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Synthesis of per-6-guanidinylated cyclodextrins

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Abstract—Reaction of per(6-amino-6-deoxy-2,3-di-*O*-methyl)-α-, β- and γ-cyclodextrins with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine and triethylamine in tetrahydrofuran gave per[6-*N*,*N*′-bis(*tert*-butoxycarbonyl)guanidino-6-deoxy-2,3-di-*O*-methyl]-α-, β- and γ-cyclodextrins, respectively. Subsequent cleavage of the protective groups with trifluoroacetic acid in dichloromethane afforded per(6-deoxy-6-guanidino-2,3-di-*O*-methyl)-α-, β- and γ-cyclodextrins in very good overall yields.

1. Introduction

The guanidine group plays an important role in many natural products as well as in synthetic pharmaceutical drugs. Its highly basic character renders this functionality protonated in aqueous media over a broad range of pH and, in common with its geometry, confers on it the ability to bind various anionic groups such as sulf(on)ates, phosph(on)ates and carboxylates.[1] Owing to these properties, guanidinium groups frequently serve as anion-binding fragments in designed supramolecular receptors.[1,2]

Recently, we have shown that cyclodextrin macrocycles bearing complementary 'sticking' groups (amino and/or carboxylic functions) can self-assemble into ordered structures in solution[3a] or solid state.[3b,c] Motivated by these results, we have sought alternative basic moieties appended to the cyclodextrin torus, which would remain protonated over a broader range of pH, thus allowing ion-pairing with complementary building blocks bearing oppositely charged functions (such as carboxylates or sulfates). The guanidine moiety appears to meet these criteria very well. Various methods have been developed for the synthesis of guanidine functions, from alkylation of protected guanidines to reactions of activated guanidinylating reagents with free amines.[4] However, the synthesis of compounds having multiple guanidinium groups in close proximity is hampered by their mutual electrostatic repulsion.[5] Thus, adding guanidine groups onto the cyclodextrin torus represents a challenging task. In this work, we report the first successful synthesis of α-, β- and γ-cyclodextrins persubstituted with guanidine groups at the primary rim.

We have employed a recently described strategy[6a] based on the reaction of a primary amino group with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine as the key step, which proved successful in the synthesis of guanidinylated oligosaccharides.[6b] Thus, hexakis(6-amino-6-deoxy-2,3-di-*O*-methyl)-α-cyclodextrin **1a** (Scheme 1) was reacted with 9 M equiv of *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine and triethylamine. The outcome of the reaction depended significantly on the solvent employed. Of the solvents examined (dichloromethane (DCM), tetrahydrofuran (THF) and dimethylformamide (DMF)), the reaction proceeded most efficiently in dry THF at room temperature. Satisfactory conversion was reached in a 48-h period, after which product **2a** was separated from the reaction mixture by chromatography in 89% yield. Attempts to increase the reaction rate by increasing the temperature led to the formation of by-products presumably due to the thermal instability of the *tert*-butoxycarbonyl protective group. In the next step, removal of the protective groups was achieved using trifluoroacetic acid in DCM in 5 h at room temperature. Free base **3a** was isolated in 85% yield by passing the trifluoroacetate salt through an anion exchange resin prepared in OH^- form followed by lyophilization of the eluate. Application of this procedure to the higher homologues **1b** and **1c** gave

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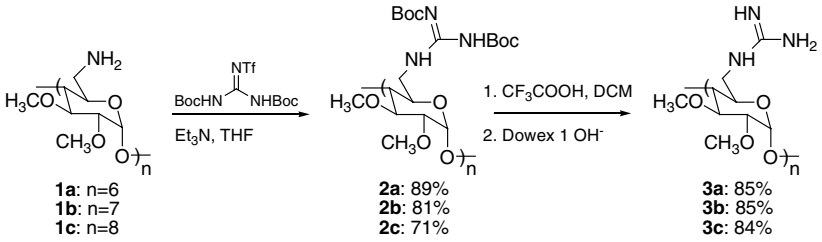

Scheme 1.

the desired guanidines **3b** and **3c**, respectively, in overall yields of 69% and 60%.

The structure of the compounds as well as their chemical homogeneity was proven by MS and homo- and heteronuclear 2D-correlation NMR spectroscopy (2D-PFG-^{1}H,^{1}H-COSY, 2D-PFG-^{1}H,^{13}C-HSQC and 2D-PFG-^{1}H,^{13}C-HMBC). Free bases **3a**, **3b** and **3c** exhibited broadened resonances in the ^{1}H and ^{13}C NMR spectra. However, the addition of DCl to the NMR sample (to pH $\sim$ 6) provided well-resolved spectra allowing full assignment of all the protons and carbons (Tables 1 and 2).

In conclusion, we have developed a method for the preparation of cyclodextrins substituted with guanidine groups at all the C(6) positions in very good overall yields. The propensity of these compounds to self-assemble with complementary per-sulfated and per-carboxylated cyclodextrins into dimeric capsules are currently under study in our laboratory.

2. Experimental part

Starting per(6-deoxy-6-amino-2,3-di-*O*-methyl) cyclodextrins were prepared by reduction[7] of the correspond-

Table 1. ^{1}H NMR (500 MHz) chemical shifts and inter proton coupling constants

Compd	Solvent (temp)	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	Other hydrogens
		J(1,2)	*J*(2,3)	*J*(3,4)	*J*(4,5)	*J*(5,6)	*J*(5,6′)	*J*(6,6′)	
2a	$CDCl_3$ (30 °C)	5.72	3.14	3.60	3.54	3.84	4.33	3.57	2 × OMe: 3.70 s, 3.52 s; 6-NH: 8.33 br;
		d	dd	dd	dd	ddd	br dd	br dd	CO–NH: 11.40 br; 2 × *t*-Bu: 1.48 s, 1.40 s
		3.4	*9.8*	*8.6*	*9.6*	*1.5*	*3.4*	*14.0*	
2b	$CDCl_3$ (30 °C)	5.57	3.16	3.64	3.59	3.94	4.18	3.58	2 × OMe: 3.64 s, 3.50 s; 6-NH: 8.33 br;
		d	dd	dd	dd	ddd	br dd	br dd	CO–NH: 11.42 br; 2 × *t*-Bu: 1.48 s, 1.40 s
		3.4	*9.5*	*8.5*	*9.2*	3.2	*2.2*	*14.0*	
2c	$CDCl_3$ (30 °C)	5.59	3.17	3.64	3.60	3.92	4.10	3.59	2 × OMe: 3.64 s, 3.50 s; 6-NH: 8.36 dd,
		d	dd	dd	t	dt	ddd	dt	*J*(NH,6) = 7.0, *J*(NH,6′) = 2.8;
		3.5	*9.2*	*8.3*	*9.0*	*2.9*	*2.9*	*14.0*	CO–NH: 11.43 br; 2 × *t*-Bu: 1.47 s, 1.42 s
3a	D_2O (30 °C)	5.28	3.36	3.71	3.62	4.04	3.74	3.58	2 × OMe: 3.61 s, 3.50 s
		d	dd	dd	dd	ddd	dd	dd	
		3.4	*10.0*	*8.0*	*9.2*	*2.5*	*6.7*	*15.2*	
3b	D_2O (55 °C)	5.32	3.46	3.76	3.70	4.06	3.65	3.57	2 × OMe: 3.60 s, 3.54 s
		d	dd	dd	t	*m*	dd	dd	
		3.3	*9.1*	*8.2*	*8.6*	*2.8*	*6.6*	*15.0*	
3c	D_2O (80 °C)	5.54	3.50	3.80	3.76	4.03	3.57	3.53	2 × OMe: 3.59 s, 3.58 s
		d	dd	t	t	ddd	dd	dd	
		3.6	*9.6*	*8.3*	*8.8*	*3.1*	*5.5*	*15.0*	

Table 2. ^{13}C NMR (125.7 MHz) chemical shifts of carbon atoms

Compd	Solvent (temp)	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
2a	$CDCl_3$ (30 °C)	98.46	81.65	81.49	81.25	70.21	41.25	2 × OMe: 61.66, 58.06; NH–C=N: 156.26;
								2 × CO: 163.17, 152.63; 2 × *t*−Bu: 82.77, 78.60, 28.16, 27.98
2b	$CDCl_3$ (30 °C)	97.80	82.31	81.44	79.25	70.18	41.10	2 × OMe: 60.99, 58.56; NH–C=N: 156.21;
								2 × CO: 163.60, 152.76; 2 × *t*−Bu: 82.26, 78.30, 28.31, 28.10
2c	$CDCl_3$ (30 °C)	97.42	82.43	81.74	78.32	70.03	41.14	2 × OMe: 60.83, 58.94; NH–C=N: 156.19;
								2 × CO: 163.67, 152.79; 2 × *t*−Bu: 82.36, 78.24, 28.38, 28.10
3a	D_2O (30 °C)	101.49	82.74	82.62	84.40	73.78	45.58	2 × OMe: 63.04, 60.50; NH–C=N: 160.65
3b	D_2O (55 °C)	100.28	82.16	82.60	80.88	73.52	45.32	2 × OMe: 62.02, 60.92; NH–C=N: 160.56
3c	D_2O (80 °C)	99.77	83.03	82.74	78.90	73.02	45.96	2 × OMe: 62.07, 60.76; NH–C=N: 160.56

ing per(6-deoxy-6-azido-2,3-di-*O*-methyl) cyclodextrins.[8] General procedures for guanidinylation and deprotection of cyclodextrins are exemplified for the α-cyclodextrin homologue.

2.1. Hexakis[6-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidino-6-deoxy-2,3-di-*O*-methyl]-α-cyclodextrin 2a

Hexakis(6-deoxy-6-amino-2,3-di-*O*-methyl)-α-cyclodextrin **1a** (188 mg, 0.166 mmol, lyophilized prior to use) in dry THF (5 mL) was added with stirring to the solution of *N*,*N*′-di-Boc-*N*′-triflylguanidine (607 mg, 1.49 mmol) and triethylamine (0.208 mL, 1.49 mmol) in THF (5 mL). The reaction mixture was allowed to stand for 48 h, then the solvents were evaporated under reduced pressure at a temperature not exceeding 30 °C. Column chromatography of the solid residue (silica, 40 g, gradient elution from DCM to DCM/MeOH 98:2) yielded **2a** as a colourless amorphous material (381 mg, 89%). ^{1}H and ^{13}C NMR spectra—see Tables 1 and 2. FAB-MS (DMSO, positive ionization): 2588.5 for $[M+H]^{+}$. Anal. Calcd for $C_{114}H_{198}N_{18}O_{48}$: C, 52.89; H, 7.71; N, 9.74. Found C, 52.16; H, 7.76; N, 9.60.

2.2. Hexakis(6-deoxy-6-guanidino-2,3-di-*O*-methyl)-α-cyclodextrin 3a

Compound **2a** (361 mg, 0.139 mmol) was dissolved in dry DCM (2.5 mL) under an argon atmosphere and trifluoroacetic acid (2.5 mL) was slowly added. The solution was allowed to react for 5 h at room temperature, then toluene (5 mL) was added and the solution was evaporated to dryness under reduced pressure at room temperature. The resulting amorphous material was dissolved in water (2 mL) and charged onto a column of Dowex 1 (20 mL) prepared in OH^{-} form and eluted with water. The eluate was collected and lyophilized to give **3a** as an amorphous white material (175 mg, 85%, calcd for the pentahydrate). ^{1}H and ^{13}C NMR spectra—see Tables 1 and 2. ESI-MS (H_2O, positive ionization): 694.4 for $[M+2H]^{2+}$. Anal. Calcd for $C_{54}H_{102}N_{18}O_{24}\cdot 5H_2O$: C, 43.89; H, 7.64; N, 17.06. Found: C, 43.67; H, 7.73; N, 16.91.

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Supplementary data

Supplementary material for this article containing hard copies of the ^{1}H NMR spectra of products **3a**–**c** can be found in the online version, at doi:10.1016/j.tetlet.2005.11.124.

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