Polarized-π Frontier Molecular Orbital (PPFMO) and Experimental Studies of Facial Selectivity in Electrophilic Attacks on Substituted Alkenes

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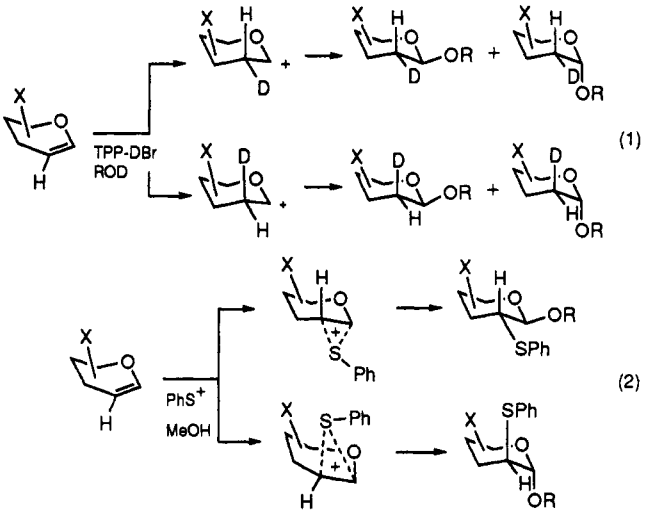
Polarized π-frontier orbital theory (PPFMO) is applied to the protonation and sulfenylation of several dihydrofurans and dihydropyrans of importance in sugar chemistry. The PPFMO method correctly predicts the observed selectivities for all experimentally observed cases, two of which are reported here for the first time.

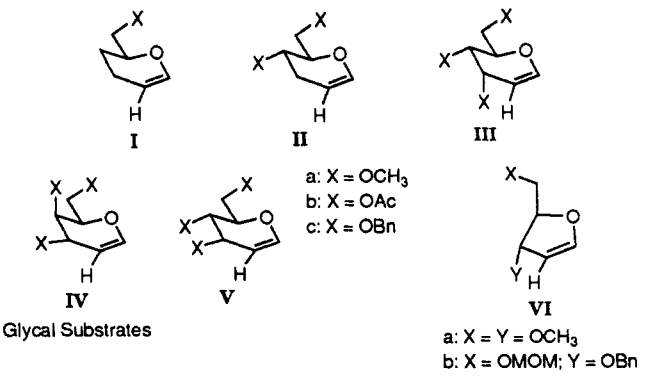
The problem of predicting and controlling diastereofacial selectivity is central to modern synthetic procedures. Several groups have suggested methods to predict the direction of attack in nucleophilic reactions, primarily carbonyl reductions. These suggestions have been thoughtfully reviewed by le Noble.[1] Two of us have recently proposed a new procedure involving polarized-π frontier molecular orbital (PPFMO) theory to predict diastereofacial selectivities.[2] This procedure involves desymmetrizing the π-orbitals by superimposing two independent gaussian functions onto each p-orbital in the π-system of concern. One of these gaussians is superimposed upon each lobe of the p-orbital. As these new functions have coefficients of different magnitudes, the difference in the magnitudes (actually the sum of the coefficients, as they generally have opposite signs) between them is used to define the polarization of the π-orbitals. The direction of the polarization indicates the preferred face for attack.

We have previously reported the successful application of this procedure to an extensive body of nucleophilic reactions.[3] While the PPFMO method ought to be applicable to electrophilic, as well as, nucleophilic reactions, several of the earlier methods were formulated specifically with nucleophilic reactions in mind. In this paper, we turn our attention to electrophilic reactions. In particular, we focus upon the protonation and sulfenylation of carbon-carbon double bonds in dihydrofurans and dihydropyrans derived from sugars (eqs 1 and 2). We chose substrates **I-VI** for study for several reasons. First, the effect of alkoxyl groups on the ring with differing stereochemical relationships to the reactive center, as well as changing ring size, can be assessed. Second, analogs to all the compounds studied theoretically are accessible for experimental study. The (kinetically controlled) diastereofacial selectivities of the sulfenylations of the entire set, as well as the deuteriations of several of them (**IIc, IIIc, IVb, Vb,c**) have been previously reported.[4,5] Two additional selectivities for deuteriation were determined after the PPFMO predictions were made (**Ic, VIb**). We report them here.



Methods

The PPFMO method is described in detail elsewhere.[2] We have followed the same procedures with respect to the distances of the new functions from the nucleus (1.3 Å) and the exponents (0.1) of the gaussians used. The geometries of the species were optimized using the AM1[6] molecular orbital method as implemented in the AMPAC program after preoptimization using the MMX empirical force field[7] as implemented in the PCMODEL program[8]



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(1) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays Bas* **1992**, *111*, 199.
(2) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertrán, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024.
(3) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017.
(4) Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.*, **1992**, *57*, 4576.
(5) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.*, **1992**, *57*, 2084.
(6) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(7) Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modeling;* Liotta, D., Ed; JAI Press: Greenwich, CT, 1990; Vol. 2, p 65.
(8) Serena Software, Bloomington, IN.

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Table I. PPFMO Results. A Positive Value for p and $-p/E^{HOMO}$ Corresponds to Axial (or topside) Predicted Attack

compound	E^{HOMO} (hartree)	polarization, p, HOMO		$-p/E^{HOMO}$, HOMO		coefficient, p_π, HOMO		coefficient, χ, HOMO	
		C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2
Ia	−.27839	−0.026	0.011	−0.093	0.040	0.365	0.522	−0.025 −0.001	0.210
IIa	−.27762	−0.028	0.010	−0.101	0.036	0.355	0.522	−0.029 0.001	0.210
IIIa	−.28163	−0.045	0.066	−0.160	0.234	0.343	0.530	−0.045 0.000	0.231
IVa	−.27728	−0.035	−0.002	−0.126	−0.007	0.352	0.510	−0.046 0.011	−0.206
IVb	−.28443	−0.024	−0.017	−0.084	−0.060	0.346	0.492	−0.030 0.006	0.181
Va	−.27856	−0.003	−0.029	−0.011	−0.104	0.334	0.493	−0.016 0.013	0.174
Vb	−.28757	0.000	−0.041	0	−0.143	0.336	0.486	−0.006 0.006	0.154
VIa	−.27675	−0.013	0.002	−0.047	0.007	0.343	0.524	−0.036 0.023	0.199

(also used as a graphical interface). We used the GAUSSIAN 92 program[9] for the STO-3G ab initio calculations. All calculations were performed on IBM RS/6000 workstations.

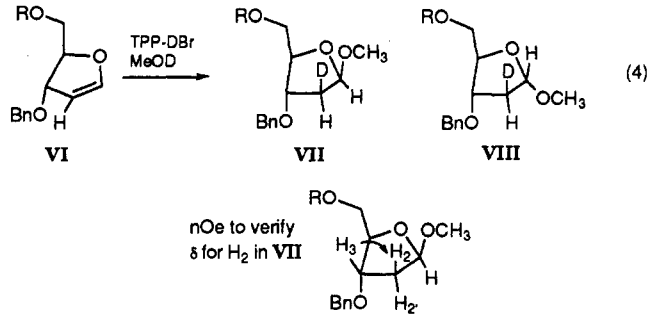
All of the molecular properties, such as optimized geometries and orbital energies are taken from the AM1 calculations. The STO-3G calculations were performed at the AM1 geometries. Two s-functions are added to each p-orbital in the π-system to be studied, one superimposed on each lobe. These s-functions desymmetrize the (antisymmetric) p-orbitals, thereby providing a probe for the polarization of these orbitals.[10] The polarizations, p, are calculated from eq 3, where c_+ and c_- are the

$$p = c_+\chi_+ + c_-\chi_- \tag{3}$$

coefficients of the added gaussian functions. When $p > 0$, the predicted attack is from the positive side. Although PPFMO, like FMO theory, is not meant to be quantitative,[11] comparisons should be made of $-p/E_{HOMO}$, rather than of p, itself.[2]

Results and Discussion

The experimental protocol for deuteriation of the new examples, dihydrofuran, **VIb**, and dihydropyran, **Ic**, follows that reported in an earlier paper.[4] The behavior of **Ic** is consistent with our past experience. The NMR assignment of deuterium configurations was straightforward, namely the more intense peak was assignable to the upfield deuterium which was axial; hence it had entered from the top face. Whereas the downfield deuterium was equatorial and had entered from the lower face. The Falck–Mioskowski method,[12] which was admirably suited for clean protonation and solvation of the double bond of dihydropyrans, was a disappointing near failure for the dihydrofuran (eq 4). By careful chromatography, we were



(4)

able to isolate a 7% yield of the desired products **VII** and **VIII**. These materials each revealed a single deuterium peak, corresponding to the downfield proton in the parent proton isotopomers. Although most published examples in the deoxyribose series assign the downfield resonance to the upper proton, there are counter examples.[13] Hence, to be completely confident of our assignment, we performed an NOE experiment with the protonated sample by irradiating H_3 and did observe that the downfield resonance of the H_2,$H_{2'}$ pair was the interacting peak. Hence protonation (deuteriation) had occurred from the top face.

The results of the PPFMO calculations are presented in Table I, while the experimentally observed selectivities for protonations and sulfenylations are presented in Table II. The models for the calculations all employ methoxy in place of the benzyloxy substituents used experimentally to economize computing time. Where acetoxy groups are present in the experimental compounds, calculations were performed both with methoxy or acetoxy groups. The experimental substrates were substituted with various other substituents, as indicated.

Experimentally, protonation always occurs at C_2. This agrees with the FMO prediction, as the coefficient of the HOMO is greater at C_2 than at C_1 for every case studied. One should note, however, that a cationic center at C_1 would be stabilized by the lone pair on the adjacent oxygen. Thus, whether initial protonation occurred at either carbon, or on the center of the π-bond, one would anticipate the ultimate location of the proton on C_2. However, Table I indicates that p_1 always predicts attack from the bottom,

(9) Gaussian Inc., Pittsburgh, PA.

(10) The small basis set used is inappropriate for accurate description of the molecules. In addition, the added s-functions might influence the molecular MO's in other ways than to probe the asymmetry. For these reasons, we use the AM1 calculations for all properties other than the asymmetry and the orbital energies. In principle, one could use the AM1 orbital energies. However, small changes in the orbital energies have little impact upon the calculated results.

(11) It is not generally possible to achieve quantitative agreement between experimental selectivities and simple parameters that are properties of one reagent, as many factors are generally different (other reagents, solvent, temperature, position of the transition state along the reaction path, etc.) for the reactions under comparison. However, in the case of the reductions of para-substituted 5-phenyladamantanones, both experimental and PPFMO predictions gave linear correlations with the Hammett σ constants.

(12) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.*, **1990**, *55*, 5812.

(13) (a) Hodge, R. P.; Brush, C. K.; Harris, C. M.; Harris, T. M. *J. Org. Chem.*, **1991**, *56*, 1553. (b) Pathak, T.; Bazin, H.; Chattopadhaya, J. *Tetrahedron*, **1986**, *42*, 5427. Examples where the lower (2″) proton resonates downfield have a thymine or cytosine at C_1.

Table II. Comparison of Experimental and Predicted Facial Selectivities

	deuteration		sulfenylation	
compound	eq/ax, exptl	predicted by PPFMO	eq/ax, exptl	predicted by PPFMO
Ic	43/57	ax	67/33[b]	eq
IIc	33/67[a]	ax	67/33[b]	eq
IIIc	<5/>95[a]	ax	9/91[b]	ax
IVb	87/13[a]	eq		eq
IVb	85/15[a]	eq		eq
IVc		eq	92/8[b]	eq
Vb	67/33[a]	eq		eq
Vc	87/13[a]	eq	79/21[b]	eq
Vc	92/8[a]	eq		eq
VIb	<5/>95	ax (top)	67/33[b]	eq

[a] From ref 3. [b] From ref 4.

while p_2 predicts attack from the top in four of the eight cases studied. Table II indicates that the experimental diastereofacial selectivities qualitatively follow the trend of p_2, suggesting that the initial attack might be at C_2. The two most selective reactions are the deuteriations of **IIIc** and **VIb**. The calculated $-p/E^{HOMO}$ for **IIIa** is the largest in magnitude among all the compounds considered, while that for **VIa**, while in the right direction, is sufficiently small (+0.007) to make its significance questionable. For this reason, we believe that much of the selectivity observed for the deuteriation of **VIb** might be due to the steric effect of the adjacent benzyloxy group, which might inhibit attack from the bottom more in the five-membered than in the six-membered ring.

While the data of Table II indicate that the experimental diastereoselectivities for deuteriation qualitatively agree with the sign of p_2, the data for sulfenylation follow a different trend. In this case, all experimentally observed selectivities are for bottom-face attack, except for that of **IIIc** (see Table II). Sulfenylation probably involves attack on the π-system at both C_1 and C_2 to form a bridged intermediate (eq 2). If this be the case, one might reasonably expect the polarizations at both positions to play a role, with the larger of the two dominating when they are of different sign. In fact, the sulfenylation selectivities do correlate with the greater of the polarizations, p_1 or p_2. Only for **IIIa** does the top-face polarization magnitude of p_2 exceed that of the bottom face p_1. In the examples of dihydrofuran **VIa** and dihydropyrans **Ia** and **IIa**, the bottom-face p_1 polarizations are greater. For the cases of **IVa,b** and **Va,b**, polarizations at both positions favor the bottom face. One should note that the selectivity for the sulfenylation of **VIb** is considerably less than that for deuteriation, although the PPFMO results appear to suggest the reverse to be expected. While we emphasize that the PPFMO results cannot usually be compared quantitatively, except for very similar reactions, we note that the steric hindrance by the adjacent group, which may contribute to the high selectivity for deuteriation of **VIb**, should be less important for sulfenylation, which is thought to involve formation of a bridged cation.

Upon accounting for the expected difference in mechanisms, application of the PPFMO method correctly predicts the differing face selectivities of two electrophiles in their attack on dissymetric alkenes. Unlike other simple methods that have been applied to the prediction of diastereofacial selectivities, PPFMO theory does not focus upon a single electronic interaction of the dissymetric σ framework as being responsible for the selectivity. Rather, it accounts for all electronic effects as part of a molecular orbital treatment. The suggestions made by Anh (interaction of an antibonding antiperiplanar orbital and the incipient bonding orbital)[14] and Cieplak (interaction of an antiperiplanar bonding orbital with the incipient antibonding orbital)[15] each focus upon a single type of interaction between a bonding and an anti-bonding orbital. These two models focus entirely upon the energetics of the orbital interactions. As such, they deal only indirectly with the desymmetrization of the π-system. Simple application of the Anh or Cieplak approaches would be problematic for explaining the differences in selectivities for protonation and sulfenylation. Using these models, one might make predictions for selectivities at either C_1 or C_2, but one could not decide which would dominate in case of conflict.

The present results confirm the applicability of the PPFMO method to diastereofacial selectivities that involve electrophilic reactions, in addition to those reactions previously reported.

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(14) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* 1977, *1*, 62.
(15) Cieplak, A. S. *J. Am. Chem. Soc.* 1981, *103*, 4540.