Novel Pyrroles from Sulfite-Inhibited Maillard Reactions: Insight into the Mechanism of Inhibition

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In the poorly understood later stages of the Maillard reaction, brown, fluorescent, and highly cross-linked pigments called melanoidins are formed. The inhibition of this process by sulfite has previously been ascribed to carbohydrate/sulfite adduct formation. We have now isolated the major chromophore-containing amino acid/carbohydrate adducts, 1-alkyl-2-formyl-3,4-diglycosylpyrroles (AFGPs (**1a,b** and **2a,b**)) from the sulfite-inhibited Maillard reactions of glucose and of xylose with 6-aminohexanoic acid. AFGPs appear to be derived from two reducing sugars and one amino acid; their precursors have been found in the normal Maillard reaction. The structures of these AFGPs suggest how sulfite inhibits the Maillard reaction: by allowing or favoring production of AFGPs and then by irreversibly reacting with the electrophilic carbons of the AFGPs.

Introduction

The Maillard reaction[1] is the complex sequence of reactions between the amino group of an amino acid or protein and a reducing sugar, such as glucose, leading to poorly characterized, brown, fluorescent, and cross-linked pigments called melanoidins.[2]

Food chemists have done much of the extant work on the Maillard reaction as they sought ways to control the flavor and nutritional value of cooked and preserved foods.[3] Recently, however, the chronic complications of diabetes and aging associated with the long-lived proteins have been linked to the occurrence of the Maillard reaction in vivo. Attempts to isolate these melanoidins have not been very successful.[4]

Our approach to a better understanding of this reaction and toward new methods for its control has been to investigate the chemistry of inhibitors of the Maillard reaction. We thought an inhibitor might be found that worked by "trapping" a reactive intermediate. If the intermediate could then be liberated from the inhibitor and shown to have melanoidin-like spectroscopic characteristics or to produce these characteristics upon exposure to amino acids or proteins, we would have an insight into how the inhibitor works, an indication of a structural component of the melanoidins, and a valuable intermediate in the Maillard reaction pathway.

In the food and pharmaceutical industries, sulfite has been the most widely used agent, until recently,[5] for control of the Maillard reaction.[6] An entire sequence of compounds derived from the interaction of reducing sugars and sulfites has been characterized but the only known carbohydrate/amino acid adducts isolated from the sulfite-inhibited Maillard reaction are mono- and difructosylglycine.

We report here the isolation from sulfite-inhibited Maillard reactions of two members of a new class of adducts containing the carbon backbones of two reducing sugars and an amino acid: glucose-derived 1-alkyl-2-formyl-3,4-diglycosylpyrrole (G-AFGP) and xylose-derived AFGP (X-AFGP). The presence of electrophilic centers in AFGPs gives insight into the mechanism by which sulfite inhibits the Maillard reaction and is consistent with a role in the Maillard reaction pathway.

Results and Discussion

In our model system, 6-aminohexanoic acid (6-AHA) was chosen as an analogue of the lysine residues of proteins. Typically, aqueous solutions of glucose or xylose (2.8 M) and 6-AHA (0.38 M) in sodium phosphate buffer (pH 7.35, 0.5 M in PO_4) in the presence or absence of sodium sulfite (0.2 M) were incubated at 37 °C in the dark for 26 or 8 days, respectively, in tightly closed tubes.

In the presence of sulfite, the result was a yellow solution that had a strong absorption maximum at 300 nm with only minor tailing into the visible region. The sugar, amino acid, sulfite, and buffer were all required for generation of the 300-nm chromophore. The same absorption spectrum was also produced when 6-AHA was replaced with methylamine, α-(*tert*-butyloxycarbonyl)lysine, or poly(L-lysine). In contrast, the sulfite-free solution became dark brown with an absorption maximum at 278 nm, a shoulder at 330 nm, and marked tailing into the visible region.

The 300-nm chromophore from the sulfite-containing reaction mixture of glucose and 6-AHA was purified by anion-exchange resin and then anion FPLC. Enough material was obtained in this manner to determine the structures of the chromophores but a substantial amount was lost when either of the chromatographically and spectroscopically pure chromophores obtained from glucose or xylose was repurified. An HPLC system for analysis was developed that showed the glucose-derived chromophore consisted of four closely eluting components (in a 1:1:4:8 ratio); the xylose-derived chromophore also consisted of four closely eluting chromophores (in a 1:1.3:1.3:1.8 ratio). When either of these samples was exposed for longer periods of time to the eluents, peaks of longer retention time began to appear and the area of the four peaks decreased.

Several observations suggested to us that the chromophore was a pyrrole-2-carboxaldehyde with a free α position. These included lack of retention by cation-exchange resins, formation of a red precipitate upon exposure to acid, loss of the absorbance in the presence of $NaHSO_3$ or $NaBH_4$, the generation of a purple chromophore (504 and 594 nm) with Ehrlich's reagent,[7] and the similarity of the 2,4-DNP derivative to known *N*-alkylpyrrole-2-carbox-

(1) Maillard, L. C. *C. R. Seances Acad. Sci.* **1912**, *154*, 66.
(2) McWeeny, D. J.; Knowles, M. E.; Hearne, J. F. *J. Sci. Food Agric.* **1974**, *25*, 735.
(3) Mauron, J. *Prog. Food Nutr. Sci.* **1981**, *5*, 5.
(4) (a) Cerami, A. *Trends Biochem. Sci. (Pers. Ed.)* **1986**, *11*, 311. (b) Mester, L.; Szabados, L.; Mester, M.; Yadav, N. *Prog. Food Nutr. Sci.* **1981**, *5*, 295.
(5) *The New York Times*, July 9, 1986, p 1.
(6) McWeeny, D. J. *Prog. Food Nutr. Sci.* **1981**, *5*, 395.
(7) Culvenor, C. C. J.; Edgar, J. A.; Smith, L. W.; Tweeddale, H. J. *Aust. J. Chem.* **1970**, *23*, 1869.

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Table I. ^{1}H NMR Spectral Data for X-AFGP (1a–1b, R = H) and G-AFGP (2a–2b) with (Trimethylsilyl)propionic Acid (D_2O) or Tetramethylsilane (DMSO-d_6) as Internal Standard[a]

δ	mult and J (Hz)	no. of H's	assigt
	G-AFGP in D_2O		
1.25	t, J = 7.2	2 H	γ-CH_2
1.55	br m	2 H	β-CH_2
1.77	br m	2 H	δ-CH_2
2.35	br t, J = 7.2 Hz	2 H	α-CH_2
3.41	dd, J = 6.5, 11.9	0.65 H	3′-CH_2
3.50	dd, J = 3.7, 11.8	0.65 H	3′-CH_2
3.62	dd, J = 6.5, 11.8	0.70 H	3′-CH_2
3.79-3.87	m, J = 10.1, 12.0	2 H	4″-CH_2
3.92	m	1 H	2′-CH
4.30	br m	3 H	ε-CH_2 + 2″-CH
4.39	br m	1 H	3″-CH_2
4.87	d, J = 8.2	0.5 H	1″-CH
4.89	d, J = 8.0	0.5 H	1″-CH
5.04	d, J = 7.0	0.5 H	1′-CH
5.05	d, J = 7.4	0.5 H	1′-CH
7.35	d, J = 3.5	1 H	H-5
9.74	d, J = 3.8	1 H	formyl
	Tautomers (2b)		
6.00, 6.19	s		acetyl methine
6.85	m		H-5
	X-AFGP in D_2O		
1.23	m	2 H	γ-CH_2
1.53	m	2 H	β-CH_2
1.77	m	2 H	δ-CH_2
2.16	t, J = 7.4	2 H	α-CH_2
3.44	dd, J = 6.9, 11.8	1 H	3″-CH_2
3.57	dd, J = 3.5, 11.8	1 H	3″-CH_2
3.71	dd, J = 4.7, 11.7	1 H	2′-CH_2
3.79	dd, J = 7.6, 11.7	1 H	2′-CH_2
3.87	dt, J = 3.5, 6.8	1 H	2″-CH
4.31	br t, J = 6.8	2 H	ε-CH_2
4.65	br s	1 H	1″-CH
5.18	dd, J = 4.7, 7.6	1 H	1′-CH
7.30	s	1 H	H-5
9.74	s	1 H	formyl
	X-AFGP in DMSO-d_6		
4.57	d, J = 5.0	1 H	1″-CH
4.93	dd, J = 4.9, 6.7	1 H	1′-CH
	Tautomers (1b, R = H)		
6.03	s		acetyl methine
6.82	m		H-5

[a] abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; δ, chemical shift. Recorded at 300 MHz.

aldehyde 2,4-DNPs.[8] The absorption maximum in the UV spectrum (300 nm, ε 8800)[9] was typical for a pyrrole-2-carboxaldehyde.[10] Additionally, the IR spectra suggested hydroxyl groups, a conjugated aldehyde, and carboxylic acid moieties.

The ^{13}C NMR spectrum of the glucose adduct also indicated a mixture as did the spectrum for the xylose-derived adduct. For both, the alkyl carbons of the hexanoate moiety appeared as five upfield resonances. The signals between 62 and 77 ppm were consistent R_3COH carbons. The downfield limit of the aromatic carbons (120–136 ppm) made both a pyridine and a furan ring unlikely and allowed the presence of a pyrrole. The carbonyl region (178.8, 181.2, and 181.8 ppm) could be explained by a carboxylic acid and at least one strongly shielded carbonyl (as in an electron-rich aldehyde).

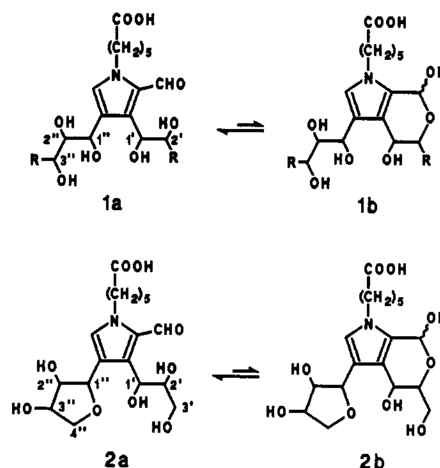

Figure 1. Structures of X-AFGP (1a–1b, R = H) and G-AFGP (2a–2b).

Proton NMR spectral data (Table I) of the glucose adduct revealed the presence of the hexanoate moiety, methylenes and methines characteristic of polyhydroxylic side chains, and two major downfield singlets characteristic of an aromatic resonance (δ 7.35) and an aldehyde (δ 9.74). There were additional minor signals in this region (δ 6.00 (s), 6.19 (s), and 6.85 (m)) that were not removed or altered after repeated purifications. The peak integrations suggested that the compound existed primarily in the form of a pyrrolylic aldehyde in D_2O but that anomeric internal hemiacetal tautomers were also present,[11] to the extent of 25–30% in the glucose adduct and 10–15% in the xylose adduct.

The parent ion (M, Table II), determined by FFII-MS,[12] was deduced to be 401. EI-MS of the peracetylated glucose adduct, the pertrimethylsilylated adduct, and the pertrimethyl-d_9-silylated adduct demonstrated the presence of five hydroxyl groups and one carboxyl group. Exact mass EI-MS of the peracetylated derivative gave an ion of a molecular formula that was most consistent with the loss of acetic acid from a derivative of the molecular formula of $C_{28}H_{37}NO_{14}$. Since the glucose-derived chromophore was shown to have five hydroxyl groups, we deduced its molecular formula to be $C_{18}H_{27}NO_9$. This corresponded to a loss of one water molecule from 1 (R = CH_2OH). Finally, FFII-MS of the BH_4-reduced glucose adduct demonstrated the presence of one carbonyl, a finding that was also supported by incorporation of only one molecule of 2,4-dinitrophenylhydrazine in the nonreduced molecule.

^{1}H NMR decoupling experiments allowed assignment (Table I) of the protons of G-AFGP. Irradiation of the signal at δ 5.05 showed it to be coupled to the multiplet at δ 3.92. The signal at δ 4.88 was coupled to the multiplet at δ 4.27. The multiplet at δ 3.92 was coupled to the multiplet at δ 5.05 and the multiplet centered at δ 3.5. When the signal at δ 4.27 was irradiated, the signals at δ 4.88 and 4.39 collapsed. Irradiation at δ 4.39 simplified the resonances at δ 4.27 and 3.8.

A 2D COSY[13] experiment confirmed the above assignments and allowed assignment of the hexanoate protons. The triplet at δ 2.35 was coupled to the multiplet at δ 1.55.

(8) Kato, H.; Fujimaki, M. *J. Food Sci.* **1968**, *33*, 445.
(9) In MeOH the absorption shifted to 296 nm. In aqueous solutions below 0.05 mM an additional absorption at 273 nm (ε variable) appeared.
(10) (a) Scott, A. I. *Interpretation of the Ultraviolet Spectra of Natural Products*; Macmillan: New York, 1964; p 168. (b) The IR spectrum contained absorption consistent with a conjugated aldehyde (2870, 1645 cm^{-1}), hydroxyl groups (3400–3100, 1100, 1040 cm^{-1}), and a carboxylic acid (1710 cm^{-1}).
(11) Silverstein, R. M.; Bassler, G. C. *Spectrometric Identification of Organic Compounds*; Wiley: New York, 1967; p 110.
(12) FFII-MS, ^{252}Cf fission fragment induced ionization mass spectroscopy; FAB-MS, fast atom bombardment mass spectroscopy; EI-MS, electron impact mass spectroscopy.
(13) Benn, R.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350.

Table II. Mass Spectroscopy (MS) of X-AFGP (1a-1b, R = H) and G-AFGP (2a-2b)[a]

compd	method	ion (m/z)	interpretation
G-AFGP	CI	384	$(M + H - H_2O)^+$
		366	$(M + H - 2H_2O)^+$
		296	$(M + H - H_2O - CO - (HO)CH{=}CH(OH))^+$
	FAB (Li)	408	$(M + Li)^+$
		390	$(M + Li - H_2O)^+$
	FFII (+)	424	$(M + Na)^+$
		396	$(M + Na - CO)^+$
G-AFGP + $(Ac)_2O$	CI	552	$(M + H$ of $(Ac)_5$-G-AFGP $- AcOH)^+$
		492	$(M + H$ of $(Ac)_5$-G-AFGP $- 2AcOH)^+$
	EI	551	$(M$ of $(Ac)_5$-G-AFGP $- AcOH)^+$
	exact mass	551.1906	$C_{26}H_{33}NO_{12}$
G-AFGP + TMSCl	EI	833	$(M$ of $(TMS)_6$-G-AFGP$)^+$
		701	$(M$ of $(TMS)_6$-G-AFGP $- (HO)CH{=}CH(OTMS))^+$
G-AFGP + TMSCl-d_9	EI	887	$(M$ of $(TMS\text{-}d_9)_6$-G-AFGP$)^+$
		746	$(M$ of $(TMS\text{-}d_9)_6$-G-AFGP $- (HO)CH{=}CH(O\text{-}TMS\text{-}d_9)^+$
G-AFGP + $NaBH_4$	FFII (+)	448	$(M$ of (G-AFGP + 2H) + 2Na - H$)^+$
	FFII (-)	425	$(M$ of (G-AFGP + 2H) + Na - H$)^-$
X-AFGP	FFII (+)	404	$(M + 2Na - H)^+$
		382	$(M + Na)^+$
	FFII (-)	380	$(M + Na - 2H)^-$
	CI	340	$(M - H_2O - H)^-$
		323	$(M - 2H_2O - H)^-$
	exact mass	323.1363	$C_{16}H_{21}NO_6$

[a] Abbreviations: m/z, mass-to-charge ratio; FFII, ^{252}Cf fission fragment induced ionization MS in either (+) positive or (−) negative mode; CI, chemical ionization MS using isobutane as the reactant gas; FAB, fast atom bombardment MS; EI, electron impact MS; exact mass, EI-MS with perfluorokerosene as internal standard; $(Ac)_2O$, acetic anhydride; TMSCl, trimethylsilyl chloride; TMSCl-d_9, perdeuteriated trimethylsilyl chloride.

Also, this experiment demonstrated the coupling between the multiplet at δ 4.30 and the multiplet at δ 1.77 and between the triplet at δ 1.25 and the signals at δ 1.55 and 1.77.

We were then able to assign the structure of **2a–2b** (Figure 1) to G-AFGP. Compound **2** very likely was derived from 1 (R = CH_2OH) via attack at C1 of the 1,2,3,4-tetrahydroxybutyl group by the terminal hydroxyl group to form the cyclic ether.

For the xylose adduct, all resonances were fully resolved and coupling patterns were consistent with a 1,2-dihydroxyethyl group and a 1,2,3-trihydroxypropyl group attached to an aromatic ring. We assigned structure **1a–1b** (R = H) to the xylose adduct, named X-AFGP. The parent ion (FFII-MS) and the exact mass EI-MS confirmed this conclusion.

Conclusions

Figure 2 shows the proposed pathway for formation of G-AFGP from the reaction of 3-deoxyglucosone (**4**) and the Amadori product of 6-AHA (**3**). Amadori products (mono- and di-1-deoxy-2-ketosyl amino acids) have been shown to form readily when reducing aldoses are incubated with amino acids, with[14] and without[15] sulfite, and are considered to be the starting point of the nonenzymatic browning portion of the Maillard reaction. We isolated compound **3** from the reaction mixture of glucose, 6-AHA, and sulfite; **4** has been shown to arise from the decomposition of difructosyl amino acids.[16] Nakano et al.[17] have isolated an enamine (similar to **6**) derived from an amino ketone and a β-keto ester and have obtained a pyrrole in good yield. Cyclization and dehydration of **6** would form pyrrole **8**. Loss of an additional molecule of water would form G-AFGP. The chromophore reported by Anet[14] may have been an AFGP derived from glycine and glucose in the presence of sulfite.

(14) Anet, E. F. L. J. *Aust. J. Chem.* **1959**, *12*, 491.
(15) Anet, E. F. L. J. *J. Am. Chem. Soc.* **1960**, *82*, 1502.
(16) Anet, E. F. L. J. *Aust. J. Chem.* **1960**, *13*, 396.
(17) Nakano, H.; Umio, S.; Kariyone, K.; Tanaka, K.; Kishimoto, T.; Noguchi, H.; Ueda, I.; Nakamura, H.; Morimoto, Y. *Tetrahedron Lett.* **1966**, *7*, 737.

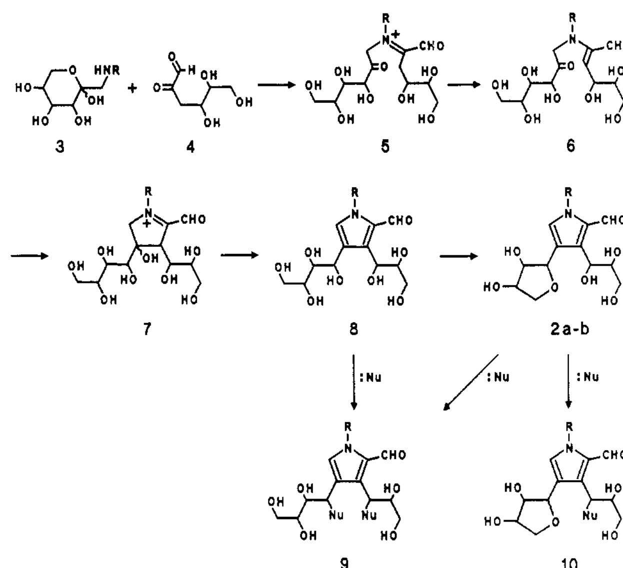

Figure 2. Proposed pathway of formation of G-AFGP and reaction with a nucleophile (:Nu).

AFGPs resemble structurally a number of pyrrolylcarbinols,[18] which are known to act as mono- and as bisalkylating agents[19] by virtue of an α-hydroxyalkyl group attached to C3 or C4 of the pyrrole.[20] AFGPs should therefore react similarly with nucleophiles (Nu) such as amino acids, proteins, or sulfite ion.[21] Previously, the ability of sulfites to inhibit browning and the gradual loss of that ability during the incubation were attributed only to reversible and irreversible reactions of sulfite with different reducing sugar derivatives formed during the

(18) (a) Mattocks, A. R.; Bird, I. *Toxicol. Lett.* **1983**, *16*, 1. (b) Mattocks, A. R. *Chem.-Biol. Interact.* **1982**, *5*, 227. (c) Butler, W. H.; Mattocks, A. R.; Barnes, J. M. *J. Pathol.* **1970**, *100*, 169.
(19) (a) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241. (b) Anderson, W. K.; Heider, A. R. *J. Med. Chem.* **1986**, *29*, 2392.
(20) Culvenor, C. C. J.; Edgar, J. A.; Smith, L. W.; Tweeddale, H. J. *Aust. J. Chem.* **1970**, *23*, 1853.
(21) Gilbert, E. E. *Sulfonation and Related Reactions*; Wiley-Interscience: New York, 1965; pp 146–8.

Maillard reaction and not to any amine-containing Maillard reaction products.[22]

We suggest that the mechanism of sulfite inhibition of the cross-linking and browning of the Maillard reaction also involves formation of AFGPs from early Maillard reaction products followed by irreversible reaction of sulfite ion with the electrophilic carbons of AFGP to form compounds **9** and **10** (Nu = SO_3H). These sites in the AFGP are then blocked from reaction with other nucleophiles that might be present such as an amino acid or a protein. Efforts are under way to isolate an AFGP/bisulfite adduct, to determine whether AFGPs are present in the noninhibited Maillard reaction, and to learn the fate of AFGPs in the presence of amino acids and proteins.[23]

Experimental Section

The sodium phosphate buffer was 0.5 M in phosphate and adjusted to pH 7.35 with NaOH and then filtered through a 0.2-μ membrane. The IR spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. The UV spectra were obtained on a Hewlett-Packard 8450A spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Nicolet/Oxford NT300 (300 MHz) instrument in D_2O with (trimethylsilyl)propionic acid or dioxane as a reference. Final purification of the AFGPs was performed with a Pharmacia FPLC and a Mono Q HR10/10 anion-exchange column. HPLC analysis was performed with a Hewlett-Packard 1084B liquid chromatograph with a HP 79850B LC terminal. A Supelcosil C18 reverse-phase column (25 cm × 4.6 mm, 5-μm packing) was used at a flow rate of 1 mL/min with detection at 300 nm and elution with 100 mM HOAc (A1), 100 mM HOAc in 5% MeOH (A2), or 100 mM HOAc in 50% MeOH (B).

Generation and Purification of G-AFGP (2a–2b). Glucose (5 g, 28 mmol) was dissolved in 10 mL of sodium phosphate buffer. Sodium sulfite (250 mg, 2.0 mmol) and 6-AHA (500 mg, 3.8 mmol) were added and the pH of the solution was adjusted to 7.35. The solution was placed in the dark at 37 °C in a tightly closed tube. After 26 days the incubation mixture was added to a column containing 50 g of Dowex AG 1X4 anion-exchange resin (acetate form, 100–200 mesh). Elution with H_2O (1 L) gave a fraction containing glucose and the Amadori product of 6-AHA. After an additional 400 mL of 100 mM HOAc, material strongly absorbing at 300 nm eluted. This fraction was neutralized with ammonium hydroxide and lyophilized to yield 380 mg (25%) of a viscous, brown oil. A portion (55 mg) of this material was purified by FPLC anion chromatography (30-min gradient from 0 to 50 mM ammonium acetate in 5% MeOH) to yield a hygroscopic, amorphous, dull yellow solid (21 mg, 38%). This material was sensitive to the chromatographic conditions: only 50% of the material purified by anion FPLC was recoverable when the spectroscopically pure compound was rechromatographed. IR (neat) 3400–3100, 2870, 1710, 1645, 1100, 1040 cm^{-1}; MS, see Table II; ^1H NMR, see Table I; ^{13}C NMR[24] 181.8 + 181.2, 178.8, 135.9 + 135.8, 131.1 + 130.7, 128.2 + 127.3, 121.6 + 120.5, 76.6 + 76.2, 75.4 + 75.1, 74.4 + 73.9, 72.2 + 71.6, 70.5, 66.9 + 66.8, 62.7 + 62.6, 48.9, 33.8, 30.0, 25.0, 23.7 ppm; HPLC; 30-min gradient from 10% Al to 90% B. The chromatogram consisted of four peaks (94.5%) at 17.9, 18.2, 19.2, and 19.8 min in a 1:1:4:8 ratio. The area of these peaks was seen to decrease when the sample was exposed for longer periods of time to the eluents.

Generation and Purification of X-AFGP (1a–1b, R = H). Xylose (1.14 g, 7.6 mmol) was dissolved in 10 mL of sodium phosphate buffer. Sodium sulfite (480 mg, 3.8 mmol) and 6-AHA (500 mg, 3.8 mmol) were added and the pH was adjusted to 7.35. The solution was placed in the dark at 37 °C in a tightly closed tube. After 8 days, the incubation mixture was added to 50 g of anion-exchange resin. The 100 mM HOAc eluate (1 L) was collected, neutralized with ammonium hydroxide, and lyophilized to yield 194 mg (14%) of a viscous, brown oil. FPLC purification (30-min gradient from 0 to 50 mM ammonium acetate in 5% MeOH) of 27 mg of this material gave 8.3 mg (31%) of a yellow, hygroscopic solid. IR (neat) 3400–3100, 2870, 1710, 1645, 1100, 1035 cm^{-1}; MS, see Table II; ^1H NMR, see Table I; ^{13}C NMR[24] 182.0 + 181.7, 179.2, 135.6 + 135.0, 131.7 + 131.4, 127.6 + 127.4, 123.0 + 122.6, 75.0, 74.5 + 74.4, 68.1 + 67.7, 66.2 + 66.0, 63.1 + 62.6, 48.9, 33.8, 30.0, 25.0, 23.8 ppm; HPLC, 30-min gradient from 10% A2 to 75% B. The chromatogram consisted of four peaks (85%) at 14.1, 14.3, 14.9, and 15.3 min in a 1:1.3:1.3:1.8 ratio. The area of these peaks was seen to decrease when the sample was exposed for longer periods of time to the eluents.

Registry No. 1a, 113778-91-9; **1b**, 113792-87-3; **2a**, 113778-89-5; **2b**, 113778-90-8; 6-AHA, 60-32-2; D-glucose, 50-99-7; D-xylose, 58-86-6.

(22) Anet, E. F. L. J.; Ingles, D. L. *Chem. Ind. (London)* **1964**, 1319.

(23) This work has been supported in part by the National Institutes of Health (Grant AM19655), The Brookdale Foundation, and Telos Development Corp. We wish to thank Drs. F. Aladar Bencsath (EI-MS and CI-MS) and Brian T. Chait (FFII-MS) of The Rockefeller University Mass Spectrometric Biotechnology Resource Center and Dr. Karst Hoogsteen (EI-MS and FAB-MS) of The Merck Institute for Therapeutic Research for obtaining mass spectrograms. We also thank Dr. David Cowburn and Francis Picart for assistance with the NMR work and Dr. Michael Yamin for help with the manuscript.

(24) Only the major resonances are presented. For both X-AFGP and G-AFGP, there were additional, smaller resonances from the pyrrolyl and glycosyl carbons of the minor isomers.

Notes

A Remarkably Simple Perfluoroalkylation in the Presence of an Electron Mediator

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Perfluoroalkyl iodides are useful reagents for the perfluoroalkylation of organic molecules.[1-10] However, synthetic methods for the compounds with long perfluoroalkyl chains in the presence of a metal (Zn, Mn, Mg, Al, or Fe) usually require some type of activation, i.e. ultrasonic ir-

(1) *Organic Fluorine Chemistry*; Sheppard, W. A., Sharts, C. M., Eds.; Benjamin Inc.: New York, 1969.

(2) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186.
(3) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1679.
(4) Kitazume, T.; Ishikawa, N. *Nippon Kagaku Kaishi* **1984**, 1725.
(5) O'Relly, N. J.; Maruta, M.; Ishikawa, N. *Chem. Lett.* **1984**, 517.
(6) Sibille, S.; D'Incan, E.; Lefort, D.; Perichon, J. *Tetrahedron Lett.* **1986**, *27*, 3219.
(7) Burton, D. J.; Wiemers, W. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014.
(8) Soueni, A. E.; Tedder, J. M.; Walton, J. C. *J. Fluorine Chem.* **1981**, *17*, 51.
(9) Wakselman, M. *Tetrahedron* **1981**, *37*, 315.
(10) (a) Feiring, A. E. *J. Org. Chem.* **1983**, *48*, 347. (b) Feiring, A. E. *Ibid.* **1985**, *50*, 3269.

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