**2,3-Dimethyl-2,3-bis(*tert*-butylazo)butane (8B).** In a 100-mL flask equipped with a magnetic stirrer and a water condenser, 0.5 g of acetone *tert*-butylhydrazone[93] (3.9 mmol) was mixed with 15 mL of acetone. A 1.0-g portion of $KMnO_4$ (6.3 mmol) dissolved in 40 mL of acetone was added dropwise under refluxing. After refluxing for 3 h, the solution was filtered to remove all solids. The residue was rotary evaporated and was extracted with $Et_2O$ to obtain crude product. After removal of the ether, the crude product (28% yield based on *tert*-butylhydrazine) was purified by recrystallization from methanol: mp 43.5–44.2 °C. UV(hexane): $\lambda_{max}$ = 372 nm; $\epsilon$ = 36. $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ (ppm) 1.21 (18 H, s), 1.32 (12 H, s). $^{13}$C NMR ($C_6D_6$): $\delta$ (ppm) 73.15, 66.87, 26.92, 21.01. Anal. Calcd for $C_{14}H_{30}N_4$: 254.2470. Found: 254.2468.

Thermolysis kinetics of **8B** monitored by UV spectroscopy gave the following rate constants: $T$ (°C), $10^4k$ ($s^{-1}$); 153.46, 0.327; 164.29, 0.953; 171.68, 1.93; 174.13, 2.20. The decomposition products of **8B** (cf. Table VII) were analyzed by GC under the following conditions: injector temperature 140 °C, detector temperature 160 °C initial oven temperature 35 °C, initial time 10 min, program rate 10 deg/min, final oven temperature 150 °C.

**2,3-Dimethyl-2-(*tert*-butylazo)butane (20).** Into a three-necked flask equipped with a magnetic stirrer, a nitrogen inlet, and an addition funnel and containing a solution of 1.97 g (19.3 mmol) of 2,3-dimethyl-2-butanol in 25 mL of hexane cooled in ice was added dropwise with stirring 5 mL of a hexane solution of 2.74 g (19.4 mmol) of chlorosulfonyl isocyanate. After the addition was complete, the reaction mixture was stirred in the cold for 1.5 h and was then allowed to stand at room temperature overnight under nitrogen. The following day, the white precipitate that formed during the addition had disappeared and two liquid layers were present. The bottom layer, a reddish oil, was the sulfamoyl chloride. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 0.98 (6 H, d), 1.45 (6 H, s), 1.90 (1 H, septet), 5.56 (1 H, br s).

Under nitrogen, 1.54 g (21.1 mmol of *tert*-butylamine, 2.1 g (19.1 mmol) of triethylamine, and 50 mL of ether were placed into a 250-mL three-necked flask cooled to −78 °C. The above crude sulfamoyl chloride (both layers) in 20 mL of ether was added dropwise to the flask with stirring over 50 min, causing formation of a white precipitate. The reaction mixture was stirred at −78 °C for 2.5 h and at room temperature for 1.5 h. The product mixture was washed with water (3 × 25 mL), dried over sodium sulfate, rotary evaporated, and evacuated. The white solid weighed 1.4 g (5.9 mmol), corresponding to a 31% yield based on 2,3-dimethyl-2-butanol. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 0.92 (6 H, d), 1.32 (6 H, s), 1.37 (9 H, s), 1.85 (1 H, septet), 4.04 (2 H, br m).

To 0.65 g of the above sulfamide in a 100-mL three-necked flask were added 10 g of Clorox (5.25% NaClO) and 40 mL of pentane. A 7.0-mL portion of 1 N aqueous NaOH was then added dropwise to the stirred suspension over 3 min, and the reaction mixture was stirred at room temperature for 80 min. The pentane layer was washed with water (3 × 15 mL), dried over potassium carbonate, and rotary evaporated to yield a pale yellow liquid. The crude product was purified by silica gel column chromatography using hexane as eluent. The pure product weighed 0.26 g (56.5% yield). UV (hexane): $\lambda_{max}$ = 372 nm; $\epsilon$ = 14.5 $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ (ppm) 0.89 (6 H, d), 1.09 (9 H, s), 1.22 (6 H, s), 2.21 (1 H, m). $^{13}$C NMR ($C_6D_6$): $\delta$ (ppm) 17.54, 25.92, 36.57, 66.32, 70.87. Thermolysis kinetics on **20** gave the following rate constants: $T$ (°C), $10^4k$ ($s^{-1}$): 172.35, 0.832; 178.49, 1.59; 183.90, 2.72; 190.90, 5.35.

**2-(Phenylazo)propane (18).** In a three-necked flask equipped with a mechanical stirrer and a nitrogen inlet was dissolved 2 g (14 mmol) of acetone phenylhydrazone in 15 mL of methanol. The pH of the methanol solution was adjusted to 3 with 20% HCl. Then 1 g (0.016 mol) of $NaBH_3CN$ was added in small portions with stirring. The reaction was monitored by TLC (silica), using 15% EtOAc in hexane as eluent. After the reaction was complete, the product was extracted with ether (3 × 15 mL), washed with water, and dried over $MgSO_4$. The solution was filtered and was then treated with HgO (3 g, 0.014 mol) followed by stirring at room temperature for 30 min. The product mixture was filtered and rotary evaporated to yield an orange-colored liquid weighing 1.8 g (90% yield). Further purification was achieved by short-path distillation under vacuum (4–5 mmHg, bath at 40 °C). UV (hexane): $\lambda_{max}$ = 406 nm; $\epsilon$ = 145. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 1.39 (6 H, d), 3.91 (1 H, septet), 7.43 (3 H, m), 7.66 (2 H, m). $^{13}$C NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 20.61, 68.50, 122.06, 128.91, 130.16, 152.12.

**Oxidation of Acetone Phenylhydrazone by $NiO_2$.** Into a three-necked flask equipped with a magnetic stirrer, a nitrogen inlet, and a thermometer were placed 0.5 g (3.38 mmol) of acetone phenylhydrazone and 10 mL of toluene. The solution was held at a known temperature (cf. Table IV), and 0.61 g (6.73 mmol) of $NiO_2$[94] was added with stirring. After 10–60 min, the suspension was filtered, and the filtrate was analyzed by HPLC using the following conditions: column, Alltech $C_{18}$, ODS (reverse phase), particle size 5 $\mu$m, 4.6-mm i.d. × 25 cm; solvent, 18% (99.5% $CH_3CN$/0.5% $Et_3N$)/82% (85% MeOH/15% $H_2O$); flow rate, 1 mL/min; detector, UV, 280-nm wavelength. In order to quantify the ratio of C–N to C–C dimer, a calibration line was made by analyzing mixtures of known molar ratio.

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# Polysaccharides as Amphiphiles

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**Abstract:** Polysaccharide chains are usually considered to be highly hydrophilic, since they contain no obvious apolar moieties but a large number of hydroxyl groups. However, it is possible even for these chains to display hydrophobic character, arising out of stereochemical constraints on the chain. We present experimental and theoretical evidence which show that the $\alpha$-1*a*,4*e*-D-glucopyranose chains, namely linear dextrin, display amphiphilic properties, since all the hydroxyl groups are disposed on one side or face of the chain and the hydrogens disposed on the other. As a result, dextrin solubilizes lipophilic compounds in water, retards organic reactions that are hydrophobically accelerated in water, destabilizes globular protein chains, and binds to a fluorescent probe dye and enhances its emission. In contrast, the $\beta$-1,4-linked glucoside cellulose and the $\alpha$-1,6-linked dextran chains exhibit only hydrophilicity. Several other oligosaccharide chains are also predicted to display amphiphilic properties. This is expected to be relevant to intermolecular recognition on cell surfaces, lectin-sugar binding, antigen–antibody interactions, and the like.

Sugar molecules are usually thought of as essentially hydrophilic, because of their high water solubility, multiple hydroxyl groups, and lack of alkyl or aryl groups. Yet, as the cyclic oligosaccharides called cyclodextrins[1,2] exemplify, appropriate ste-

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reochemical features can generate hydrophobic or apolar surfaces even in sugar chains. We show here that amphiphilicity is exhibited even by linear oligosaccharides. We illustrate this with dextrin, which is the 1*a*,4*e*-α-D-glucopyranoside chain (Glcpα1-4Glc...) wherein all the hydroxyls are disposed on one sice of the chain backbone, making it hydrophilic, while the methines make up the other, relatively apolar, face of the ribbon. Such amphiphilicity in sugar chains is dictated by the monomer ring conformation, the epimeric structure, and the stereochemistry of the glycosidic linkages. Thus, while the dextrin chain is amphiphilic, dextran (α-1,6-linked glucose units or Glcpα1-6Glc...) and cellulose (β-1*e*,4*e*-D-glucose chain or Glcpβ1-4Glc...) are not able to project any apolar face and can only be hydrophilic. Energy minimization calculations predict hydrophobic surfaces to be present in some of the galactans, mannans, and xylans as well. This realization of hydrophobic surfaces in sugar chains is a facet of possible importance to their intermolecular interactions with proteins and cell surface components.

## Materials and Methods

**Materials.** Dextrin-20 (MW 900), dextrin-15 (MW 1400), dextrin-10 (MW 1600), and dextran-4 (MW 4000–6000) were obtained from Serva Chemicals, while all the other fine chemicals were from Sigma Chemical Co., St. Louis, MO. Anthracene-9-carbinol was synthesized in the laboratory.

**Solubility Studies.** Solubilization experiments were done in an incubator shaker at 298 K, incubating the solid solubilizate with known concentrations of the oligosaccharide solution in water for over 12 h and centrifuging the solid residue, followed by membrane filtration. The concentrations of progesterone, β-estradiol, and pyrene were determined from their absorbance values at 249 nm (log ε 4.23), at 280 nm (log ε 3.33), and at 335 nm (log ε 4.78), respectively. The free energy of tranfer, $\Delta G_{tr}$, was calculated from the equation $\Delta G_{tr} = -RT \ln (C_s/C_w)$, where $C_s$ and $C_w$ are the solubilities of the compound in the chosen solution of the oligosaccharide and in water, respectively. The critical micellar concentration (cmc) of the surfactants and the minimum hydrotropic concentration (mhc) of the hydrotropic compound[3] sodium cumenesulfonate (NaCS) were determined by the surface tension method, using a White platinum ring tensiometer, at ambient temperature (ca. 298 K).

**Diels–Alder Reaction.** The cycloaddition reaction between anthracene-9-carbinol and *N*-ethylmaleimide was conducted at 318 K and assayed as per the published method[4] by following the time-dependent loss in the optical density (at 385 nm) of the carbinol, for a time of about 60 min, which was adequate.

**Protein Denaturation.** The thermal denaturation of the proteins was monitored by following the change in the optical absorption at 287 nm with temperature, in the presence of the various additives. α-Chymotrypsin was studied in pH 2.75 buffer, where its denaturation temperature ($T_m$) was seen to be 317 K. Ribonuclease A was studied in pH 7.1 buffer, where its $T_m$ was 331.5 K.

**Spectroscopy.** Optical absorption spectra were measured using a Hitachi 330 spectrophotometer and a Physitemp type T thermocouple. Fluorescence spectra were measured in a Hitachi F4000 instrument. The extrinsic emission probe 8-anilinonaphthalene-1-sulfonate (ANS) was excited at 365 nm and its emission followed in the 500-nm region. Circular dichroism (CD) spectra were recorded in a Jobin–Yvon dichroigraph at room temperature.

**Conformational Calculations.** Energy minimization calculations were done using the procedure of Rao,[5,6] choosing the coordinates of Arnott and Scott[7] for the sugar rings.

## Results and Discussion

**(i) Solubilization Ability.** A characteristic property of an amphiphilic compound is its ability to enhance the solubility of lipophilic compounds in water. Figure 1 shows that dextrin-20, dextrin-15, and dextrin-10 increase the solubilities of the two steroids progesterone and β-estradiol by as much as a factor of 10 in water. In contrast, dextran, β-1,4-D-xylan, and several mono- and disaccharides do not solubilize but "sugar out" the steroids. The efficiency of solubilization of dextrin is far lower than that of deoxycholate micelles and comparable to that of the hydrotrope[3] sodium cumenesulfonate (NaCS). The values of the free energies of transfer ($\Delta G_{tr}$) of these compounds from water to the dextrins and to dextran are given in Table I. It is clear that dextrin solubilizes these compounds, while dextran does the opposite; as Figure 1 shows, dextran "sugars out" these compounds from aqueous solution. Such contrasting solubilization behavior of the α-1,4-D-glucosides (dextrin) and the α-1,6-D-glucosides (dextran) toward tyrosine has been seen earlier.[8] Indeed, dextran typifies the usual behavior of sugars, namely "sugaring out" or decreasing the solubility of lipophilic compounds in water.[9,10] The ability of the dextrin chain to enhance the solubility of apolar compounds is unexpected.

Dextrins also postpone or increase the critical micellar concentration (cmc) of surfactants in water.[8] In contrast, dextran,

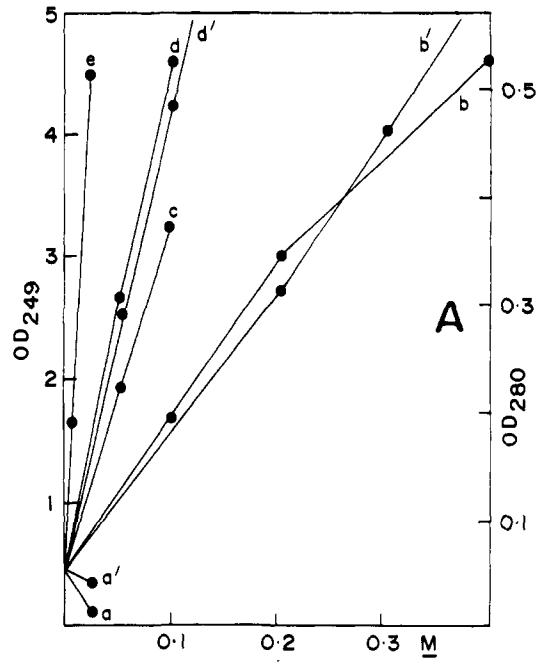


**Figure 1.** Solubilization, at 298 K, of progesterone (left ordinate values; curves a, b, c, d, and e) and of β-estradiol (right ordinate values; curves a′, b′, and d′) in dextran-4 (a and a′), dextrin-20 (b and b′), dextrin-15 (c), dextrin-10 (d and d′), and deoxycholate (e).

**Table I.** Free Energies of Transfer of Steroids and Pyrene from Water to Oligosaccharides[a]

| solute | medium | $\Delta G_{tr}$ (cal/mol) |
|---|---|---|
| progesterone | 100 mM dextrin-10 | −1440 |
| | 400 mM dextrin-20 | −1450 |
| | 18 mM dextran-4 | +540 |
| β-Estradiol | 150 mM dextrin-10 | −1680 |
| | 400 mM dextrin-20 | −1560 |
| | 18 mM dextran-4 | +1470 |
| pyrene | 150 mM dextrin-10 | −2090 |

[a] All measurements were made using 10 mM sodium phosphate pH 7.2 buffer; concentrations measured using absorbance values, as given in Materials and Methods; temperature 298 K; and $\Delta G_{tr}$ calculated from the equation $\Delta G_{tr} = -RT \ln (1/a)$, where $a$ = activity coefficient (= $C_w/C_m$, where $C_w$ and $C_m$ are solubilities in buffer and in the oligosaccharide solution).

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Table II. Second-Order Rate Constants of the Reaction between Anthracene-9-carbinol and *N*-Ethylmaleimide[a]

| medium | $k_2$ ($\times 10^3$ $M^{-1}$ $s^{-1}$) |
|---|---|
| water | 220 |
| 20 mM dextran-4 | 210 |
| 200 mM cellobiose | 210 |
| 2 M D-glucose | 280 |
| 4 M LiCl | 460 |
| 500 mM maltose | 200 |
| 100 mM maltotriose | 190 |
| 100 mM dextrin-20 | 150 |
| 50 mM dextrin-10 | 140 |
| 100 mM dextrin-10 | 130 |
| 100 mM dextrin-10 + 4 M LiCl | 280 |

[a] Temperature 318 K; the concentrations of the carbinol and *N*-ethylmaleimide were 30 M and 1 mM, respectively, and the rates were measured as in ref 4.

maltose, cellobiose, sucrose, trehalose, and glucose marginally advance the cmc. Sugars such as glucose and sucrose are thought to enhance hydrophobic interactions by increasing the structure of water.[9,10] Dextrins appear to do the opposite and weaken hydrophobic self-aggregation. In support of this, we have found that the minimum hydrotropic concentration (mhc) of NaCS, beyond which self-association of these molecules occurs,[3] is increased from 0.1 M in water to 0.4 M in 50 mM dextrin-10.

**(ii) Modulation of Chemical Reaction Rates.** Breslow and co-workers[4,11,12] have used the hydrophobic effect to accelerate organic reactions between lipophilic compounds by placing them in water. The rationale behind this strategy is that the two lipophilic reactants would be brought into close proximity through the hydrophobic effect that operates in water; in organic solvents where this mechanism does not operate, the reaction rates are slower than those in water. Likewise in aqueous solution, an additive which promotes hydrophobic interactions (e.g., glucose or LiCl) should accelerate the reaction, while an additive that weakens them (e.g., urea or guanidinium chloride) should retard the reaction rate. In this connection, we find that the Diels–Alder reaction between anthracene-9-carbinol and *N*-ethylmaleimide in aqueous solution is slowed down upon adding dextrins (rate at 45 °C in water 220 × $10^{-3}$ $M^{-1}$ $s^{-1}$; $k_{rel}$ = 1 with no additive; $k_{rel}$ = 0.86, 0.68, and 0.60 in 100 mM maltotriose, dextrin-20, and dextrin-10, respectively). In contrast, the rate is unaffected by dextran and accelerated by 2 M glucose ($k_{rel}$ = 1.27) and by 4 M LiCl ($k_{rel}$ = 2.1). We found $k_{rel}$ to be 1.27 in a solution that contained both 4 M LiCl and 100 mM dextrin-10, which reflects the mutually opposing effects of the two additives rather well. Table II lists the second-order rate constants of this Diels–Alder reaction in a variety of sugar solutions. Thus, in the matter of affecting the hydrophobically aided Diels–Alder reaction too, the behavior of the dextrins is unusual and suggests that the dextrin chain might weaken the hydrophobic interaction between the reactant molecules.

**(iii) Destabilization of Globular Proteins.** Dextrin is also able to destabilize globular proteins that are held together largely by intramolecular hydrophobic forces. The denaturation temperature of α-chymotrypsin is reduced from 44.0 °C in pH 2.75 buffer solution to 39.9 °C in 10 mM dextrin-10 and to 37.8 °C in 100 mM dextrin-20. Similar results have been obtained with ribonuclease A (RNase A) as well. Dextran, cellobiose, maltose, sucrose, monosaccharides, and glycerol are inert or tend to marginally stabilize the native structure of these globular proteins.

**(iv) Competitive Surface for Dye Binding.** The basis of action of dextrins cannot be a simple solvent polarity effect, since the polarity of the medium is expected to be altered to comparable extents by the other sugars as well. Instead, we suggest that dextrins weaken hydrophobic forces in water by offering a competing hydrophobic surface of their own for interaction. One experiment to test the validity of this idea is to use the dye 8-anilinonaphthalene-1 sulfonate (ANS), which displays a blue-shift

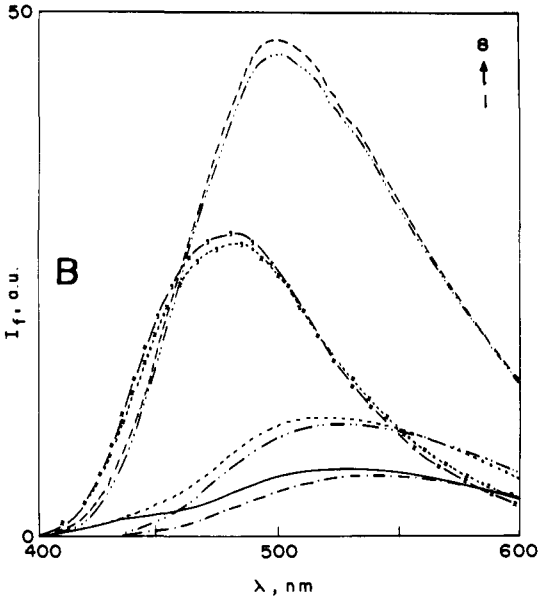


Figure 2. Fluorescence spectra of 50 μM ANS. Curve 1 is in the presence of 1 mg/mL solution of α-chymotrypsin alone in pH 7.2 phosphate buffer, while curves 3 and 7 are obtained when dextran-4 (20 mM) or dextrin-10 (50 mM) is added to it. Curve 2 is in the presence of 1 mg/mL solution of RNase A alone in buffer, while curves 4 and 8 are when dextran-4 (20 mM) or dextrin-10 (50 mM) is added to it. Curve 6 is in the presence of 1 mg/mL of BSA in buffer, while curve 5 is obtained when dextrin-10 (50 mM) is added to it. Curves 5 and 6 have been scaled down by a factor of 6 so as to accommodate them in the same graph for comparison.

and an intensification of its emission upon binding to hydrophobic surfaces of proteins.[13,14] This property has enabled us to perform a binding assay in which the polysaccharide is used to compete with the protein in binding to the dye. Figure 2 shows that while no significant emission changes occur in an aqueous solution of ANS when RNase A (or α-chymotrypsin) is added, addition of a dextrin to this mixture causes a blue-shift and intensification of ANS emission. RNase A and chymotrypsin possess hydrophilic surfaces and thus do not bind the dye and enhance its emission. The effect of dextran is a typical polarity-based one; the behavior of the dextrin chain is, however, different and consistent with the interpretation that it offers a hydrophobic surface for the dye to bind to. We have also found dextrin chains to be able to compete successfully with lysozyme and with ovalbumin for binding to ANS and enhance its emission (data not shown in Figure 2). Contrarily, as Figure 2 shows, bovine serum albumin (BSA) appears to offer too hydrophobic an environment to allow the dislodgement of ANS by the added dextrin.

The average hydrophobicity values of various proteins have been tabulated,[15] and the values for RNase A, lysozyme, ovalbumin, and BSA are 780, 890, 980, and 1000, respectively. The fact that dextrin is able to displace ANS from the first three proteins but not from BSA would suggest that the average hydrophobicity of its binding surface is intermediate between those of ovalbumin and BSA.

**(v) Molecular Model of the Apolar Surface in Dextrin.** The invocation of amphiphilicity would also explain the ability of dextrin chains to uncoil compounds such as substituted alkanoate derivatives that exist in the hairpin form or the self-coiled conformation in water.[8,16,17] Confirmation of this point comes from calculations on energy-minimized conformations on dextrin[5-7]

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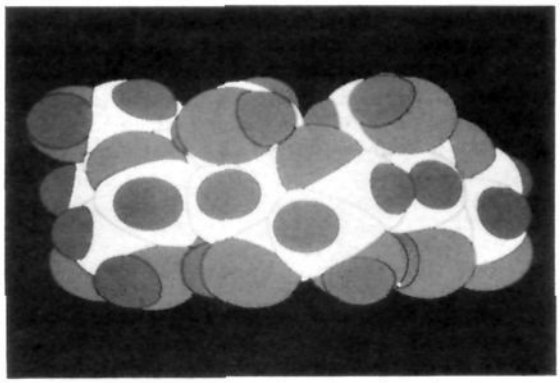

**Figure 3.** Energy-minimized conformation of the dextrin chain; the trimer molecule is illustrated. The small gray balls are hydrogens, the large white ones are carbons, and the large gray ones are oxygen atoms.

(Figure 3). The $\alpha$-1$a$,4$e$-linkage constrains the chain into generating a hydrophobic surface; in contrast, the $\alpha$-1,6-linked and the $\beta$-1,4-linked chains are only hydrophilic. Our calculations have also revealed the presence of amphiphilic surfaces in $\beta$-1,3- and $\beta$-1,4-D-galactans, $\alpha$-1,2-, $\alpha$-1,4-, and $\beta$-1,3-D-mannans, and $\beta$-1,3- and $\alpha$-1,4-D-xylans. The $\beta$-1,4-D-glucan (cellulose) and $\beta$-1,4-D-xylan that we have used in this paper are only hydrophilic.

The concept of hydrophobicity in sugars, unexpected as it may seem, is important to many aspects of their molecular interactions, such as with lectins and with antibodies, and in cell surface events. Johnson et al.[18] have reviewed crystallographic evidence for the occurrence of apolar contacts between oligosaccharide chains and enzymes such as lysozyme, phosphorylase, and the amylases. Surolia and co-workers[19,20] have provided thermodynamic evidence for hydrophobic interactions between sugars and proteins in aqueous solution. Lemieux et al.[21,22] have shown a pattern of interactions between oligosaccharides and antibodies that involves the recognition of an amphiphilic surface presented to the protein by the sugar chain. It would be interesting to investigate whether the hydrophobic effect plays a contributory role in the interaction of cell surface polysaccharides.

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# Mono- and Di-$\mu$-hydrido-Bridged Carbodications in Acyclic Systems

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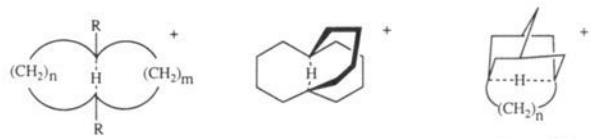
**Abstract:** $\mu$-Hydrido-bridging in carbocations $(\geqslant C\text{---}H\text{---}C\leqslant)^+$ involves a two-electron three-center bond. Such structures have previously been observed only when the two carbons are part of a medium ring (monocyclic, bicyclic, or tricyclic frameworks). Using appropriately constructed carbodications, acyclic systems are now shown to form such structures, including a novel example containing two $\mu$-hydrido-bridged units.

Observable $\mu$-hydrido-bridged solution carbocations have been previously prepared using monocyclic **1**,[1-7] bicyclic **2**,[8-10] and tricyclic **3**[11] ring systems. The existence of monocyclic (medium




**1** **2** **3** n=5,6

R=H or alkyl
n = 3,4,5,6
m =3,4,5

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