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Stereoselective Epoxidation of 4-Deoxypentenosides: A Polarized-π Model

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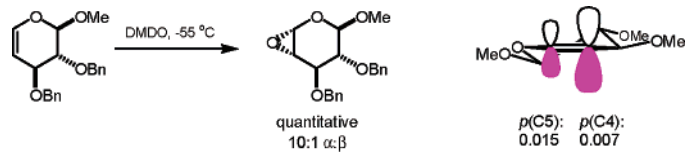
ABSTRACT



The high facioselectivity in the epoxidation of 4-deoxypentenosides (4-DPs) by dimethyldioxirane (DMDO) correlates with a stereoelectronic bias in the 4-DPs' ground-state conformations, as elucidated by polarized-π frontier molecular orbital (PPFMO) analysis.

4-Deoxypentenosides (4-DPs) are unsaturated pyranoside derivatives with structural homology to glycals but bear heteroatomic substituents at the anomeric position rather than carbon. Studies from our laboratory have shown that 4-DPs and glycals have similar reactivity profiles, with intriguing ramifications for carbohydrate and natural product synthesis.[1] For example, the 4-DP derived from α-methyl glucoside (α-*Glc*-4-DP, **1**) can be epoxidized stereoselectively at low temperatures by dimethyldioxirane (DMDO), followed by nucleophilic additions to produce pyranosides with rare or unnatural configurations.[2]

Additional DMDO oxidation studies involving 4-DPs derived from the methyl glycosides of glucose, mannose, and glucosamine (**2**−**10**) reveal a striking trend with respect to stereochemical outcome (see Table 1).[3] The facioselective epoxidation proceeds anti to two of the three substituents on the 4-DP reactant, producing epoxyacetals in essentially quantitative yield in nearly all cases.[4] This empirical "majority rule" is independent of the relationship among contiguous stereocenters (**1**−**4**) or transannular substituents with different electronic character (**5**−**8**, **10**) and cannot be simply explained by previously established stereodirecting effects.[5−7] The epoxidations of α-methyl 4-DPs **1**, **5**, and **7** proceed syn rather than anti with respect to the C3 stereocenter, which precludes the allylic oxygen from being the dominant director.[8] The direct involvement of local steric effects is also unlikely: for instance, in the ground-state conformation of β-methyl 4-DP **2**, both density functional theory (DFT) calculations and NMR coupling constant analysis[9] suggest

(1) (a) Tolstikov, A. G.; Tolstikov, G. A. *Russ. Chem. Rev.* **1993**, *62*, 579−601. (b) Ferrier, R. J.; Hoberg, J. O. In *Adv. Carbohydr. Chem. Biochem.*; Horton, D., Ed.; Academic Press: New York, 2003; Vol. 58, pp 55−119.

(2) (a) Boulineau, F. P.; Wei, A. *Org. Lett.* **2002**, *4*, 2281−2283. (b) Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2004**, *69*, 3391−3399.

(3) The synthesis of compounds **5**−**10** will be reported elsewhere.

(4) The anticipated β-epoxide from 2-dibenzylamino-4-DP derivative **9** could not be isolated presumably due to its cross reactivity with the C2 dibenzylamino group, although the α-epoxide derived from **10** was stable upon isolation.

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(6) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117. (b) Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchison, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204−2210.

(7) Washington, I.; Houk, K. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 4485−4488.

(8) In comparing these results with earlier reports on the DMDO oxidation of glycals, we note that a gulal derivative (stereoanalogue of **1**) produced a 1:1 mixture of stereoisomers at 0 °C: Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661−6666.

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Table 1. Stereoselective DMDO Epoxidation of 4-DPs

entry	react cond[a]	product[b]	α:β
1[c]	A		1:10
2	A		10:1
3[c]	B		>20:1
4	B		15:1
5	C		1:10
6	A		10:1
7	A		<1:20
8	A		10:1
9	C	n/a[d]	
10	C		>20:1

[a] Reaction conditions: (A) DMDO (2−3 equiv), −55 °C, 2 days; (B) DMDO (2 equiv), 0 °C, 15 min; (C) DMDO (1.1 equiv), −55 °C, 1 day. [b] Stereochemistry determined by ^{1}H NMR analysis after S_N2 ring opening with EtSLi. [c] Reported previously in ref 2a. [d] See ref 4.

that all substituents are preferentially pseudoequatorial and project away from the site of epoxidation.

Transition-state geometries for the addition of dioxirane to the α or *β* face of the *β-Glc*-4-DP triol (the parent structure of **2**) were calculated at the B3LYP/6-31G* level of theory, followed by computation of B3LYP/6-311+G(2df,2p) single-point energies (see Figure 1). Addition to either face proceeds

(9) See Supporting Information for details.

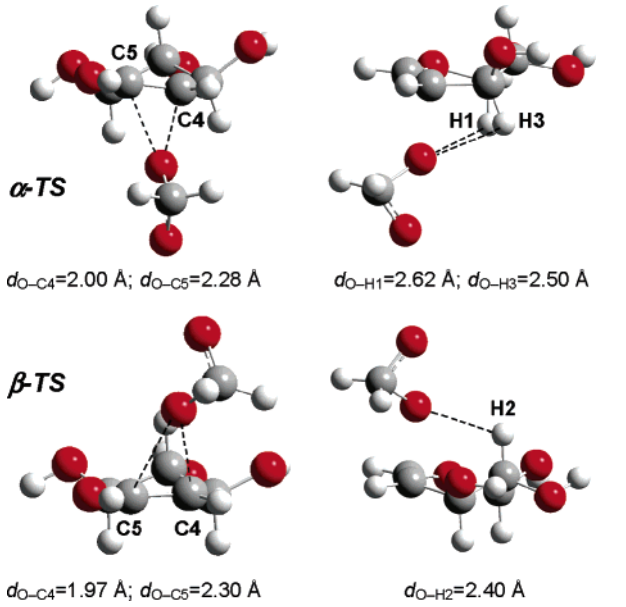

Figure 1. Front and side views of the transition-state geometries for dioxirane addition to *β-Glc*-4-DP triol, the parent structure of **2**, based on DFT-B3LYP calculations (α-TS favored over *β*-TS, but differences in torsional strain or O···H interactions appear to be insignificant). Output files are available upon request.

through an early transition state with an asynchronous spiro geometry and very little change from the 4-DP's initial ground-state conformation, in accord with earlier studies of dioxirane addition to simple alkenes and enol ethers.[10] The difference in the activation energies of α- and *β*-epoxide formation compares favorably with the experimental results for **2** ($\Delta G^{\ddagger}_{calcd}(\alpha)$ and $\Delta G^{\ddagger}_{calcd}(\beta) = 18.7$ and 20.8 kcal/mol, using the 6-31G* basis set).

The transition-state geometries do not reveal specific enthalpic interactions which would explain the preference for α epoxidation. No significant differences in torsional strain could be determined,[6] and the axial hydrogens do not approach the incoming oxygen, ruling out the possibility of CH···O hydrogen bonding (see Figure 1).[7] On the other hand, the early transition states and low activation energies allow for the possibility of an intrinsic polarization in *π*-orbital reactivity. We thus considered theoretical models that could describe stereoelectronic bias in the *π*-orbitals of the 4-DPs based on their ground-state conformations.

We found the polarized-*π* frontier molecular orbital (PPFMO) approach developed by Dannenberg to be appealing in this regard,[11] and its implementation into DFT calculations proved to be straightforward.[9] Briefly, the PPFMO approach is a perturbation method which desymmetrizes 2p orbitals by introducing *s*-functions near each lobe

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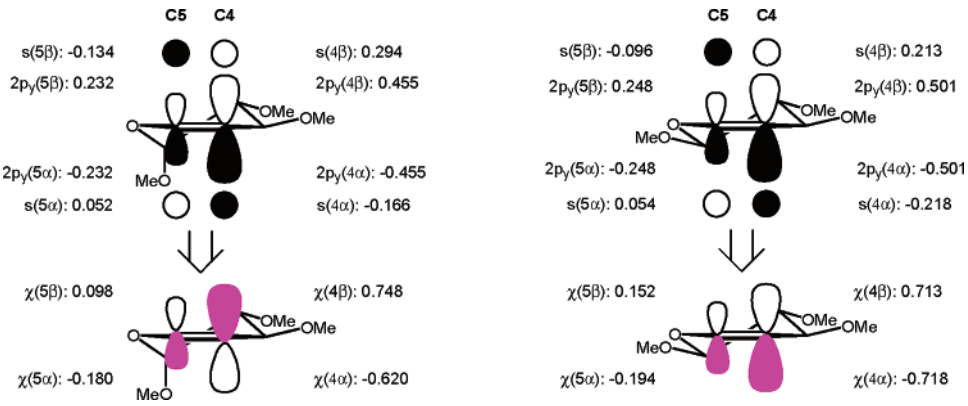

Figure 2. PPFMO analysis of α- and *β-Glc*-4-DP trimethyl ether (analogues of **1** and **2**). Two *s*-functions are superimposed onto the 2p$_y$ orbitals at C4 and C5 to produce an asymmetric function χ, whose coefficients can be used to derive *p*, the net electronic polarization per orbital (in purple). 2p orbitals and added *s*-functions are spatially separated for clarity. ± values refer to the sign of the coefficients for each lobe (open/filled).

(see Figure 2).[11] The linear combination of these orbitals yields an asymmetric function whose coefficients (c_α and c_β) describe the polarization of each 2p orbital. PPFMO analysis is qualitative but not computationally demanding and has been used to examine the facioselectivity of electrophilic additions to cyclic enol ethers such as glycals.[12] However, the validity of the predicted outcomes depends strongly on the similarities of the reactants' ground-state and transition-state structures, which appears to be the case in the epoxidation of 4-DPs.

Table 2. PPFMO Analysis of 4-DP Permethyl Ethers[a]

compd	atom	c_α[b]	c_β[b]	p[c]
α-*Glc*-4-DP (**1**)	C4	−0.620	0.748	0.175 (β)
	C5	−0.180	0.098	0.023 (α)
β-Glc-4-DP (**2**)	C4	−0.718	0.713	0.007 (α)
	C5	−0.194	0.152	0.015 (α)
α-*Man*-4-DP (**3**)	C4	−0.616	0.615	0.002 (α)
	C5	−0.116	0.095	0.004 (α)
β-Man-4-DP (**4**)	C4	−0.641	0.575	0.081 (α)
	C5	−0.185	0.235	0.021 (β)
α-*Glc*-2-deoxy-4-DP (**11**)	C4	−0.719	0.719	0.000
	C5	−0.201	0.180	0.008 (α)

[a] All structures optimized by DFT-B3LYP calculations (6-31+G(d,p)) prior to insertion of *s*-functions. [b] Each coefficient is calculated as the linear combination of *s*-function and 2p$_y$; ± values refer to the sign of the coefficients for each lobe. [c] Polarization of each orbital in parentheses. See Supporting Information for procedures.

Applying the PPFMO theory to the permethyl ethers of **1**−**4** yields c_α and c_β for the occupied 2p orbitals and the polarization in electron density for each orbital, calculated as $p = |c_\alpha^2 - c_\beta^2|$ (see Table 2). In all cases, the combined polarizations at C4 and C5 agree with the epoxidation outcomes. The influence of C4 outweighs that of C5 in cases of opposing polarizations, which coincides with its dominant role in the asynchronous transition state. Overall, these calculations support a significant stereoelectronic bias in the π-bond reactivity of the 4-DPs.

To determine if PPFMO analysis could be used in a predictive manner, we further considered the epoxidation of 4-DP derivatives with only two substituents. For example, the epoxidation of 2,4-dideoxypent-4-enoside derivative **11** is subject to competing directing effects from the anomeric and allylic substituents, and its outcome cannot be predicted on the basis of a "majority rule". However, PPFMO calculations performed on the DFT-optimized structure suggest 2p$_y$ polarization in the α direction (see Table 2 and Figure 3, left). This was confirmed by the DMDO oxidation of **11** followed by S_N2 ring opening with MeOH, which produced the corresponding C4 alcohol **12** with high stereoselectivity (α: β > 10:1).

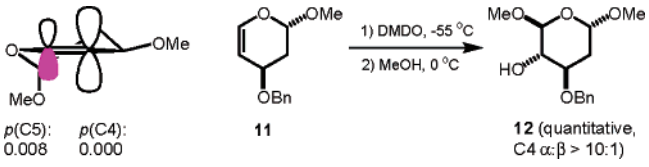

Figure 3. Left: PPFMO analysis of 2-deoxy-4-DP dimethyl ether. Right: stereoselective epoxidation of 2-deoxy-4-DP derivative **11**.

These studies indicate that the facioselectivity in 4-DP epoxidation can be predetermined by the polarized-π model. The absence of local interactions in the transition state makes this reaction especially well-suited for PPFMO analysis, enabling stereochemical outcome to be correlated with ground-state electronic structure.

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Supporting Information Available: Experimental procedures and NMR spectra and characterization related to 4-DP epoxidation and S_N2 ring opening (PDF); output log files for DFT geometry optimizations and transition-state and PPFMO calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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