoupling ^{1}H-NMR and by HMQC experiments. [7] HPLC monitoring of this reaction in a reverse phase column showed the existence of only one another important compound (**9**), probably the asymmetric glycophane that results from only one transposition from position 4' to 6'. The double transesterification is not complete and arrives to an equilibrium between the three species (**3** ≈90%; **1** ≈4%; **9** ≈4%).[8] A pure sample of compound **3** was isolated by HPLC and after 3-4 days at 25°C the previous equilibrium was reestablished. Transacylations in carbohydrates, catalysed by acid or basic conditions, was described a long time ago.[9] For glycophane **1**, traces of acid coming from the deprotection step were avoided with removal of trifluoroacetic acid under high vacuum and purifying the sample using reverse phase column chromatography. The 4'-O-benzoylated model compound

10 (see Scheme 1) was also synthesised to study the transacylation under the same conditions as those for compound **1**. In this case transesterification to 6' was much slower and only approx. 20% of transacylated compound was detected by HPLC after six days at room temperature. The spontaneous transacylation of **1** is not observed in DMSO, and is much slower in methanol and in a micellar aqueous solution of sodium dodecyl sulfate (conc. 0.02 M)[10], indicating that water is important for the interconversion. However, conformational changes in the glycophane due to the solvent may also influence the transacylation rate. The different behaviour of **1** and **10** in water may be due to the rigidity imposed by the macrocycle on the ester funcionality, which allows attainment of a more favourable geometry for reaction with the adjacent hydroxymethyl group than in the model compound **10**. A release of strain on going from **1** to **3** might also provide a driving force, but no significant strain is present in **1** according to CPK models.

Glycophanes **1** and **3** seems to have different conformations in solution. Differences in chemical shift ($\Delta\delta$) of the proton signals in the NMR spectra of glycophanes **1**, **3** and the model compound **11** can give some information about their conformations. Whereas H1, H2 and H4 for compound **1** have similar chemical shifts as those in **11** (H1, $\Delta\delta$=-0.04; H2, $\Delta\delta$=-0.02; H4, $\Delta\delta$=0.05)[11], these protons in glycophane **3** are considerable shielded (H1, $\Delta\delta$=0.37; H2, $\Delta\delta$=0.40; H4, $\Delta\delta$=0.22). This could indicate a close proximity of the aromatic rings to the β face of one glucose unit in the case of glycophane **3**, thus favouring self-saccharide/aromatic interactions. This proximity could possibly be due to the great flexibility of **3** (four methylene groups take part in the cycle). Furthermore, the orientation of the hydroxymethyl groups linked to the aromatic ring clearly adopts a *gauche-trans* (*gt*) conformation as deduced from the coupling constants between 5', 6' and 6'b for compound **3** in D_2O,[12] in contrast with the *gg-gt* equilibrium always found for this group in glucose configuration.[13] Preliminary molecular mechanics calculations by a Monte Carlo approach using the MACROMODEL v4.5 package[14] gave for glycophane **1** conformational minima with a shape and cavity similar to those of cyclodextrins. However, the calculations for **3** show conformational minima where H1, H2 and H4 are 3 to 4 Å away from the aromatic ring. These conformations, rather different from those of **1** and cyclodextrins, imply a strong change in the interglycosidic torsional angles, and is 22 $kJ \cdot mol^{-1}$ more stable than those obtained with similar geometry to those of **1** and cyclodextrins.

Glycophanes **1** and **3** form complexes in water with different aromatic guests as observed by ^{1}H-NMR spectroscopy. Different chemical induced shifts patterns of the compounds **1** and **3** appeared upon addition of the guests. Upfield shifts for aromatic protons, H3', H5' and H6', and downfield shifts for H3 were observed in the case of **1**, indicating a geometry of the complex similar to that found in cyclodextrins.[15] In contrast, upfield shifts for protons H1', H4', H6', H6'b and aromatics, and downfield shifts for H1, H2, H4, H6 and H6b were observed for glycophane **3**. This probably indicates that glycophanes **1** and **3** have different conformations in solution and therefore different geometries for the complexes are observed. The binding constants (K) were determined by ^{1}H-NMR titration. Small K values were found for all guests, compared with those usually found for cyclodextrins.[15] Some examples are, for electron-deficient aromatic guests: 1-(*p*-nitrophenyl) glycerol (with **1**, 28 M^{-1}; with **3**, 9 M^{-1}), picric acid (with **1**, 50 M^{-1}; with **3**, 100 M^{-1}) and for electron-rich aromatic guests: benzyl β-D-glucopyranoside (with **1**, 13 M^{-1}; with **3**, 6 M^{-1}), 1,3,5-trihydroxybenzene (with **1**, 25 M^{-1}; with **3**, 5 M^{-1}). Additionally, the interaction of different guests with glycophane **1** influences the transacylation to glycophane **3**. Whereas the presence of paraquat, 1-(*p*-nitrophenyl) glycerol and *p*-nitrophenyl α-D-mannopyranoside do not change the rate of transacylation other

guests such as picric acid, 2,4-dinitrophenol, 2,6-naphthalene dicarboxylic acid, dichlorodicyanoquinone and 1,3,5-trihydroxybenzene decrease the rate considerably and afford a different equilibrium between **1**, **3** and **9**. Additional work is in progress for a better understanding of this phenomena.

In summary, the reorganisation of glycophane **1** into the more stable glycophane **3** seems to be favoured by self-sugar/aromatic interactions and can, to some extent, be controlled either by the solvent or by interaction with aromatic guests.

Acknowledgement

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6. Significant spectroscopical data of **2**: ^{1}H-NMR ($CDCl_3$): δ 8.02 (d, 2H), 7.49 (d, 2H), 7.34-6.56 (m, 48H), 5.18 (t, 2H, J=10.26 Hz, H4'), 5.00 (d, 2H, J=3.32 Hz, H1'), 4.82 (d, 2H, J=3.66 Hz, H1); ^{13}C-NMR ($CDCl_3$): δ 164.84, 99.14, 96.84; Anal. Calcd for $C_{136}H_{148}O_{36}$: C, 69.25; H, 6.32. Found: C, 68.98; H, 6.21.
7. Significant spectroscopical data of **1**: ^{1}H-NMR (500 MHz, D_2O, 30°C): δ 8.11 (d, 4H), 7.61 (d, 4H), 5.24 (d, 2H, H1', J=3.66 Hz), 5.13 (d, 2H, H1, J=3.30 Hz), 5.11 (t, 2H, H4', J=9.89 Hz), 4.86-4.77 (AB system, 4H, CH_2), 4.15-3.55 (m, 22H); ^{13}C-NMR (CD_3OD): δ 167.17, 103.94, 100.30; HRFABMS : m/z 939.2754 [M+Na$^+$] (calcd. for $C_{40}H_{52}O_{24}Na$, m/z 939.2746).
   Significant spectroscopical data of **3**: ^{1}H-NMR (500 MHz, D_2O, 30°C): δ 8.02 (d, 4H), 7.48 (d, 4H), 5.43 (d, Hz), 4.92 (m, 2H, H6', J=-11.8 Hz, J<1 Hz), 4.71 (s, 4H, CH_2), 4.30 (m, 2H, H6b', J=-11.8 Hz, J=10.2 Hz), 3.96-3.55 (m, 14H), 3.45 (t, 2H, H4, J=9.3 Hz), 3.38 (t, 2H, H4', J=9.2 Hz), 3.20 (dd, 2H, H2, J=3.4 Hz, J=10.2 Hz); ^{13}C-NMR (D_2O): 170.29, 101.88, 99.82; HRFABMS : m/z 939.2778 [M+Na$^+$] (calcd. for $C_{40}H_{52}O_{24}Na$, m/z 939.2746).
8. Achievement of the equilibrium takes 5-6 days at T=25°C, 2 days at T=37°C and aprox. 28h at T=50°C. Only 2-4% of other products were detected.
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10. Glycophane **1** must be partially included in the micelle. Broadening of the methylene groups is significant and upfield shifts of aromatic and some sugar signals are also observed in the ^{1}H-NMR spectrum.
11. δ values are given in ppm. Δδ=δ(**11**)-δ(**1** or **3**).
12. Coupling constants measured for compound **3** (in Hz) : $J_{5'6'}$=<1, $J_{5'6'b}$=10.2, $J_{6'6'b}$=-11.812
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