

Highly polar carbohydrates stack onto DNA duplexes via CH/ π interactions

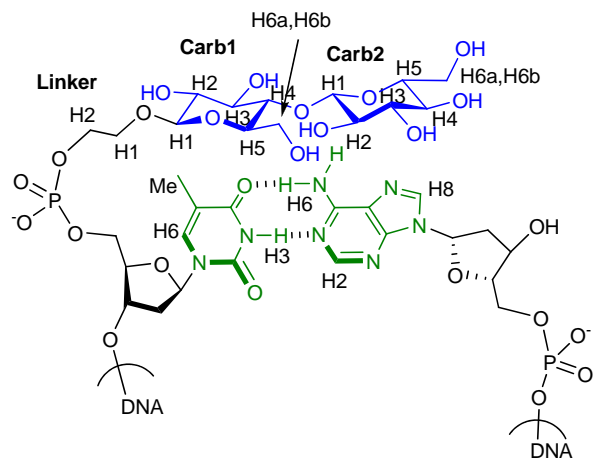
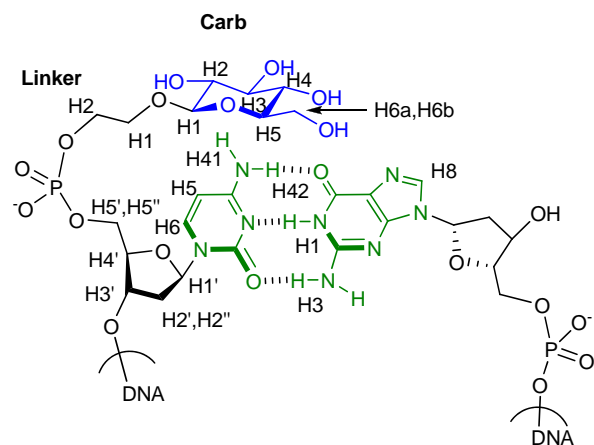
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Table S1: NMR proton assignments of carbohydrate oligonucleotide conjugates **1-6**, **8**, **11** and controls **13** and **15** at 5 °C.



Conjugate 1: glucose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.67	2.28/2.5	4.88	4.20	3.98	5.99	7.7	--	7.29/8.48
G2	5.93	2.74		4.37	4.02/4.12	--	8.01	13.19	--
C3	5.76	2.10/2.46	4.91	4.24	4.05/4.15	5.49	7.42	--	6.64/8.49
G4	5.93	2.68/2.75		4.40	4.05/4.14	--	7.97	13.14	--
C5	5.74	1.86/2.31	4.84	4.23	4.08/4.17	5.53	7.38	--	6.81/8.58
G6	6.21	2.69/2.37	4.71	4.22	4.09	--	8.00	13.30	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
glc			4.29	3.20	3.34	3.27	3.22	3.53	3.71

Conjugate 2: galactose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.67	2.26/2.5	4.87	4.22	3.98	6.01	7.7	--	7.26/8.41
G2	5.93	2.74		4.37	4.03/4.14	--	8.01	13.18	--
C3	5.77	2.11/2.46	4.91	4.24	4.05/4.15	5.49	7.42	--	6.64/8.44
G4	5.93	2.69/2.75		4.40	4.06/4.15	--	7.98	13.14	--
C5	5.74	1.87/2.31	4.84	4.23	4.09/4.17	5.53	7.38	--	6.81/8.55
G6	6.21	2.69/2.39	4.71	4.23	4.08	--	8.00	13.30	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
gal			4.24	3.46	3.53	3.75	3.55	--	--

Conjugate 3: fucose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.67	2.24/2.5	4.83	4.19	3.97	6.00	7.68	--	7.32/8.47
G2	5.93	2.74		4.37	4.05/4.15	--	8.01	13.19	--
C3	5.77	2.11/2.46	4.91	4.24	4.05/4.15	5.49	7.42	--	6.65/8.49
G4	5.93	2.68/2.76		4.40	4.06/4.15	--	7.97	13.14	--
C5	5.75	1.86/2.30	4.84	4.22	4.08/4.16	5.53	7.38	--	6.82/8.59
G6	6.21	2.70/2.39	4.72	4.22	4.08	--	8.00	13.31	--
	L1	L2	H1	H2	H3	H4	H5	Me	
fuc			4.15	3.38	3.51	3.65	3.56	1.05	

Conjugate 4: maltose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.73	2.31/2.52	4.90	4.20	3.99	6.00	7.70	--	7.35/8.57
G2	5.93	2.74		4.38	4.03/4.13	--	8.00	13.18	--
C3	5.75	2.10/2.45	4.91	4.24	4.06/4.15	5.49	7.42	--	6.64/8.49
G4	5.92	2.69/2.75		4.40	4.06/4.15	--	7.97	13.13	--
C5	5.73	1.93/2.35	4.86	4.23	4.09/4.18	5.54	7.40	--	6.80/8.57
G6	6.21	2.71/2.39	4.71	4.23	4.09	--	8.03	13.40	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
Carb1			4.27	3.18	3.40	--	--	--	--
Carb2			4.27	3.20	--	--	--	--	--

Conjugate 5: cellobiose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.64	2.30/2.51	4.87	4.18	3.98/4.02	6.00	7.70	--	7.31/8.46
G2	5.94	2.74		4.38	4.03/4.13	--	8.02	13.19	--
C3	5.75	2.09/2.45	4.91	4.23	4.06/4.15	5.48	7.41	--	6.64/8.48
G4	5.93	2.69/2.75		4.41	4.06/4.14	--	7.97	13.15	--
C5	5.75	1.89/2.33	4.85	4.23	4.08/4.18	5.52	7.39	--	6.81/8.58
G6	6.21	2.72/2.41	4.72	4.23	4.09	--	8.04	13.32	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
Carb1			4.12	3.15	3.37	3.25	3.25	3.54	3.54
Carb2			4.16	2.87	3.26	3.37	3.17	3.72	--

Conjugate 6: lactose-C2-CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.67	2.29/2.51	4.87	4.19	3.95/3.99	6.00	7.69	--	7.32/8.53
G2	5.93	2.74		4.37	4.03/4.13	--	8.00	13.19	--
C3	5.77	2.10/2.46	4.90	4.23	4.05/4.15	5.48	7.41	--	6.65/8.50
G4	5.92	2.68/2.75		4.40	4.06/4.14	--	7.96	13.14	--
C5	5.75	1.88/2.32	4.84	4.23	4.09/4.17	5.52	7.38	--	6.81/8.58
G6	6.21	2.68/2.40	4.71	4.22	4.08	--	8.02	13.35	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
Carb1			4.29	3.20	3.32	3.44	3.33	3.59	--
Carb2			4.12	3.34	3.80	3.67	3.54	3.74	--

Conjugate 8: glucose-C2-TGCGCA

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	Me	H5/H2	H6/H8	H1/H3
T1	5.88	2.22/2.45	4.87	4.40	3.99/3.93	1.81	--	7.53	12.99
G2	5.98	2.73/2.80		4.40	4.13/4.05		--	8.04	12.99
C3	5.78	2.08/2.46	4.89	4.25	4.16/4.07		5.45	7.41	6.65/8.50
G4	5.87	2.69/2.64		4.39	4.15/4.07		--	7.94	13.11
C5	5.75	1.97/2.33	4.79		4.01		5.49	7.36	6.77/8.49
A6	5.96		4.71	4.51	4.31		7.91	8.30	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
glc			4.35	3.20	3.36	3.23	3.23	3.52	3.73

Conjugate 11: cellobiose-C2-TGCGCA

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	Me	H5/H2	H6/H8	H1/H3
T1	5.89	2.30/2.51	4.89	4.22	3.99/3.89	1.86		7.57	12.98
G2	5.97	2.79/2.73	5.02	4.40	4.15/4.07		--	8.03	12.98
C3	5.76	2.09/2.46	4.90	4.25	4.16/4.06		5.46	7.42	6.64/8.50
G4	5.89	2.70/2.65	4.99	4.39	4.14/4.07		--	7.95	13.11
C5	5.70	1.99/2.36	4.82		4.16		5.50	7.38	6.76/8.50
A6	5.98		4.73	4.51	4.33		7.98	8.35	--
	L1	L2	H1	H2	H3	H4	H5	H6a	H6b
Carb1			4.29	3.17	3.27	3.26	3.41	3.55	3.70
Carb2			4.10	3.13	3.24	3.24	3.35	3.56	3.71

Conjugate 13: CGCGCG

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	H5	H6/H8	H1/H3	H41/H42
C1	5.79	2.06/2.47	4.75	4.09	3.74	5.96	7.69	--	7.21/8.24
G2	5.95	2.76		4.38	4.01/4.12	--	8.03	13.15	--
C3	5.77	2.10/2.46	4.90	4.24	4.06/4.15	5.46	7.41	--	6.60/8.45
G4	5.93	2.67/2.75		4.40	4.06/4.14	--	7.97	13.11	--
C5	5.77	1.95/2.38	4.85	4.17	4.13	5.50	7.39	--	6.75/8.54
G6	6.22	2.65/2.37	4.70	4.21	4.09	--	7.99	13.25	--

Conjugate 15: TGCGCA

	H1'	H2'/H2''	H3'	H4'	H5'/H5''	Me	H5/H2	H6/H8	H1/H3
T1	5.84	1.75/2.23	4.64	4.07	3.65	1.62		7.37	13.15
G2	6.01	2.85/2.88		4.41	4.06/4.01		--	8.08	13.15
C3	5.85	2.10/2.45	4.90	4.26	4.13/4.16		5.49	7.42	6.64/8.57
G4	5.88	2.63		4.40	4.14		---	7.95	13.15
C5	5.84	1.97/2.23	4.67				5.50	7.38	6.75/8.47
A6	6.29	2.88/2.62	4.71	4.20	4.06/4.01		7.89	8.26	--

Table S2: Structurally relevant carbohydrate-DNA NOE contacts for the carbohydrate - oligonucleotide conjugates **1-6, 8** and **11**. Strong NOE: s, medium NOE: m, weak NOE: w.

Monosaccharide-CGCGCG conjugates: Conjugate **1**: glucose-C2-CGCGCG, conjugate **2**: galactose-C2-CGCGCG and conjugate **3**: fucose-C2-CGCGCG.

	1		2		3	
	Carb	Linker	Carb	Linker	Carb	Linker
C1	H5-H1: w	H6-H1: s	H5-H1: m	H6-H1: s	H5-H1: m	H6-H1: s
	H5-H2: w	H6-H2: s	H5-H2: m	H6-H2: s	H5-H3: w	H6-H2: s
	H6-H1: w	H5-H1: s	H5-H3: w	H5-H1: s	H5-H4: m	H5-H1: s
		H5-H2: s	H6-H1: w	H5-H2: s	H6-H4: m	H5-H2: s
			H6-H2: w		H1'-Me: w	
			H1'-H3: w		H1'-H4: w	
G6					H1'-Me: w	
					H8-Me: w	

Disaccharide-CGCGCG conjugates: conjugate **4**: maltose-C2-CGCGCG, conjugate **5**: cellobiose-C2-CGCGCG and conjugate **6**: lactose-C2-CGCGCG.

	4			5			6			
	Carb1	Carb2	Linker	Carb1	Carb2	Linker	Carb1	Carb2	Linker	
C1	H5-H1: m		H6-H1: s	H5-H1: m		H6-H1: s	H5-H1: w		H6-H1: s	
	H6-H1: m		H6-H2: s	H6-H1: m		H6-H2: s	H6-H1: w		H6-H2: s	
	H6-H2: w		H5-H1: s	H5-H2: w		H5-H1: s	H6-H2: w		H5-H1: s	
	H5-H2: w		H5-H2: s	H5-H3: m		H5-H2: s	H5-H3: w		H5-H2: s	
				H6-H3: w			H6-H3: w			
			H1'-H3: w			H41-H2: w				
						H42-H2: w				
G6	H1'-H2: w			H1'-H2: w			H1'-H2: m			
	H1'-H3: s			H1'-H3: w			H1'-H4: w			
	H8-H2: w			H1'-H6a: m			H1'-H5: w			
	H8-H3: w			H1'-H6b: m			H8-H2: m			
	H8-H4: w			H8-H2: m			H8-H3: w			
	H2'-H4: w			H8-H3: w			H8-H4: w			
	H2''-H4: w			H8-H1: w			H2'-H4: w			
	H2'-H3: w			H2'-H6a: w			H2''-H4: w			
	H2''-H3: w			H2'-H6b: w			H2'-H3: w			
	H2'-H2: w			H2''-H6a: w			H2''-H3: w			
	H2''-H2: w			H2''-H6b: w			H2'-H2: w			
	H1:H2: w				H2'-H2: w			H2''-H2: m		
					H2''-H2: m					
					H8-H6a: w					
				H8-H6b: w						

Sugar-TGCGCA conjugates: conjugate **8**: glucose-C2-TGCGCA and conjugate **11**: cellobiose-C2-TGCGCA.

	8		11		
	Carb1	Linker	Carb1	Carb2	Linker
T1	H1'-H2/H4/H5: w	H6-H1: s	Me-H1: m		H6-H1: s
	H6-H2/H4/H5: w	H6-H2: s	H6-H1: m		H6-H2: s
	H6-H1: w	Me-H1: m	H6-H2: w		Me-H1: m
	H1'-H6a: w	Me-H2: m	H6-H3: w		Me-H2: m
	H1'-H6b: w		Me-H3: w		
			H1'-H6a: w		
			H1'-H6b: w		
A6	H2-H2/H4/H5: m			H1'-H2: w	
	H2-H6a: m			H1'-H3/4: m	
	H2-H6b: m			H8-H2: m	
				H8-H3/4: m	
				H8-H1: w	
				H8-H6a: w	
				H8-H6b: w	
				H1'-H6a: w	
				H2-H6a: m	
				H2-H6b: m	
				H2-H2: w	
			H2-H5: w		
			H2-H3/4: m		

Table S3: Structurally relevant NOE contacts between the carbohydrate moieties of the disaccharide oligonucleotide conjugates **4-6** and **11**. ov. Overlapped signals.

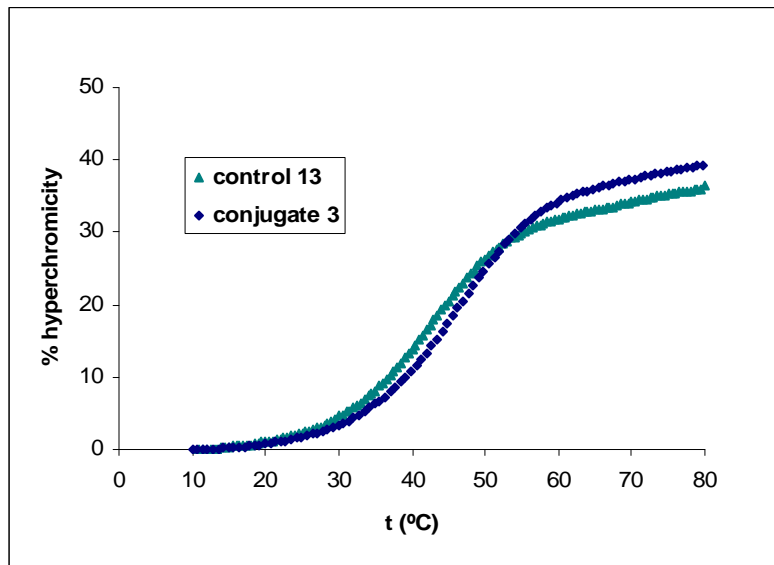
	Carb1-Carb2	Carb1-Linker	Carb2-Carb2
4	ov.		
5	ov.		
6	H4-H1: s	H4-H1: s	H1-H3: s
		H2-H1: m	H1-H5: s
			H3-H5: s
11		H1-H1: s	
		H1-H2: s	

Table S4: Glycosidic angle values of the disaccharide oligonucleotide conjugates **4-6** and **11**.

Angle (°)	4	5	6	11
Φ (H ₁ -C ₁ -O ₄ -C ₄)	-22 ± 8	26 ± 6	49 ± 5	41 ± 8
Ψ (C ₁ -O ₄ -C ₄ -H ₄)	-7 ± 9	-33 ± 7	-3 ± 7	-5 ± 13

Figure S1: Melting curves for: a) control CGCGCG **13** and fucose-C2-CGCGCG **3** and b) control GGCGCC **14** and cellobiose-C2-GGCGCC **10**.

a)



b)

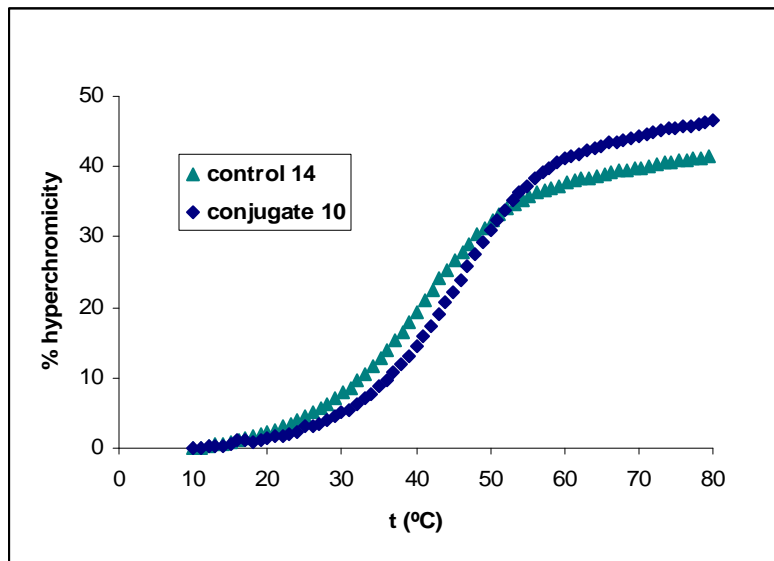
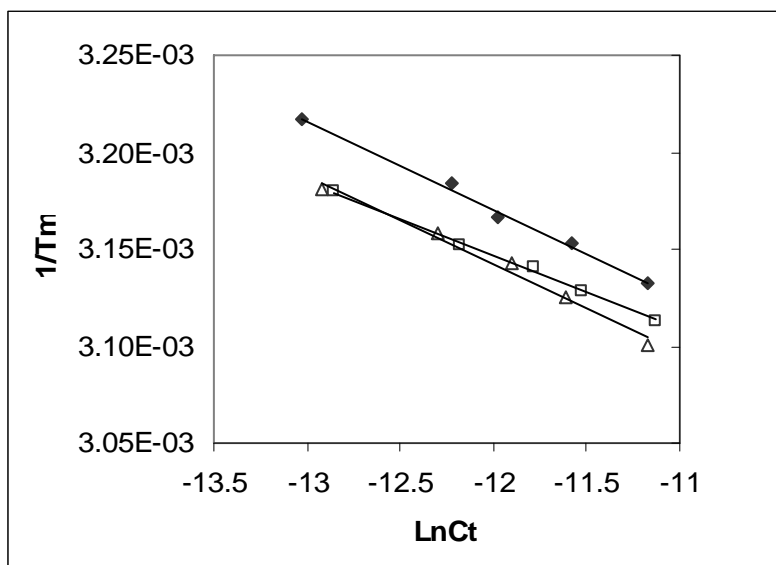
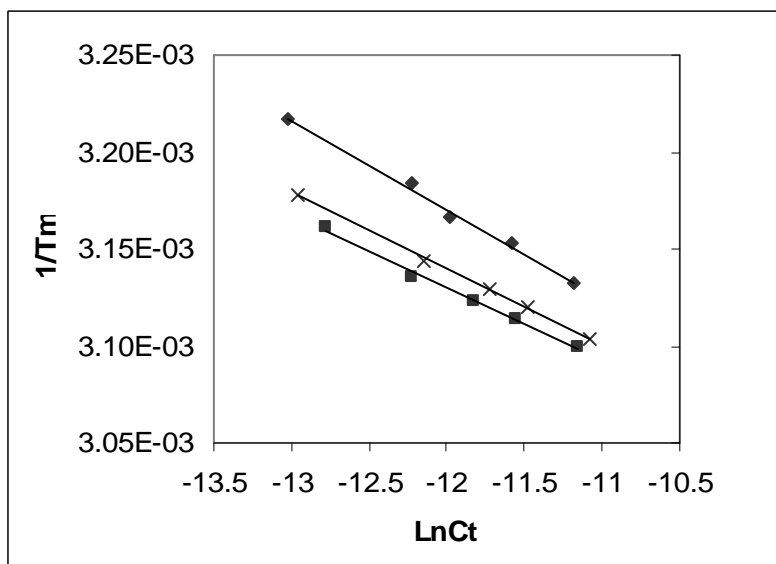


Figure S2: Van't Hoff curves for DNA controls **13-16** and for carbohydrate-oligonucleotide conjugates **1-6, 8** and **11**.

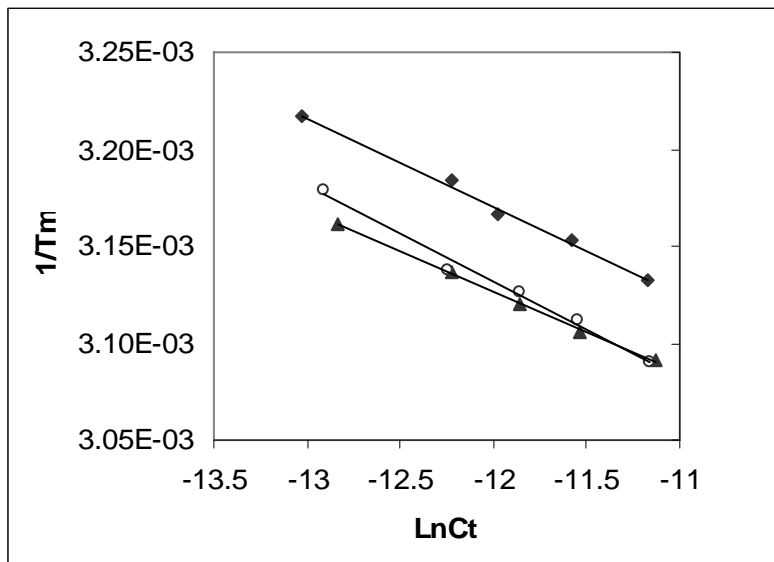
DNA control **13**: CGCGCG (◆), conjugate **1**: glucose-C2-CGCGCG (□) and conjugate **2**: galactose-C2-CGCGCG (△).



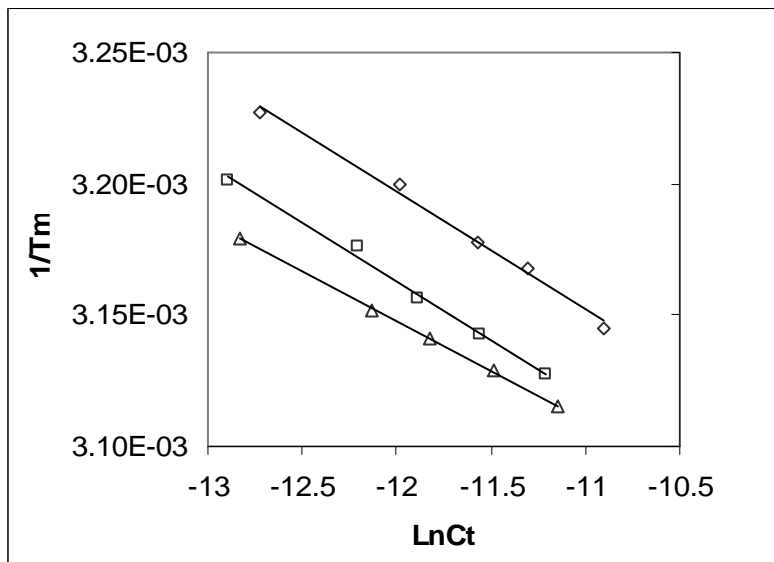
DNA control **13**: CGCGCG (◆), conjugate **3**: fucose-C2-CGCGCG (×) and conjugate **4**: maltose-C2-CGCGCG (■).



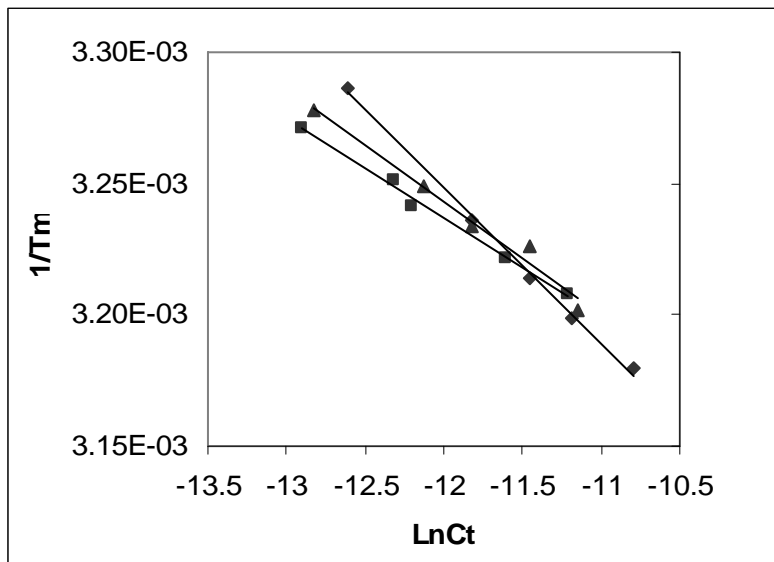
DNA control **13**: CGCGCG (\blacklozenge), conjugate **5**: cellobiose-C2-CGCGCG (\blacktriangle) and conjugate **6**: lactose-C2-CGCGCG (\circ).



DNA control **14**: GGCGCC (\diamond), conjugate **7**: glucose-C2-GGCGCC (\square) and conjugate **10**: cellobiose-C2-GGCGCC (\triangle).



DNA control **15**: TGCGCA (◆), conjugate **8**: glucose-C2-TGCGCA (■) and conjugate **11**: cellobiose -C2-TGCGCA (▲).



DNA control **16**: AGCGCT (◆), conjugate **9**: glucose-C2-AGCGCT (■) and conjugate **12**: cellobiose -C2-AGCGCT (▲).

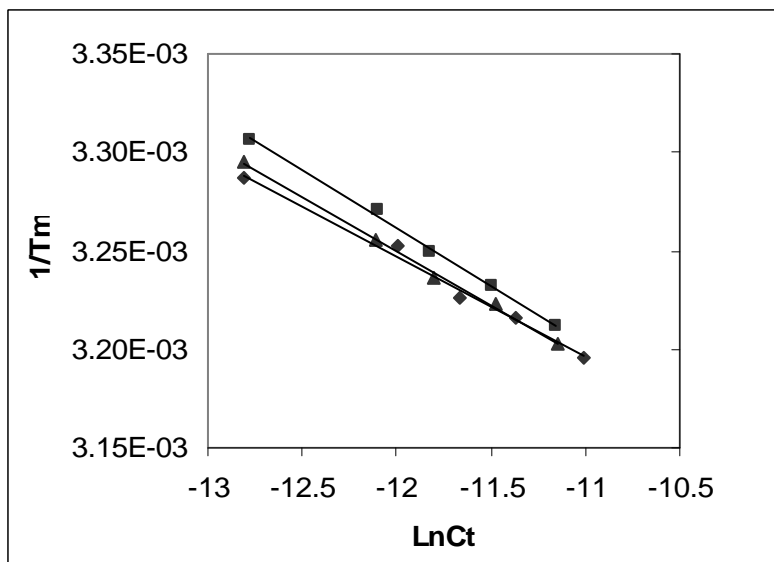
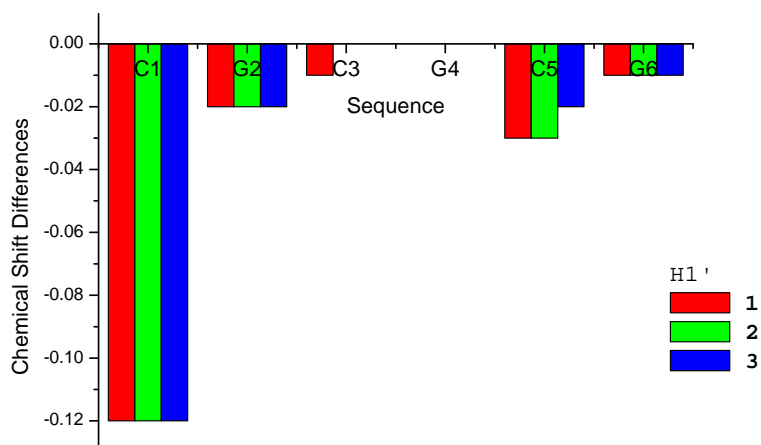
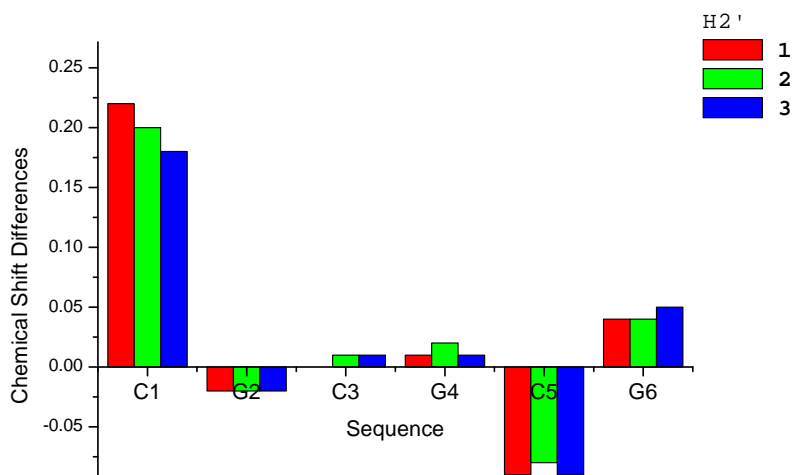


Figure S3: More significant changes in proton chemical shifts along the sequence for the carbohydrate-oligonucleotide conjugates **1-6, 8** and **11**.

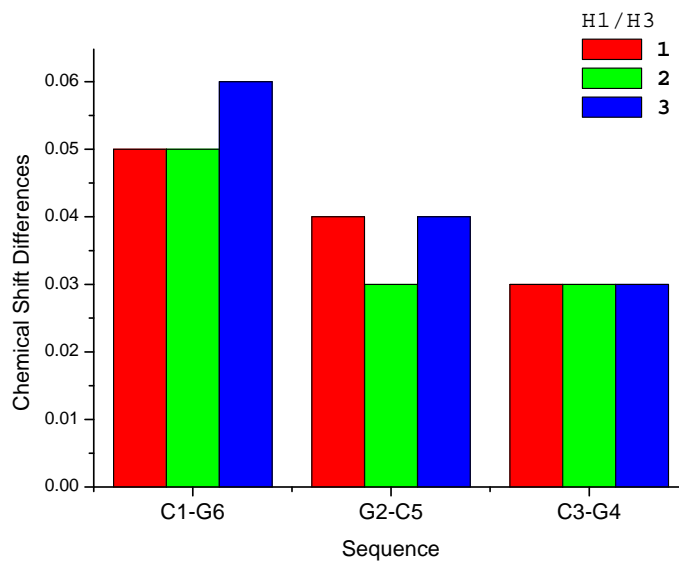
Conjugate **1**: glucose-C2-CGCGCG, conjugate **2**: galactose-C2-CGCGCG and conjugate **3**: fucose-C2-CGCGCG (**proton H1'**).



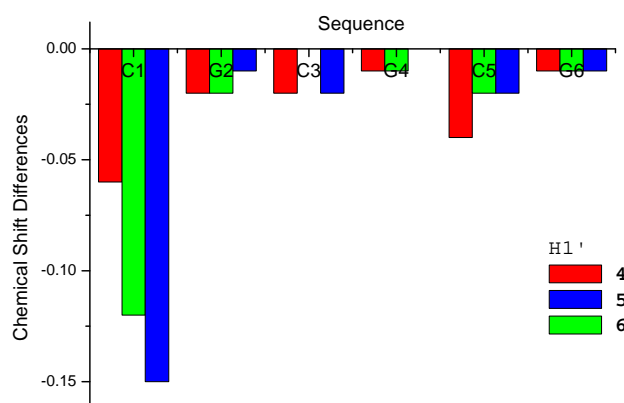
Conjugate **1**: glucose-C2-CGCGCG, conjugate **2**: galactose-C2-CGCGCG and conjugate **3**: fucose-C2-CGCGCG (**proton H2'**).



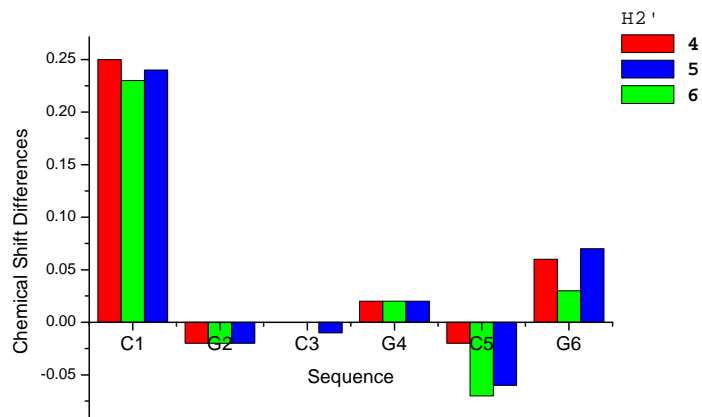
Conjugate **1**: glucose-C2-CGCGCG, conjugate **2**: galactose-C2-CGCGCG and conjugate **3**: fucose-C2-CGCGCG (**protons H1/H3**).



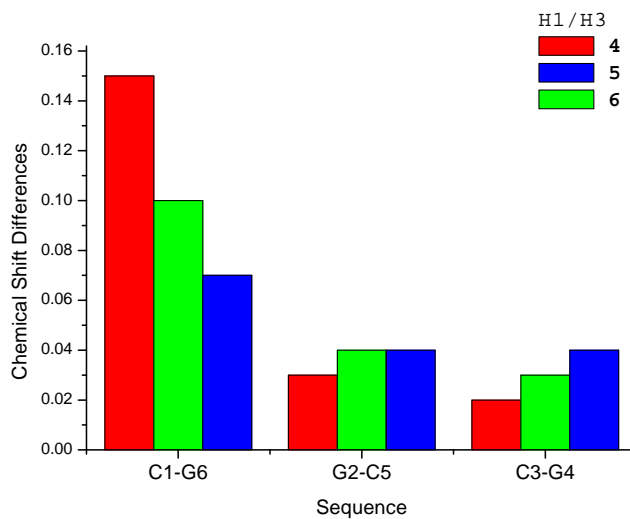
Conjugate **4**: maltose-C2-CGCGCG, conjugate **5**: cellobiose-C2-CGCGCG and conjugate **6**: lactose-C2-CGCGCG (**proton H1'**).



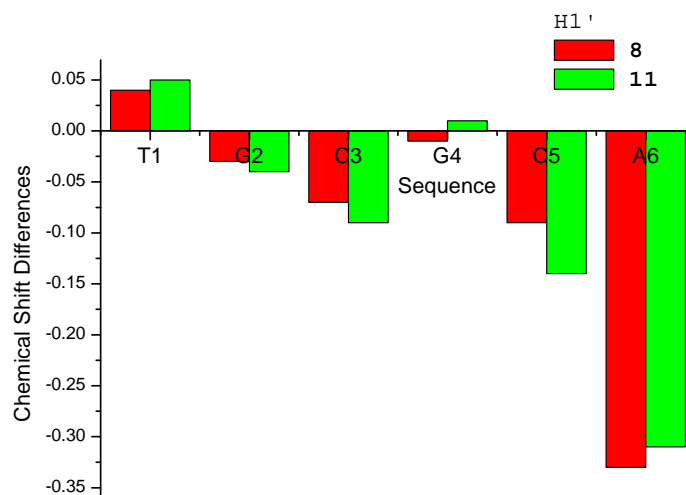
Conjugate **4**: maltose-C2-CGCGCG, conjugate **5**: cellobiose-C2-CGCGCG and conjugate **6**: lactose-C2-CGCGCG (**proton H2'**).



Conjugate **4**: maltose-C2-CGCGCG, conjugate **5**: cellobiose-C2-CGCGCG and conjugate **6**: lactose-C2-CGCGCG (**protons H1/H3**).



Conjugate **8**: glucose-C2-TGCGCA and conjugate **11**: cellobiose-C2-TGCGCA (**proton H1'**).



Conjugate **8**: glucose-C2-TGCGCA and conjugate **11**: cellobiose-C2-TGCGCA (**protons H6/H8**).

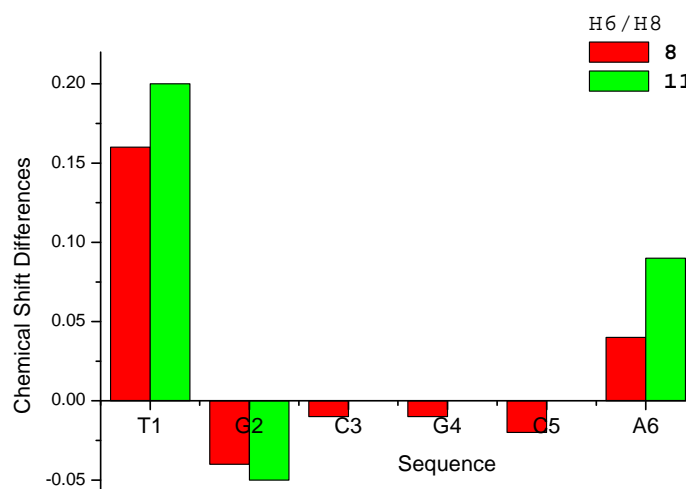


Figure S4: Glycosidic torsion angle fluctuation along a 500 ps restrained molecular dynamics trajectory for conjugate **4** (right) and conjugate **11** (left) (Φ y in black, and Ψ in red). Values are averaged for the two disaccharides at both ends of the duplex.

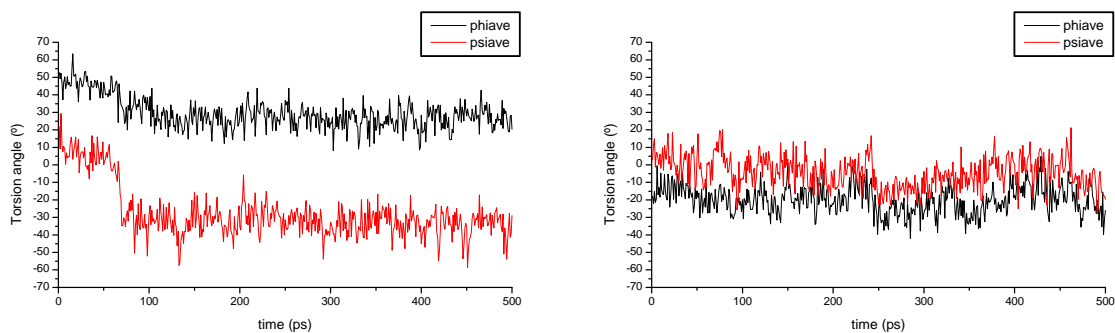
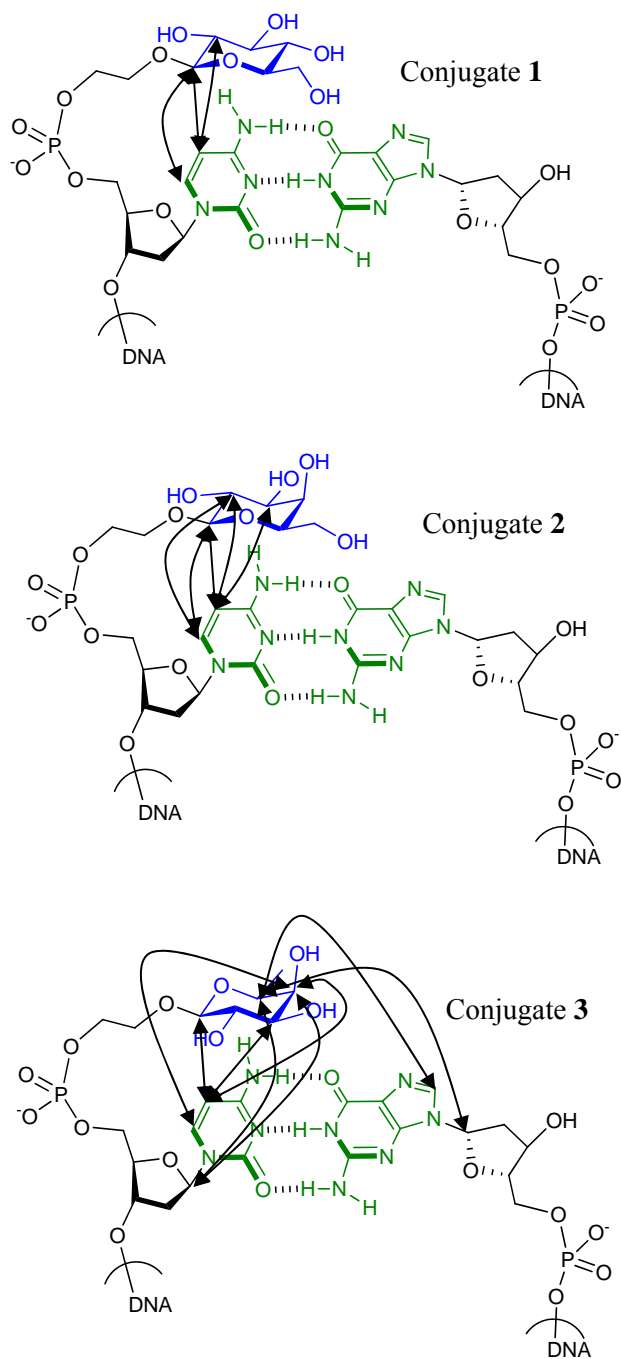
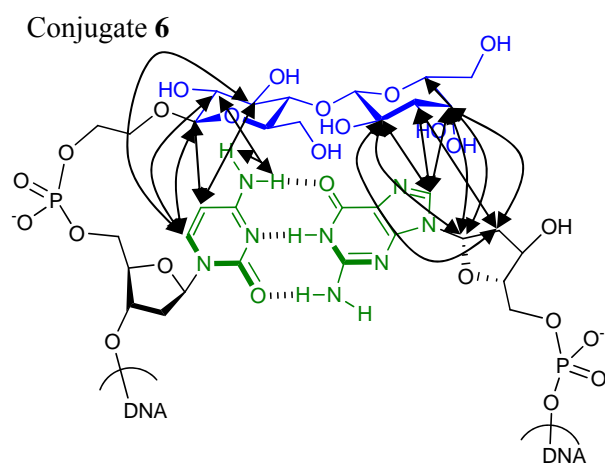
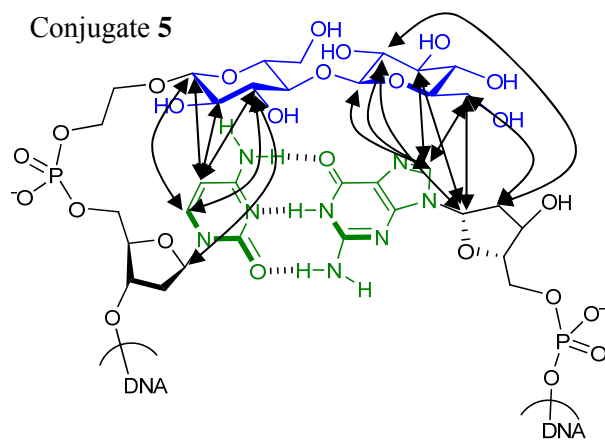
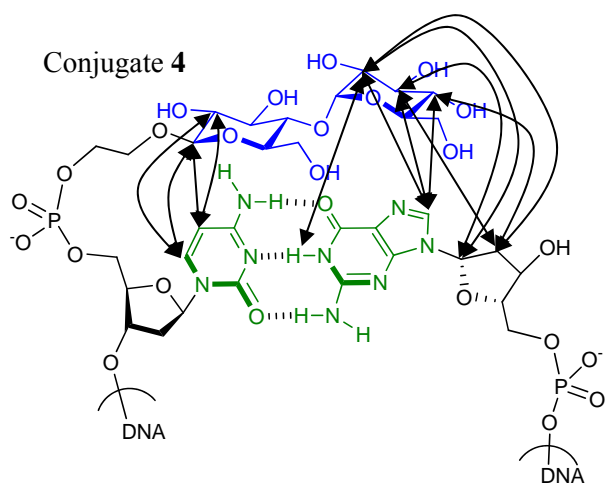
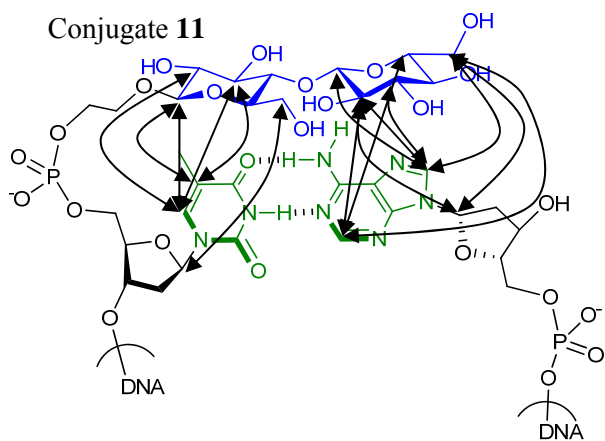
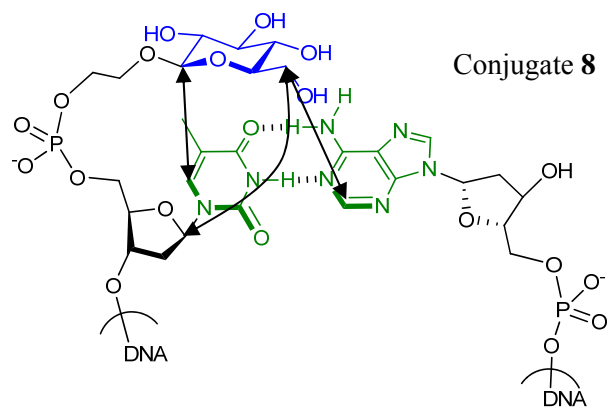


Figure S5: Schematic drawings of conjugates **1-6**, **8** and **11** indicating the proton-proton constraints included in the structure calculations.







Note. Distance restrictions related to protons H2, H4 and H5 in conjugates **8** and **11** were not included within the structure calculations due to proton overlapping.

Supplementary Methods

Synthesis. General information.

All chemicals were obtained from chemical suppliers and used without further purification, unless otherwise noted. All reactions were monitored by TLC on precoated Silica-Gel 60 plates F254, and detected by heating with Mostain (500 ml of 10% H₂SO₄, 25g of (NH₄)₆Mo₇O₂₄•4H₂O, 1g Ce(SO₄)₂•4H₂O). Products were purified by flash chromatography with silica gel60 (200-400 mesh).

NMR spectra were recorded on either a Bruker AVANCE 300 or ARX 400 or Bruker Advance DRX 500 MHz [300 or 400 MHz (1H), 75 or 100 (¹³C)], at room temperature for solutions in CDCl₃, D₂O or CD₃OD]. Chemical shifts are referred to the solvent signal and are expressed in ppm. 2D NMR experiments (COSY, TOCSY, ROESY, and HMQC) were carried out when necessary to assign the corresponding signals of the new compounds. High resolution FAB (+) mass spectral analyses was obtained on a Micromass AutoSpec-Q spectrometer.

Preparation and characterization of compounds 17-19, 21, 23 and 25.

2-Hydroxyethyl- 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl)- β -D-glucopyranoside (21)

To a solution of the peracetylated maltose bromide¹ (1.4 g, 2.00 mmol) and ethylene glycol (1.01 mL, 20.0 mmol, 10 eq.) previously dried over molecular sieves, in anhydrous CH₂Cl₂ (20 mL) was added Ag₂CO₃ (1.2 g, 4.40 mmol, 2.2 eq.). The reaction was then stirred for 24 h. The mixture was then filtered over celite and washed with CH₂Cl₂. The solvents were then removed and the crude was purified by flash column chromatography (hexane: ethyl acetate from 1:2 to 0:1) to afford **21** (740 mg, 54%) as glassy solid; [α]_D²² +48.2 (c 1 in CHCl₃); literature² [α]_D²⁶ +49.5 (c 1 in CHCl₃); HRMS (ES⁺) Calcd. for C₂₈H₄₀O₁₉Na: 703.2061, found; 703.2061.

2-Hydroxyethyl- 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)- β -D-glucopyranoside (23)

To a solution of the peracetylated cellobiose bromide³ (1.5 g, 2.14 mmol) and ethylene glycol (1.08 mL, 21.4 mmol, 10 eq.) previously dried over molecular sieves, in anhydrous CH₂Cl₂ (20 mL) was added Ag₂CO₃ (1.3 g, 4.71 mmol, 2.2 eq.). The reaction was then stirred for 24 h. The mixture was then filtered over celite and washed with CH₂Cl₂. The solvents were then removed and the crude was purified by flash column chromatography (hexane: ethyl acetate from 1:2 to 0:1) to afford **23** (665 mg, 49%) as glassy solid; $[\alpha]_D^{22}$ -13.5 (c 1 in CHCl₃); δ_H (500 MHz, CDCl₃): 5.15-5.06 (m, 2H, H_{3B}, H_{3A}), 4.99 (t, 1H, *J*=9.6 Hz, H_{4B}), 4.88-4.82 (m, 2H, H_{2A}, H_{2B}), 4.51-4.44 (m, 3H, H_{1B}, H_{1A}, H_{6A}), 4.30 (dd, 1H, *J*=4.2 & 12.3 Hz, H_{6B}), 4.06-3.95 (m, 2H, H_{6'A}, H_{6'B}), 3.79-3.57 (m, 7H, H_{4A}, H_{5A}, H_{5B}, -OCH₂-CH₂OH), 2.06, 2.02, 1.98, 1.97, 1.95, 1.94, 1.91 (6s, 21H, OCOCH₃). $\delta^{13}C$ (125 MHz, CDCl₃): 170.4, 170.3, 170.1, 169.7, 169.6, 169.2, 169.0 (C=O), 101.2 (C_{1B}), 100.7 (C_{1A}), 76.5 (C_{4A}), 73.5 (CH₂O-), 73.1 (C_{3B}), 72.8, 72.7, 72.3 (C_{3A}, C_{5A}, C_{5B}), 71.9, 71.5 (C_{2A}, C_{2B}), 67.7 (C_{4B}), 61.9, 61.8, 61.5 (C_{6A}, C_{6B}, CH₂OH), 20.7, 20.8, 20.65, 20.6, 20.4, 20.3 (OCOCH₃). HRMS (ES⁺) Calcd. for C₂₈H₄₀O₁₉Na: 703.2061, found; 703.2061.

2-Hydroxyethyl- 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)- β -D-glucopyranoside (25)

To a solution of the peracetylated lactose bromide⁴ (2.5 g, 3.57 mmol) and ethylene glycol (1.8 mL, 35.7 mmol, 10 eq.) previously dried over molecular sieves, in anhydrous CH₂Cl₂ (20 mL) was added Ag₂CO₃ (2.1 g, 7.86 mmol, 2.1 eq.). The reaction was then stirred for 24 h. The mixture was then filtered over celite and washed with CH₂Cl₂. The solvent were then removed and the crude was purified by flash column chromatography (hexane: ethyl acetate from 1:2 to 0:1) to afford **25** (1.35 mg, 56%) as glassy solid; $[\alpha]_D^{22}$ -2.0 (c 1 in CHCl₃); δ_H (400 MHz, CDCl₃): 5.32 (d, 1H, *J*=2.5 Hz, H_{4B}), 5.19 (t, 1H, *J*=9.3 Hz, H_{3A}), 5.09 (dd, 1H, *J*=8.0 & 10.5 Hz, H_{2B}), 4.94 (dd, 1H, *J*=3.5 & 10.5 Hz, H_{3B}), 4.89 (dd, 1H, *J*=8.0 & 9.5 Hz, H_{2A}), 4.49-4.46 (m, 3H, H_{6A}, H_{1A}, H_{1B}), 4.11 (dd, 1H, *J*=6.3 & 11.5 Hz, H_{6'A}), 4.07-4.02 (m, 2H, H_{6B}, H_{6'B}), 3.87-3.64 (m, 7H, H_{5A}, H_{4A}, H_{5B}, CH₂O-, CH₂OH), 2.14, 2.11, 2.04, 2.03, 2.02, 1.94 (6s, 21H, OCOCH₃). $\delta^{13}C$ (100 MHz, CDCl₃): 170.4, 170.3, 170.1, 170.0, 169.7, 169.4, 169.1 (C=O), 101.3 (C_{1B}),

101.1 (C_{1A}), 76.3 (C_{4A}), 73.2 (CH₂O-), 72.8 (C_{3B}), 72.7, 71.7, 71.0 (C_{3A}, C_{5A}, C_{5B}), 70.8, 70.6, 69.1, 66.6, 62.0, 61.8, 60.8, 29.7, 20.8, 20.7, 20.6, 20.5 (OCOCH₃). HRMS (ES⁺) Calcd. for C₂₈H₄₀O₁₉Na: 703.2061, found; 703.2060.

2-[(2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl-(1 \rightarrow 4)-2,3,6-tri-*O*-acetyl- β -D-glucopyranosyloxy)]ethyl (2-cyanoethyl) (*N,N*-diisopropyl) phosphoramidite (17**).**

DIEA (0.14 mL, 0.80 mmol) and 2-cyanoethyl-*N,N'*-diisopropylamino-chlorophosphoramidite (71 μ L, 0.32 mmol) were added to a solution of compound **21** (145.0 mg, 0.21 mmol) in anhydrous CH₂Cl₂ (3 mL) at room temperature under an argon atmosphere. After 2.0 h no starting material was observed. Solvent was then removed and the crude was purified by silica gel column chromatography by using Hex/EtOAc (1:1 to 1:3 with 5% of NEt₃) to give compound **17** (158 mg, 85%) as a syrup. δ_{H} (300 MHz, CDCl₃): 5.41-5.30 (m, 2H, H_{1B}, H_{3B}), 5.24 (t, 1H, *J*=9.0 Hz, H_{3A}), 5.05 (t, 1H, *J*= 9.9 Hz, H_{4B}), 4.88-4.80 (m, 2H, H_{2A}, H_{2B}), 4.62 (m, 1H, H_{1A}), 4.48 (dd, *J* = 2.4, 12.3 Hz, H_{6A}), 4.28-4.20 (m, 2 H, CH₂, H_{6'A}), 4.07-3.57 (m, 12H, OCH₂, H_{5A}, H_{4A}, H_{5B}, H_{6B}, H_{6'B}, OCH₂CH₂CN, CHisopropyl), 2.65 (m, 2 H, OCH₂CH₂CN), 2.15-2.00 (6s, 21H, OCOCH₃), 1.16 (t, 12 H, CH₃isopropyl). $\delta^{13}\text{C}$ (75 MHz, CDCl₃): 170.4, 170.3, 170.1, 170.0, 169.7, 169.6, 169.1 (C=O), 117.7, 100.0 (C_{1A}), 95.3 (C_{1B}), 76.5, 72.8, 72.5, 71.0, 70.9, 69.5, 69.4, 69.1, 66.6, 62.5, 62.3, 62.0, 60.7, 58.5, 58.3, 48.5, 43.1, 42.9, 39.1, 29.7, 20.8, 20.7, 20.6, 20.5. HRMS (ES⁺) Calcd. for C₃₇H₅₇O₂₀N₂Na: 903.3140, found; 903.3146.

2-[(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl-(1 \rightarrow 4)-2,3,6-tri-*O*-acetyl- β -D-glucopyranosyloxy)]ethyl (2-cyanoethyl) (*N,N*-diisopropyl) phosphoramidite (18**).**

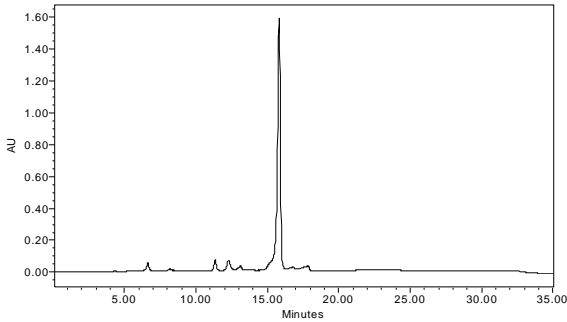
DIEA (0.177 mL, 1.01 mmol) and 2-cyanoethyl-*N,N'*-diisopropylamino-chlorophosphoramidite (94.0 μ L, 0.41 mmol) were added to a solution of compound **23** (190.0 mg, 0.21 mmol) in anhydrous CH₂Cl₂ (3 mL) at room temperature under an argon atmosphere. After 2.0 h no starting material was observed. Solvent was then removed and the crude was purified by silica gel column chromatography by using Hex/EtOAc (1:1 to 1:3 with 5% of NEt₃) to give compound **18** (200 mg, 85%) as a syrup. δ_{H} (300 MHz, CDCl₃): δ_{H} (300 MHz, CDCl₃): 5.17-5.00 (m, 2H, H_{3B}, H_{3A}), 5.04 (t, 1H, *J*=9.3 Hz, H_{4B}), 4.92-4.84 (m, 2H, H_{2A}, H_{2B}), 4.58-4.47 (m, 3H, H_{1B}, H_{1A},

H_{6A}), 4.33 (dd, 1H, *J*=3.9 & 12.5 Hz, H_{6B}), 4.10-3.91 (m, 2H, H_{6'A}, H_{6'B}), 3.99-3.59 (m, 1H, H_{4A}, H_{5A}, H_{5B}, -OCH₂-CH₂OH, OCH₂CH₂CN, CHisopropyl), 2.65-2.61 (m, 2H, OCH₂CH₂CN), 2.10, 2.06, 2.02, 2.01, 1.99, 1.98, 1.96 (6s, 21H, OCOCH₃), 1.15 (t, 12 H, CH₃isopropyl). δ¹³C (75 MHz, CDCl₃): 170.5, 170.3, 170.2, 169.8, 169.6, 169.3, 169.0 (C=O), 100.8 (C_{1B}), 100.7 (C_{1A}), 76.4 (C_{4A}), 72.9 (CH₂O-), 72.6 (C_{3B}), 72.4 (CH₂O-P), 71.9, 71.6, 71.5 (C_{3A}, C_{5A}, C_{5B}), 69.5, 67.8, 62.5, 61.8, 61.5 (C_{6A}, C_{6B}, CH₂OH), 58.6, 58.3, 43.1, 42.9, 24.6, 24.5, 20.7, 20.6 (OCOCH₃). HRMS (ES⁺) Calcd. for C₃₇H₅₇O₂₀N₂Na: 903.3140, found; 903.3146.

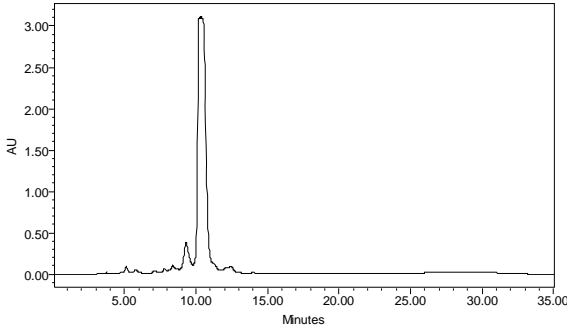
2-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyloxy)]ethyl (2-cyanoethyl) (*N,N*-diisopropyl) phosphoramidite (19**).**

DIEA (0.33 mL, 1.91 mmol) and 2-cyanoethyl-*N,N'*-diisopropylamino-chlorophosphoramidite (172 μL, 0.77 mmol) were added to a solution of compound **25** (350.0 mg, 0.51 mmol) in anhydrous CH₂Cl₂ (5 mL) at room temperature under an argon atmosphere. After 2.0 h no starting material was observed. Solvent was then removed and the crude was purified by silica gel column chromatography by using Hex/EtOAc (1:1 to 1:3 with 5% of NEt₃) to give compound **19** (215 mg, 93%) as a syrup. δ_H (400 MHz, CDCl₃): 5.32 (d, 1H, *J*=2.8 Hz, H_{4B}), 5.13 (t, 1H, *J*=9.2 Hz, H_{3A}), 5.07 (dd, 1H, *J*=8.0 & 10.4 Hz, H_{2B}), 4.92 (dd, 1H, *J*=3.2 & 10.4 Hz, H_{3B}), 4.89 (m, 1H, H_{2A}), 4.57 (m, 1 H, H_{1A}), 4.46 (m, 2 H, CH₂, H_{1B}), 4.08 (m, 3H, CH₂), 3.89-3.55 (m, 11H, H_{5A}, H_{4A}, H_{5B}, H_{6A}, H_{6'A}, H_{6B}, H_{6'B}, OCH₂CH₂CN, CHisopropyl), 2.63 (m, 2 H, OCH₂CH₂CN), 2.12-1.94 (7s, 21H, OCOCH₃), 1.16 (t, 12 H, *J*=6.5 Hz, CH₃isopropyl). δ¹³C (100 MHz, CDCl₃): 170.4, 170.3, 170.1, 170.0, 169.7, 169.6, 169.1 (C=O), 117.7, 101.0, 101.1, 76.2, 72.8, 72.5, 71.6, 70.9, 70.6, 69.5, 69.4, 69.1, 66.6, 62.5, 62.3, 62.0, 60.7, 58.5, 58.3, 48.5, 43.1, 42.9, 39.1, 29.7, 20.8, 20.7, 20.6, 20.5 (7 x -OCOCH₃). HRMS (ES⁺) Calcd. for C₃₇H₅₇O₂₀N₂Na: 903.3140, found; 903.3146.

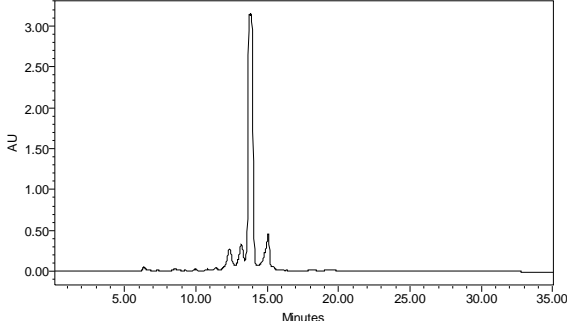
HPLC chromatograms of carbohydrate oligonucleotide conjugates 1-12.



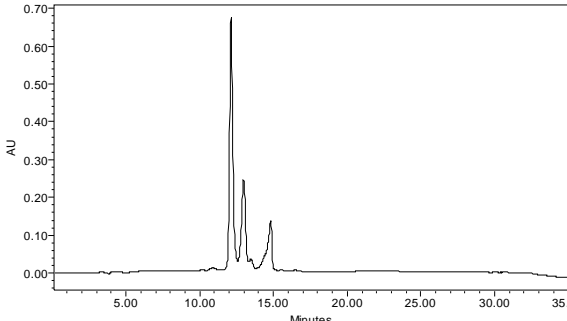
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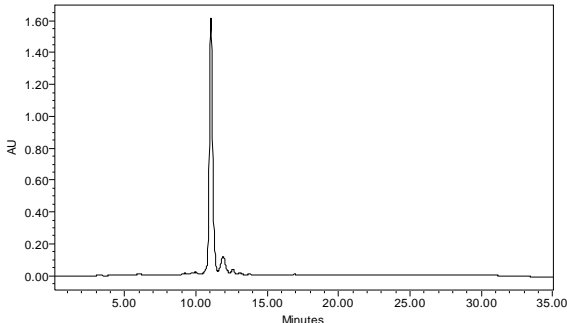
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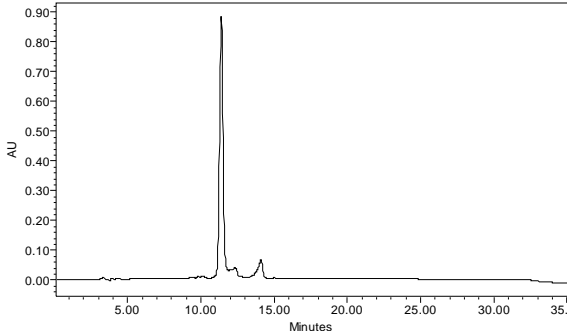
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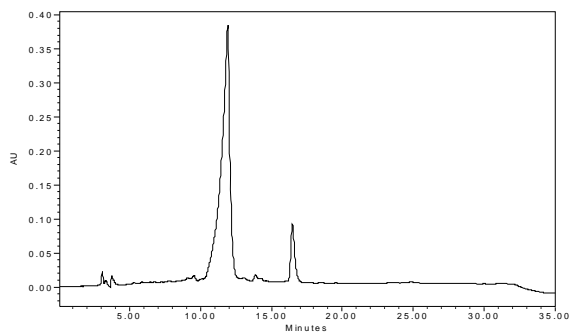
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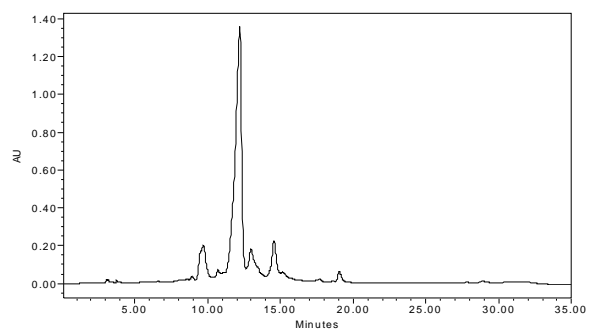
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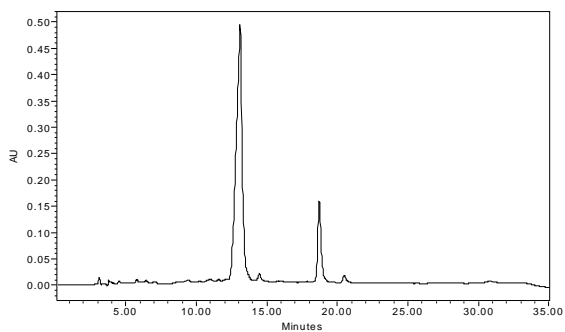
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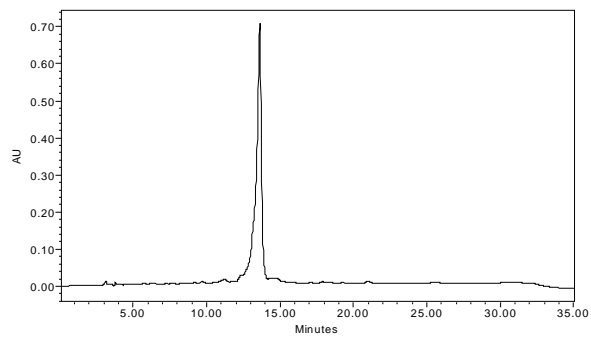
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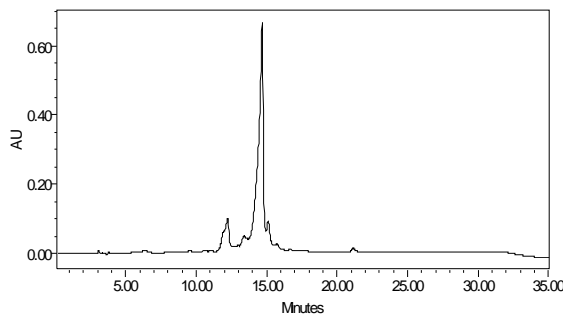
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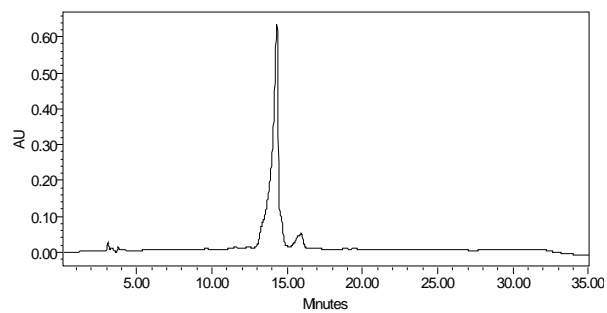
9



10



11



12

Maldi-TOF mass spectra of carbohydrate oligonucleotide conjugates 1-12.

MALDI-TOF spectra were performed using a Perseptive Voyager DETMRP mass spectrometer, equipped with nitrogen laser at 337 nm using a 3ns pulse. The matrix used contained 2,4,6-trihydroxyacetophenone (THAP, 10 mg/ml in ACN/ water 1:1) and ammonium citrate (50 mg/ml in water).

Carbohydrate oligonucleotide conjugates	[M-H] calc.	[M-H] exp.
β -D-glucose-C2-CGCGCG (1)	2078.3	2078.1
β -D-galactose-C2-CGCGCG (2)	2078.3	2076.8
β -L-fucose-C2-CGCGCG (3)	2062.3	2061.8
β -D-maltose-C2-CGCGCG (4)	2239.3	2240.3
β -D-cellobiose-C2-CGCGCG (5)	2239.3	2240.7
β -D-lactose-C2-CGCGCG (6)	2239.3	2240.1
β -D-glucose-C2-GGCGCC (7)	2078.3	2077.0
β -D-glucose-C2-TGCGCA (8)	2077.3	2076.0
β -D-glucose-C2-AGCGCT (9)	2077.3	2075.7
β -D-cellobiose-C2-GGCGCC (10)	2239.3	2238.9
β -D-cellobiose-C2-TGCGCA (11)	2238.3	2238.0
β -D-cellobiose-C2-AGCGCT (12)	2238.3	2237.7

References

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- ² Tsuzuki, M. and Tsuchiya, T. Synthesis of alpha,alpha-, alpha,Beta-, and Beta,Beta-(dimaltoside)s of ethane-1,2-diol, propane-1,3-diol, and butane-1,4-diol: a proposal for an initial adhesion mode. *Carbohydr. Res* **311** (1-2), 11-24 (1998).
- ³ Fischer, E. and Zemplen, G. *Ber.* **48**, 2536 (1910).
- ⁴ Hudson, C. S. and A., K. Relations between rotatory power and structure in the sugar group. X. The chloro-, bromo- and iodo-acetyl derivatives of lactose. *J. Am. Chem. Soc.* **47**, 2052–2055 (1925).