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Synthesis and Use of Some *p*-Substituted 6-*O*-Phenyl Ethers of Glucose as Water Soluble 'Molecular Tweezers'

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Abstract. Refluxing 4,4′-isopropylidenediphenol (**1**) and 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**) with potassium carbonate in dry acetonitrile afforded molecular tweezers (**3**) and (**4**) which, on deprotection with aqueous acetic acid, yielded water soluble tweezers (**5**) and (**6**). These water soluble tweezers were explored for the solubilization of neutral arenes, viz. naphthalene, biphenyl, durene, fluorene, anthracene and phenanthrene in aqueous medium. These solid liquid extraction studies revealed that 6,6′-*O*-(4″,4‴-isopropylidenediphenyl)bis[α-D-glucopyranose] (**5**) causes an approximate 17-fold increase in the solubility of naphthalene in aqueous medium.

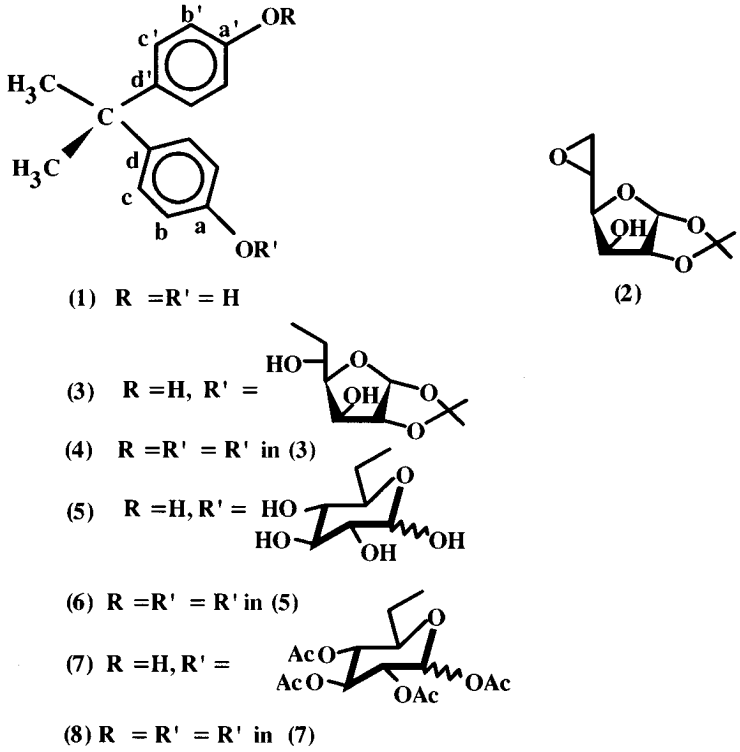
Key words: glucose ethers, aqueous medium, arenes, tweezers.

1. Introduction

The phenomenon of complex formation by organic molecules having an appropriate cavity to bind substrates was termed 'Host–Guest Complexation' by D.J. Cram [1]. The formation of such a host–guest complex is analogous to the enzyme–substrate complex in biological processes. In recent years the term 'receptor' has come to be used synonomously with 'host' [2]. The non-macrocyclic hosts which contain preorganised aromatic clefts are called 'molecular tweezers' [3].

Recently the synthesis and design of a variety of types of molecular tweezers has been reported [4–8], most of which are soluble only in organic solvents. Water soluble molecular tweezers might be expected to complex a wide range of aromatic guests with the binding affinities dependent more on the extent of overlap between the host and guest than on their electronic complementarity [9].

This paper describes the synthesis of new 6-phenol ethers of glucose and their use for the solubilization of neutral arenes in aqueous medium. This is the first example of using carbohydrate derivatives as water soluble 'molecular tweezers'. Studies for exploring these types of carbohydrate derivatives as reverse phase transfer catalysts are in progress.



Formula 1 .

2. Experimental

2.1. General spectral studies

Melting points were determined in capillaries and are uncorrected. ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker FT NMR 200 Spectrometer and at 60 MHz on a JEOL JNM PMX 60 SI spectrometer and ^{13}C-NMR spectra at 200 MHz on a Bruker FT NMR 200 Spectrometer. TMS was used as internal reference for solutions in deuteriochloroform and J values are given in Hz. UV spectra were recorded with a Shimadzu UV-160 UV-VIS spectrophotometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1 dm cell. NMR spectra and rotations were recorded at the Department of Chemistry, GND University, Amritsar and mass spectra at CDRI, Lucknow. Column chromatography was performed on silica gel (60–120 mesh) and TLC plates were coated with silica G. The spots were developed in iodine and/or charring with 1% sulfuric acid in water. n-Hexane and doubly distilled water was used for spectroscopy. Other samples were used as obtained.

2.2. SOLUBILIZATION OF NEUTRAL ARENES IN AQUEOUS MEDIUM

The aqueous solution of tweezer **5** or **6** (10 mL, 5 mM) was shaken with arene (20 mg) for 20 minutes and filtered. The filtrate was extracted with n-hexane (2×25 mL) and the arene concentration determined by electronic absorption spectroscopy. Solubilities thus obtained were corrected for the solubility of the tweezer in hexane (tweezers **5** and **6** were insoluble in n-hexane) and the stoichiometry of the tweezer–arene complex assigned. Similarly, the solubilities of arenes in aqueous medium without tweezer were found in the same way.

2.3. PREPARATION OF 5,6-ANHYDRO-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE (**2**)

The compound was synthesised by the method of Ohle and Vargha [11], mp 133 °C, $[\alpha]_D^{27}$-26.5°. *Anal. calcd.* for $C_9H_{14}O_5$: C, 53.46; H, 6.98. *Found*: C, 53.20; H, 6.83.

2.4. PREPARATION OF 6-*O*-[4(4′-ISOPROPYLIDENEPHENOL)PHENYL]-1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE (**3**) AND 6,6′-*O*-(4″,4‴-ISOPROPYLIDENEDIPHENYL)BIS[1,2-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE] (**4**)

A mixture of **2** (404 mg, 20 mM), 4-4′-isopropylidenediphenol (228 mg,10 mM) and anhydrous potassium carbonate (500 mg) was refluxed in dry acetonitrile (40 mL) for 20 h. The solvent was evaporated and residual mass dissolved in water (20 mL), extracted with dichloromethane (2×50 mL) and washed with water (2×10 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography on silica gel [dichloromethane–ethyl acetate (1 : 1)] afforded first substrate **3** (232 mg, 27%) as syrup. $[\alpha]_D^{27} - 11.4$ (c 1.5, EtOH); UV (EtOH) λ_{max} (log ε) 277.4 (3.51); 228.2 (4.17); ^{1}H-NMR (200 MHz) δ 1.31 and 1.48 (each 1s, 3H, CH_3-a); 1.61 (s, 6H, CH_3-b); 4.05 (dd,1H, J 5.8, 5.8 H-6_b); 4.22 (m, 4H, H-6_a, OH and H-4); 4.35 (br, 1H, H-5); 4.43 (s, 1H, H-3); 4.55 (d, 1H, J 3.4, H-2); 5.97 (d, 1H, J 3.4, H-1); 6.69–6.82 (dd, 4H, J 8.8, 8.6, Ar H); 7.03–7.14 (dd, 4H, J 8.8, 8.6, Ar H); ^{13}C-NMR (200 MHz) δ 26.1 and 26.7 (CH_3-a); 31.0 (CH_3-b); 41.6 ($C_{quart.}$); 68.9 (C-5); 69.2 (C-6); 75.5 (C-3); 79.5 (C-4); 85.0 (C-2); 104.8 (C-1); 111.7 (Me_2C of $-1,2$); 114.1 and 114.7 (Ar $C_{b,b'}$); 127.7 (Ar $C_{c,c'}$); 142.8 and 143.9 (Ar $C_{d',d}$); 153.3 and 55.9 (Ar $C_{a',a}$); (M^+) ion *m/z* 415 ($M^+ - 15$).

The second fraction with ethyl acetate as eluent afforded **4** (645 mg, 51%); mp 60–62 °C (foam); $[\alpha]_D^{27} - 4.9°$ (c, 2.0, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 284 (3.46), 277 (3.52), 228.4 (4.29), ^{1}H-NMR (200 MHz) δ 1.29 and 1.49 (s, 6H, CH_3-a); 1.61 (s, 6H, CH_3-b); 4.05 (dd, 2H, J 5.8, 6.0 H-6_b); 4.20 (m, 8H, OH and H-6_a); 4.35 (br, 2H, H-5); 4.41 (s, 2H, H-3); 4.56 (d, 2H, J 3.4, H-2); 5.96 (d, 2H, J 3.5, H-1); 6.80 and 7.10 (each 4H, AB q, J 8.2, Ar H); ^{13}C-NMR (200 MHz) δ 26.1 and

26.7 (CH_3-a); 31.0 (CH_3-b); 41.7 (C_{quart}); 68.8 (C-5); 69.3 (C-6); 75.4 (C-3); 79.5 (C-4); 85.0 (C-2); 104.9 (C-1); 111.7 (Me_2C of −1,2); 114.5 (Ar C_b); 127.7 (Ar C_c); 143.7 (Ar C_d); 156.1 (Ar C_a); (M^+) ion 632 *m/z* (M^+); 617 ($M^+ - 15$).

2.5. Removal of isopropylidene moiety from **3** and **4**

A solution of the respective tweezer (500 mg) in aqueous 80% acetic acid (10 mL) was refluxed for 1 h and concentrated. The residue (**5** or **6**) showed a homogeneous spot on TLC and was characterized via its acetylated derivative.

2.6. Preparation of 6-*O*-[4(4′-isopropylidenephenyl acetate)phenyl]-1,2,3,4-tetra-*O*-acetyl-D-glucopyranose (**7**)

A solution of **5** (1.0 g) in aqueous 80% acetic acid (20 mL) was refluxed for 1 h and concentrated. The solution of the residue in acetic anhydride (1.0 mL) and pyridine (5.0 mL) was aged for 1 h at room temperature and poured into ice water. Purification of the product by column chromatography on silica gel (dichloromethane-ethyl acetate (4 : 1)] afforded **7** (1.12 g, 80%) as an anomeric mixture [α/β = 37.5/62.5]. mp 70–75 °C; $[\alpha]_D^{27} - 47.0$ (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz) δ 1.62 (s, 6H, gem dimethyl); 1.99–2.15 (m, 15H, $OCOCH_3$); 3.97–4.13 (br, H-6 and H-5); 5.14–5.31 (m, 3H, H-2 and H-4); 5.77 (d, H-1_β); 6.36 (d, H-1_α); 6.77 (d, 2H, *J* 8.4, Ar H); 6.95 (d, 2H, *J* 8.6, Ar H); 7.11 (d, 2H, *J* 8.4, Ar H); 7.19 (d, 2H, *J* 8.6, Ar H); ^{13}C-NMR (200 MHz) δ 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 21.0 (ester CH_3); 30.8 (CH_3); 41.9 ($C_{quart.}$); 66.4 (C-6_α); 66.6 (C-6_β); 68.6 (C-4_β); 68.7 (C-4_α); 69.1 (C-2_α); 69.5 (C-3_α and C5_α); 70.2 (C-2_β); 72.7 (C-3_β and C-5_β); 88.9 (C-1_α); 91.5 (C-1_β); 114.0, 120.7, 127.6, 128.2, 143.1, 148.1, 148.3, 156.1 (Ar C); 168.6, 168.8, 169.1, 169.2, 169.3, 169.5, 170.0, 170.1 (C=O); (M^+) ion *m/z* 602 (M^+).

2.7. Preparation of 6,6′-*O*-[4″,4‴]-isopropylidenediphenyl)bis[1,2,3,4-tetra-*O*-acetyl-D-glucopyranose (**8**)

A solution of **6** (500 mg) in 80% aqueous acetic acid (10 mL) was refluxed for 1 h and concentrated. The solution of the residue in pyridine (5.0 mL) and acetic anhydride (1.0 mL) was aged for 1 h at room temperature and poured into ice water. Purification of the product by column chromatography (dichloromethane–ethyl acetate (4 : 1)] afforded the title-compound (519 mg, 74%) as an anomeric mixture [α/β = 28.5/71.5]. mp 78–80 °C; $[\alpha]_D^{27}$ + 69.3 (c 0.59, $CHCl_3$); ^{1}H-NMR (200 MHz) δ 1.60 (s, 6H, gem dimethyl); 2.0–2.17 (m, 24H, $OCOCH_3$); 3.97–4.16 (br, H-6 and H-5); 5.14–5.31 (m, H-2, H-3 and H-4); 5.77 (d, H-1_β); 6.35 (d, H-1_α); 6.75 and 7.09 (AB q, each 4H, Ar H); ^{13}C-NMR (200 MHz) δ 20.3, 20.4, 20.5, 20.6, 20.7, 20.8 (ester CH_3); 30.8 (CH_3); 41.5 ($C_{quart.}$); 66.4 (C-6_α); 66.6 (C-6_β); 68.6 (C-4_β); 68.7 (C-4_α); 69.8 (C-3_α and C-5_α); 69.1 (C-2_α); 70.2 (C-2_β); 72.7

(C-3_β and C-5_β); 88.9 (C-1_α); 91.5 (C-1_β); 114.0, 127.5, 143.5, 155.9 (Ar C); 168.6, 168.7, 169.0, 169.2, 169.4, 169.9, 170.1 (C=O).

3. Results and Discussion

3.1. SYNTHESIS

4,4′-Isopropylidenediphenol (Bisphenol A) was chosen as the basic skeleton since it is bent and is equipped at the *para* position with glucose moiety/ies to design a 'molecular tweezer'. The glucose moiety contributes to the water solubility of these hosts and the aromatic rings provide a hydrophobic surface which in an aqueous medium would help complex non-polar guest molecules.

The compounds **3** and **4** were deprotected by refluxing in 80% aqueous acetic acid for 1 h to afford water soluble molecular tweezers **5** and **6**, which were used for solubilization of neutral arenes in aqueous medium. The water soluble tweezers were characterized via their acetylated derivatives.

The NMR spectra of compounds **3** and **4** are nearly identical except for the aromatic region. In the ^{1}H-NMR spectra the position of all the sugar protons and the isopropylidene group were found to be constant. The aromatic protons in the former were assigned as a doublet of doublets at δ 6.69–6.82 and 7.03–7.14, respectively, whereas the AB quartet at δ 6.80 and 7.10 was assigned to aromatic signals in the latter. Similarly in the ^{13}C-NMR spectra aromatic carbons in the former were assigned at 114.4, 114.7, 127.0, 142.8, 143.9, 153.3 and 155.9 ppm, respectively, whereas being symmetrically substituted the latter gave aromatic carbons at 114.0, 127.7, 143.7 and 156.1 ppm, respectively.

The removal of the isopropylidene group was confirmed by the disappearance of the same signals in the acetylated derivatives **7** and **8**. These glucopyranose derivatives were found as an anomeric mixture in which the β-protons were assigned occuring upfield relative to their α-analogs. Similarly β-carbons were found occuring downfield compared to α-carbons. These acetylated derivatives gave more complex spectra than **3** and **4**.

In the ^{1}H-NMR spectra of **7** and **8**, ester methyls were assigned at δ 1.99–2.17. The aromatic protons of the former were found at δ 6.77–6.95 and 7.11–7.19 as a doublet of doublets, however being spherically symmetrical the latter showed an AB quartet at δ 6.75 and 7.09. In the ^{13}C-NMR spectra of these tweezers, the carbonyls were found at δ 168–170 and the ester methyl signals at 20.2–21.0, respectively. For aromatic carbons the former gave signals at δ 114.0, 120.7, 127.6, 128.2, 143.1, 148.1, 148.3 and 156.1, whereas in the latter the same ring carbons were assigned at δ 114.0, 127.5, 143.5 and 155.9, respectively.

3.2. SOLUBILIZATION OF ARENES IN AQUEOUS MEDIUM

The results of solid–liquid extraction of neutral arenes in aqueous media in the absence and presence of water soluble molecular tweezers are documented in

Table I. Solubilization of arenes in aqueous medium with tweezer **5**.

Arene	Solubility ratio Solubility in water : In presence of tweezer in water	Stoichiometry of complex* (tweezer : arene)
Naphthalene	1 : 12.0	1 : 0.54
Biphenyl	1 : 6.7	–
Durene	1 : 1.1	–
Fluorene	1 : 2.6	–
Anthracene	1 : 3.0	–
Phenanthrene	1 : 2.4	–

* Only (1 : 0.01) or greater stoichiometric ratio quoted.

Table II. Solubilization of arenes in aqueous medium with tweezer **6**.

Arene	Solubility ratio Solubility in water : In presence of tweezer in water	Stoichiometry of complex* (tweezer : arene)
Naphthalene	1 : 16.9	1 : 0.787
Biphenyl	1 : 9.6	1 : 0.013
Durene	1 : 1.8	1 : 0.030
Fluorene	1 : 2.9	1 : 0.031
Anthracene	1 : 3.4	–
Phenanthrene	1 : 3.1	–

* Only (1 : 0.01) or greater stoichiometric ratio quoted.

Tables I and II. The results clearly prove the importance of the hydrophobic cavity for the host–guest complexation in aqueous medium by reducing the unfavourable contacts between water molecules and apolar guests.

In all these studies the better affinity of **6** compared with **5** suggested that the increase in solubility was due to the increase in the van der Waals interactions. The importance of these interactions has previously been recognised for the inclusion complexes formed by cyclodextrins [10]. Hydrophobic interactions are however the main driving force for complexation of tweezers with arenes.

From Tables I and II, it is found that naphthalene is most suitable for complementarity between host and guest. In fact, for larger arenes the solubility decreases as the size increases. The greater solubility of anthracene than phenanthrene is also due to its more linear shape being better recognised by the hydrophobic cavity.

Unfortunately it was not possible to isolate the arene-tweezer complexes directly. But clearly these studies confirm the use of synthesised 6-O-phenyl ethers of glucose as reverse phase transfer reagents. The emphasis will now be on exploring these and similar tweezers, as phase/reverse phase transfer catalysts for reactions resulting in asymmetric inductions.

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