Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also acknowledge support by the National Science Foundation (via its EPSCoR program), the Louisiana Board of Regents, and the Tulane University Center for Bioenvironmental Research.

Torsional Effects in Glycoside Reactivity: Saccharide Couplings Mediated by Acetal Protecting Groups†,‡

Bert Fraser-Reid,* Zufan Wu, C. Webster Andrews,§ and Evan Skowronski

Department of Chemistry
Paul M. Gross Chemical Laboratory, Duke University
Durham, North Carolina 27706

J. Phillip Bowen

Laboratory for Molecular Modelling
Division of Medicinal Chemistry and Natural Products
School of Pharmacy
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599
Received October 9, 1990

The use of protecting groups in synthetic carbohydrate chemistry is unavoidable, and since esters and ethers are chemically different, *O*-acyl and *O*-benzyl groups are favorites for "temporary" and "persistent" protection,[1] respectively. However, these groups profoundly affect the reactivity of glycosyl donors,[2] and under the armed/disarmed rubric,[3] we recently disclosed[4] that these reactivity differences provided a basis for chemoselective assembly of oligosaccharides.[5] Cyclic acetals[6] such as shown in Chart I are also temporary[1] protecting groups, and the fact that 1,3-dioxane or 1,3-dioxolane derivatives can be formed competitively[7,8] has made their use a mainstay of synthetic carbohydrate chemistry.[9] However, in this manuscript we disclose that cyclic acetals profoundly affect pyranoside reactivity, thereby paving the way for an armed/disarmed protocol based on torsional effects, complementary to that disclosed earlier[4] which was based on electronic effects.[10]

The ability to "oxidatively hydrolyze" *n*-pentenyl glycosides (NPGs) under neutral conditions allows us to cleave the anomeric center without affecting other acid-sensitive functionalities,[11,12] and in the course of exploiting this potential,[12] we were struck by the range of relative reaction rates of compounds **1b–4b** (Table I, entry a). These results suggested that it might be possible to use cyclic acetals not only for the traditional protecting group role but also to induce chemoselectivity in the formation of cyclic oxo carbenium ions.

Our first requirement was to carry out a sophisticated conformational analysis as a basis for predicting reactivity. While the ground-state conformations of the starting pyranosides were expected to be $^4C_1$ chairs, those for the oxo carbenium ions had to be determined. PM3[13] was chosen for this task, because of its capability to analyze both ground states and reactive intermediates. The C_5O_5–C_1C_2 dihedral angle (ω) is ideally 0° in oxo carbenium ions, and hence the conformational energies of the ions derived from the tetra-*O*-methyl glycosides **1a**, **5a**, and **7a** were determined. The energy curves for the oxo carbenium ions derived from **1a**, **5a**, and **7a**, as determined by PM3, are parabolic with minima at 0°, which confirms planarity of the $C_5O_5^+$–C_1C_2 segments with perfect π overlap. For the conformationally restrained glucosides **3a** and **4a**, the energy curves are still parabolic but the minima have been shifted to +20°.

With PM3 data therefore available for both glycosides and oxo carbenium ions, the relative activation energies (E_a) could now be computed,[14] and these are shown in Table I. Their validity could be checked against known experimental rates of hydrolysis. Thus the computed activation energies for **1a**, **3a**, and **4a** are in keeping with the experimental rates for oxidative hydrolysis[11,12] of **1b**, **3b**, and **4b**, respectively (Table I, entries a and b). Similarly the reactivity trends galacto > manno > gluco of Isbell and Frush[15] were upheld in our studies (Table I, entries c and d).

The computed values in Table I therefore implied that acetalated species such as **2**, **6**, and **8** should react less readily than their torsion-free analogues **1**, **5**, and **7**, respectively. These predictions were borne out by the rates for the oxidative hydrolysis of **1b**/**2b**, **5b**/**6b**, and **7b**/**8b** (Table I, entry c). The corresponding computed values (Table I, entry d) show how well the $\Delta\Delta E_a$ values predict these reactivity trends.

These developments suggest a strategy for disarming glycosyl donors based solely on the presence of acetal protecting groups. Indeed it proved possible to chemospecifically couple glucosides **1b** + **2c**,[16] mannosides **5b** + **6c**, and galactosides **7b** + **8c** to give **9**, **10**, and **11**, respectively,[17] with no evidence for self-condensation

†This study was supported by grants from the National Science Foundation (CHE 8920033), the National Institutes of Health (GM-41071), and Glycomed, Inc. Alameda, CA.

‡Taken in part from the Year IV Research Report of E.S., Duke University, 1990.

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(17) Experimental procedure: In a typical experiment the acetalated alcohol donor (e.g., **6c**, 1.5 mM), the glycosyl donor (e.g., **5b**, 1.0 mM), and iodonium dicollidine perchlorate[18] (2.0 mM) were dissolved in THF (10 mL). The reaction was followed by TLC (petroleum ether/ethyl acetate mixtures, 3:1) until the alcohol disappeared or until there was no further change. The R_f of the disaccharide usually fell between the two reactants. The coupling was complete in 1–2 h. The reaction mixture was diluted with anhydrous ether and filtered and the filtrate washed with 10% aqueous sodium thiosulfate solution and brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography afforded the cross-coupled disaccharides **9**, **10**, and **11** in 52%, 41%, and 54% unoptimized yields. Identification of the cross-coupled products was facilitated by the fact that both reactants had different protecting groups. On this basis, we have failed to detect products resulting from self-coupling of the acetalated alcohols.

0002-7863/91/1513-1434$02.50/0

Chart I

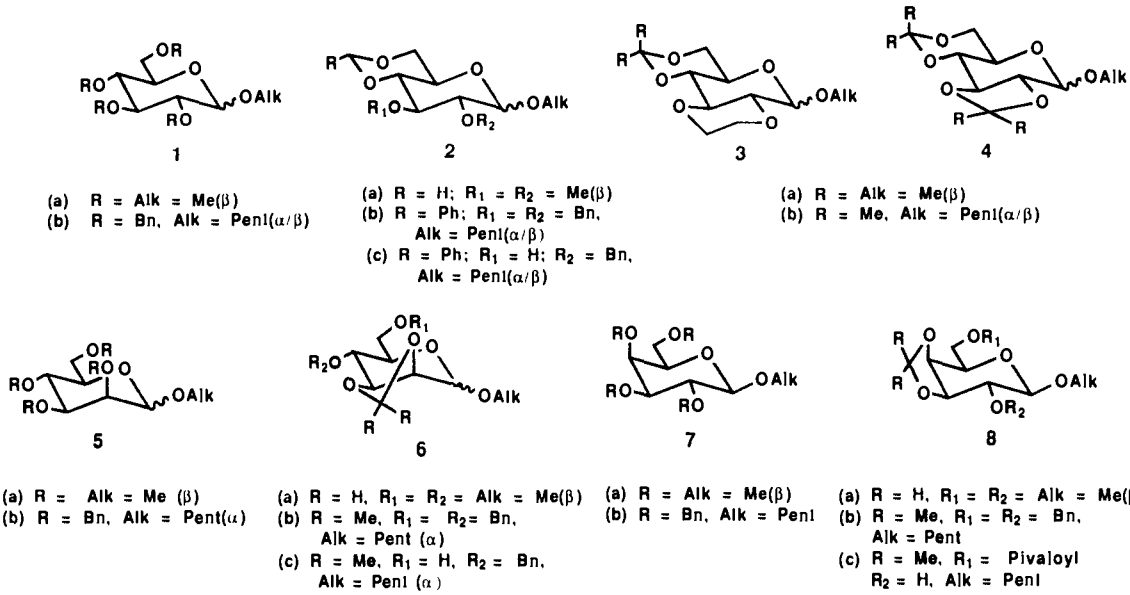
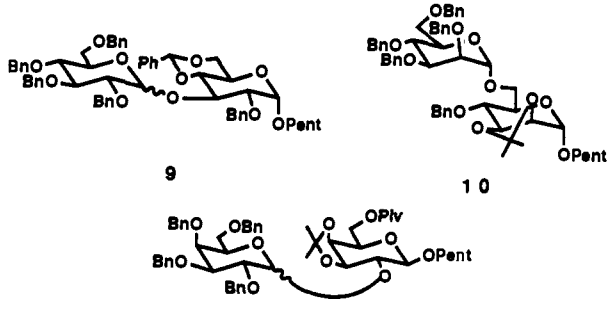


Table I. Comparisons of Experimental Relative Rates of Hydrolysis with Computed Relative Activation Energies (E_a) for Some Acetalated Versus Nonacetalated Glycosides

(a) relative rates[a]	**1b** 1	**2b** 2.0	**3b** 6.6	**4b** 22.0		
(b)[b,c] computed	**1a** 0.0 kcal	**2a** 6.5 kcal	**3a** 9.4 kcal	**4a** 16.9 kcal		
	glucosides		mannosides		galactosides	
	non-acetalated	acetalated	non-acetalated	acetalated	non-acetalated	acetalated
(c) relative rates[c]	**1b** 3.0	**2b** 6.0	**5b** 1.5	**6b** 10.0	**7b** 1	**8b** 8.0
(d) computed	**1a** 5.8 kcal	**2a** 12.3 kcal	**5a** 4.0 kcal	**6a** 6.9 kcal	**7a** 0.00 kcal	**8a** 6.3 kcal
	$\Delta\Delta E_a$ = 6.5		$\Delta\Delta E_a$ = 2.9		$\Delta\Delta E_a$ = 6.3	

[a] From oxidative hydrolysis of *n*-pentenyl glycosides.[11,12] Based on the TLC analysis and **1b** being 3 h. [b] For method of calculation, see footnote 18. [c] From acid-catalyzed hydrolyses.[19] Based on **7b** being 1.0 h.

of the alcohol donor in any of the three cases. The absence of such products is undoubtedly subject to the same rationalization, recently advanced by us, as for the electronic armed/disarmed phenomenon.[10]



The above results indicate that when acetals are used as temporary protecting groups,[1] their profound effects on glycoside reactivity must be taken into account. The correspondence between computed and experimental values in Table I encourages the hope that PM3 data can be used routinely as a *qualitative* guide to determine how or whether torsional effects can be exploited in an armed/disarmed sense. Further exploration of this methodology is underway.

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Reactions of Phenylfluorocarbene with Lithium Salts. Absolute Kinetics of Carbenoid Formation†

Robert A. Moss,* Hong Fan, Ramaswamy Gurumurthy, and Guo-Jie Ho

Department of Chemistry
Rutgers, The State University of New Jersey
New Brunswick, New Jersey 08903

Received October 10, 1990
Revised Manuscript Received December 18, 1990

The noun *carbenoid* was offered in 1964 to describe "intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species."[1] The intermediates in question were α-halo lithium derivatives of toluene. Subsequently, α-halo lithium chemistry was broadly developed, especially by Köbrich,[2] while structural features were elucidated by NMR.[3] The chemistry of α-halo lithium carbenoids remains topical, with emphases on theory,[4] synthesis,[5]

† Dedicated to Professor Ronald Breslow on the occasion of his 60th birthday.

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