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Comparison of the Polarized π-Frontier Molecular Orbital Method with Other Theoretical Analyses and Experimental Data

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Abstract: The polarized π-frontier molecular orbital (PPFMO) method is used to analyze several experimental observations that have been previously discussed in terms of other theoretical models for predicting the electronic component of π-diastereofacial selectivities. In particular, the reductions of propanal, fluoroethanal, and 2-fluoropropanal as a function of rotational angle are compared with other high-level calculations. The reductions of many (ca. 50 cases) substituted cyclohexanones, methoxydioxanes, 1,3-dioxin-4-ones, norbornanones, and adamantanones are compared with other calculations and experimental data. The PPFMO polarizations are in qualitative agreement with the experimental results in all cases. Comparison with ab initio transition states (TS) leads to only one discrepancy, where an unusual repulsive factor in the TS seems to be responsible.

In a previous paper, we have described a method of predicting the electronic contributions to diastereofacial selectivity.[1] In this paper, we critically evaluate the polarized π-frontier molecular orbital (PPFMO) method by comparing its results with those of other theoretical techniques as well as with experimental results. In particular, we shall focus upon the facial selectivities of the reduction of carbonyl groups. This problem has been analyzed by several theoretical techniques including MO calculations of transition states and the Cieplak[2] and Anh[3] models for predicting the interactions.

In the PPFMO method, the normally antisymmetric p-orbitals of the reactive center(s) are desymmetrized by adding two Gaussian s-type functions, one superimposed over each lobe of the p-orbital in question. The three functions (atomic *p*- and both added s-functions) are allowed to have different coefficients in the LCAO expansion for the MOs. The difference in the magnitudes of the coefficients for the additional s-functions is used to define a polarization, **p**, which is then used in connection with frontier molecular orbital (FMO) theory to predict the preferred face of attack. In the case of nucleophilic attack on carbonyl compounds, the polarization of the LUMO of the reactant should be the focus of interest.

At the outset, we emphasize that since the PPFMO method is based upon frontier orbital theory, it is subject to the limitations of a method that only treats electronic effects in the reagents. Thus, one should not expect perfect agreement with experimental results or with accurate transition-state calculations. The method does have the advantages of frontier orbital theory in that it is simple to apply.

We divide our comparisons into three categories. In the first, we compare our results with more sophisticated MO calculations on reagents. In the second, we compare the PPFMO results with MO transition-state calculations. In the third, we compare the PPFMO results with experimental results. We expect the method to agree well with ground-state calculations. However, transition-state calculations and experimental results add effects that the PPFMO method does not treat directly. Transition-state calculations should introduce steric and other interactions that are important in gas-phase reactions. Experimental results introduce a myriad of other problems such as solvent effects, experimental analysis, competing reactions, etc.

The specific cases that we shall consider are (1) reduction of cyclohexanone and its 3- and 4-substituted derivatives (2) reductions of propanal, fluoroethanal, and 2-fluoropropanal, (3) reaction of Grignard reagents with ortho esters, (4) reactions of 2,6-disubstituted 1,3-dioxin-4-ones, (5) reductions of substituted norbornanones, and (6) reductions of substituted adamantanones.

Methods

The PPFMO calculations were performed using an STO-3G basis with two s-type Gaussian functions superimposed upon each atomic p-orbital of the π-systems studied. The same exponent (0.1) and distance from the nucleus (1.3 Å) used in our previous report[1] are employed here. The polarization, **p** is calculated using eq 1, where c_+ and c_- refer to the

$$\mathbf{p} = c_+\chi_+ + c_-\chi_- \tag{1}$$

coefficients of the s-functions placed along the positive and negative directions of the p-orbital axis. The direction of attack expected for **p** > 0 is indicated for each of the structures in the following discussion. The π-orbitals of the C and O of the carbonyl were used for ketones and aldehydes, the O–C–O fragment for the cationic intermediate in the reactions of Grignard reagents with ortho esters, and the three Cs and the O for the dioxin-4-ones. The geometry of each species was initially optimized using the AM1 MO method.[4] The plane of the π-system was taken to be that of the carbonyl and an α-carbon. When the other α-carbon was out of this plane, each was used separately. When they differed, the average was reported.

Results and Discussion

Cyclohexanones. The reduction of cyclohexanone (**Ia**) has been widely discussed in the literature. Attack of hydride upon the carbonyl comes from the more hindered face of the carbonyl, strongly suggesting that the selectivity operative be electronic (rather than steric) in origin. Application of PPFMO here results in a strong preference for attack at the correct face. The calculations were performed both on cyclohexanone, itself, and upon protonated cyclohexanone. The latter was used to mimic reaction of a cyclohexanone that is precoordinated to a cation (i.e., Li or Na) during the course of its reduction. For cyclohexanone, itself, the LUMO is highly polarized in the

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[1] Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertran, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024.

[2] Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

[3] Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 62.

[4] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

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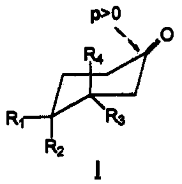

I

a: $R_1=R_2=R_3=R_4=H$
b: $R_1=F$, $R_2=R_3=R_4=H$
c: $R_2=F$, $R_1=R_3=R_4=H$
d: $R_1=Cl$, $R_2=R_3=R_4=H$
e: $R_2=Cl$, $R_1=R_3=R_4=H$
f: $R_1=OH$, $R_2=R_3=R_4=H$
g: $R_2=OH$, $R_1=R_3=R_4=H$
h: $R_1=NH_2$, $R_2=R_3=R_4=H$
i: $R_2=NH_2$, $R_1=R_3=R_4=H$
j: $R_3=F$, $R_1=R_2=R_4=H$
k: $R_4=F$, $R_1=R_2=R_3=H$
l: $R_3=Cl$, $R_1=R_2=R_4=H$
m: $R_3=CH_3$, $R_1=R_2=R_4=H$
n: $R_3=NH_2$, $R_1=R_2=R_4=H$

Table I. Cyclohexanones

compd	c_+	c_-	p	$2p^{LUMO}$	E^{LUMO} (hartrees)	ΔE (kcal)	p/E^{LUMO}
Ia	0.798	−0.632	0.166	0.618	0.193	1.0[a]	0.861
Ib eq	0.798	−0.622	0.176	0.617	0.185	1.3[a]	0.952
Ic ax	0.837	−0.576	0.261	0.614	0.187	2.5[a]	1.390
Id eq	0.790	−0.631	0.159	0.617	0.179	1.3[a]	0.889
Ie ax	0.850	−0.555	0.295	0.611	0.182	2.9[a]	1.622
If eq in	0.809	−0.604	0.205	0.618	0.188	0.9[a]	1.090
eq out	0.820	−0.601	0.219	0.614	0.186	1.6[a]	1.179
Ig ax in	0.836	−0.579	0.256	0.615	0.192	2.3[a]	1.338
ax out	0.804	−0.622	0.181	0.615	0.184	1.0[a]	0.987
Ih eq in	0.816	−0.586	0.230	0.619	0.191	0.6[a]	1.205
eq out	0.828	−0.581	0.247	0.616	0.189	1.2[a]	1.303
Ii ax in	0.887	−0.569	0.318	0.593	0.194	2.2[a]	1.640
ax out	0.828	−0.581	0.247	0.615	.18	1.0[a]	1.320
Ij eq	0.810	−0.607	0.203	0.615	0.184	2.7[b]	1.107
Ik ax	0.712	−0.642	0.070	0.634	0.190	−2.3[b]	0.366
Il eq	0.805	−0.615	0.191	0.610	0.176		1.084
Im eq	0.801	−0.623	0.178	0.619	0.194		0.919
In eq	0.802	−0.607	0.195	0.621	0.191		1.019

[a] Reference 5. [b] Reference 7.

direction of the observed attack at the carbonyl carbon (0.166). Protonation at the carbonyl slightly increases the polarization to 0.171.

This calculation is in good agreement with the recent suggestion by Frenking[5] that the facial selectivity could be explained by a polarized LUMO. His ab initio calculations indicated both the LUMO *and* the HOMO to be polarized in the same (axial) direction, in agreement with the PPFMO results. Klein had previously suggested that the LUMO might be polarized in the axial direction but that the HOMO would be oppositely polarized.[6] Also, both Frenking[5] and Houk[7] have reported ab initio calculations (using MP2/6-31G(d)//HF/3-21G and HF/3-21G, respectively) that favor the axial transition state.

The results for substituted cyclohexanones are reported in Table I where we have used the convention that a positive polarization indicates a larger lobe in the direction of axial attack. The calculated polarizations for substituted cyclohexanones **Ib–j** are in agreement with the ab initio calculations for the addition of LiH to these compounds, as reported by Houk and Frenking. In all cases, the preferred attack was axial (see Table I). For the cases of 4-hydroxy- and 4-aminocyclohexanones (**If–i**), the conformations with and without the lone pairs directed into the ring were considered, as calculated by Houk.[7] Examination of the ratio p/E^{LUMO} shows an approximate correlation with the reported ab initio activation energy differences for the axial and equatorial attacks. Three other cyclohexanones, 3-chloro, 3-methyl, and 3-amino derivatives **Il–n**, have also been calculated. However, no ab initio calculations have been performed on the corresponding transition states.

II
a: $R_1=CH_3$; $R_2=H$
b: $R_1=F$; $R_2=H$
c: $R_1=F$; $R_2=CH_3$

Table II. Polarization of Acyclic Aldehydes

	LUMO			HOMO		
angle	p	E (hartrees)	p/E	p	E (hartrees)	−p/E
			Propanal			
0	0.000	0.164	0.000	0	−0.441	0.000
30	0.174	0.158	11.014	26	−0.440	0.591
60	0.006	0.152	0.394	32	−0.440	0.728
90	−0.140	0.156	−8.982	26	−0.443	0.587
120	−0.071	0.162	−4.390	39	−0.443	0.881
150	0.073	0.159	4.596	39	−0.437	0.892
180	0.000	0.155	0.000	0	−0.435	0.000
			Fluorethanal			
0	0.000	0.151	0.000	0	−0.489	0.000
30	0.136	0.143	9.494	7	−0.487	0.144
60	−0.049	0.132	−3.707	−45	−0.482	−0.934
90	−0.213	0.132	−16.145	−25	−0.477	−0.524
120	−0.165	0.140	−11.819	−52	−0.483	−1.076
150	0.003	0.143	0.210	−60	−0.490	−1.224
180	0.000	0.141	0.000	0	−0.493	0.000
			(*R*)-Fluoropropanal			
0	0.062	0.154	4.024	0.023	−0.480	0.479
30	0.137	0.147	9.313	0.015	−0.475	0.316
60	−0.029	0.139	−2.081	−0.034	−0.469	−0.725
90	−0.223	0.137	−16.230	−0.036	−0.471	−0.764
120	−0.183	0.144	−12.748	−0.059	−0.477	−1.237
150	0.019	0.146	1.300	0.028	−0.479	0.584
180	0.003	0.144	0.209	−0.057	−0.482	−1.183
210	−0.106	0.144	−7.381	0.043	−0.469	0.916
240	0.069	0.148	4.656	0.041	−0.474	0.866
270	0.146	0.142	10.272	0.031	−0.471	0.658
300	0.058	0.139	4.177	0.035	−0.480	0.729
330	−0.056	0.147	−3.798	0.054	−0.479	1.126
0	0.062	0.154	4.024	0.023	−0.480	0.479

The only discrepancy between the PPFMO and ab initio results is for attack on axial 3-fluorocyclohexanone (**Ik**). In this case, while we calculate a polarization that is significantly lower than for the other cyclohexanones, we do not find a reversal of the polarization. However, Frenking's ab initio calculation on the transition state predicts that the attack will be preferred from the equatorial side of **Ik**. It is not clear whether this is a deficiency in the PPFMO method, a problem in the ab initio calculations (no BSSE corrections were made), or simply a reflection of the repulsion between the axial fluorine and the attacking hydride that is included in the ab initio calculation on the transition state but not in the PPFMO calculation on the reagent. This reaction is not experimentally verifiable (without a 4-*tert*-butyl group or other such substitution) due to the conformational mobility of **Ik** which is in equilibrium with **Ij**.

In a recent paper, Houk has questioned some of Frenking's analyses. He also suggests that the facial selectivities might be due to ring strain in the transition state and electrostatic effects, although he mentions that orbital interactions are not excluded by his arguments. We should note, however, that the PPFMO results do not take into account either of the two effects mentioned

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[5] Frenking, G.; Koehler, K. F.; Reetz, M. T. *Angew. Chem.* **1991**, *103*, 1167.

[6] (a) Klein, J. *Tetrahedron Lett.* **1973**, *29*, 4307. (b) Eisenstein, O.; Klein, J.; lefour, J. M. *Tetrahedron* **1979**, *35*, 225.

[7] Wu, Y. D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

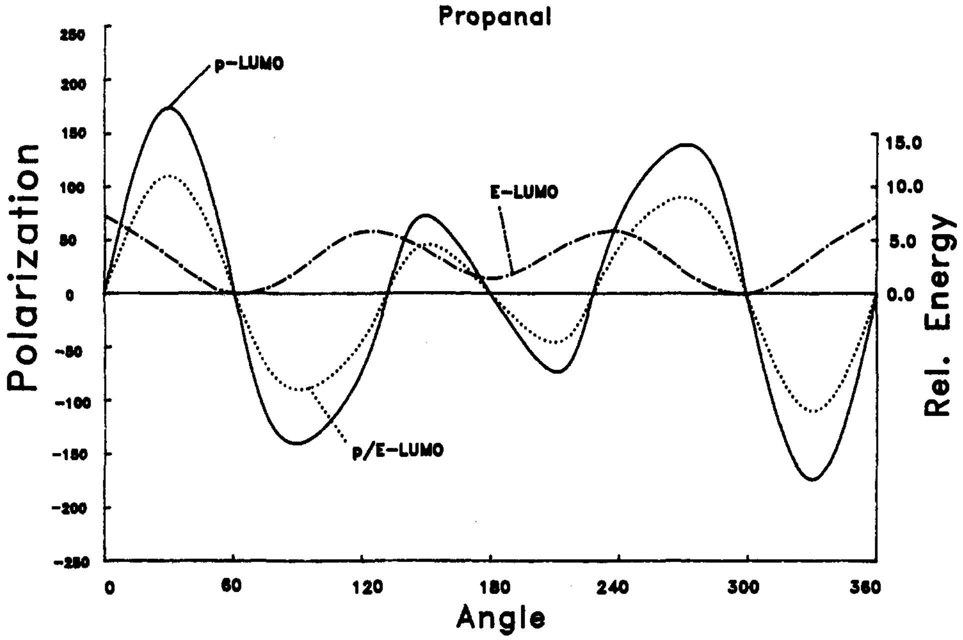

Figure 1. p, E^{LUMO}, and $10\mathrm{p}/E^{\mathrm{LUMO}}$ plotted against OCCC dihedral angle for propanal.

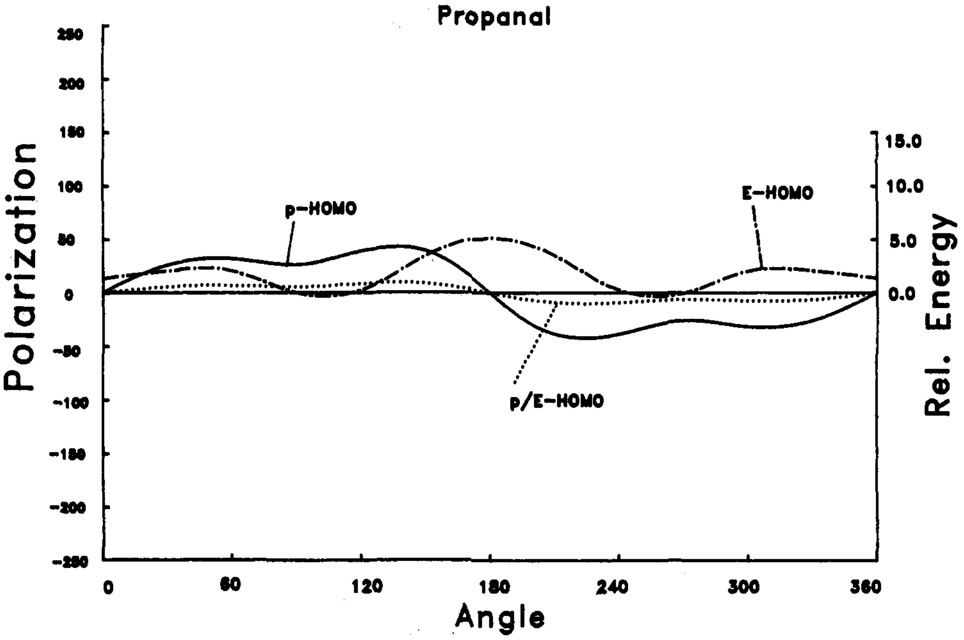

Figure 2. p, E^{HOMO}, and $-10\mathrm{p}/E^{\mathrm{HOMO}}$ plotted against OCCC dihedral angle for propanal.

by Houk yet lead to the same general conclusions. In particular, equatorial F-substitution at C_3 increases the extent to which axial attack is preferred in Houk's ab initio calculations on the transition states. He attributed this to an electrostatic attraction between C_3 and the nucleophile, an effect apparent in the transition state but not the reagent. Nevertheless, the PPFMO calculations on the reagents show the same trend as $\mathrm{p}/E^{\mathrm{LUMO}}$ increases from 0.861 for cyclohexanone (**Ia**) to 1.107 for equatorial 3-fluorocyclohexanone (**Ij**). Thus, at least some of the increased selectivity is already inherent in the reagent, itself.

Aldehydes. The π-polarization and the orbital energies of three aldehydes, propanal (**IIa**), fluoroethanal (**IIb**), and 2-fluoropropanal (**IIc**), were calculated as a function of the torsional angle about the C–C bond adjacent to the carbonyl. They are reported in Table II and Figures 1–7. The orbital energies (STO-3G) for the π- and π*-orbitals (stated in hartrees in the table) are plotted in kcal/mol in the figures. The relative energies of the π- and π*-orbitals of propanal as a function of torsional angle agree reasonably well with those of Frenking.[8] The polarization of the π*-orbital (Figure 1) varies quite significantly with the torsional angle, changing signs several times within the unique 0-180° range. The largest effect is at about 90°. However, the polarization of the π-orbital (Figure 2) remains positive from 0 to 180° (note that the positive side of the carbonyl is syn to the methyl from 0 to 180° but anti from 180 to 360°). For purpose of comparison, in cyclohexanone, the torsional angles between each of the ring carbons and the C=O is about 130 degrees, which is in the range of positive polarization values for propanal. All three of the transition states found by Frenking[9] using MP2/6-31G9(d)//HF/6-31G(d) ab initio calculations for the addition of LiH to propanol have the predicted facial selectivities that agree with the three unique torsional angles (approximately 30,

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[8] Frenking, G.; Koehler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 8991.

[9] Frenking, G.; Koehler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005.

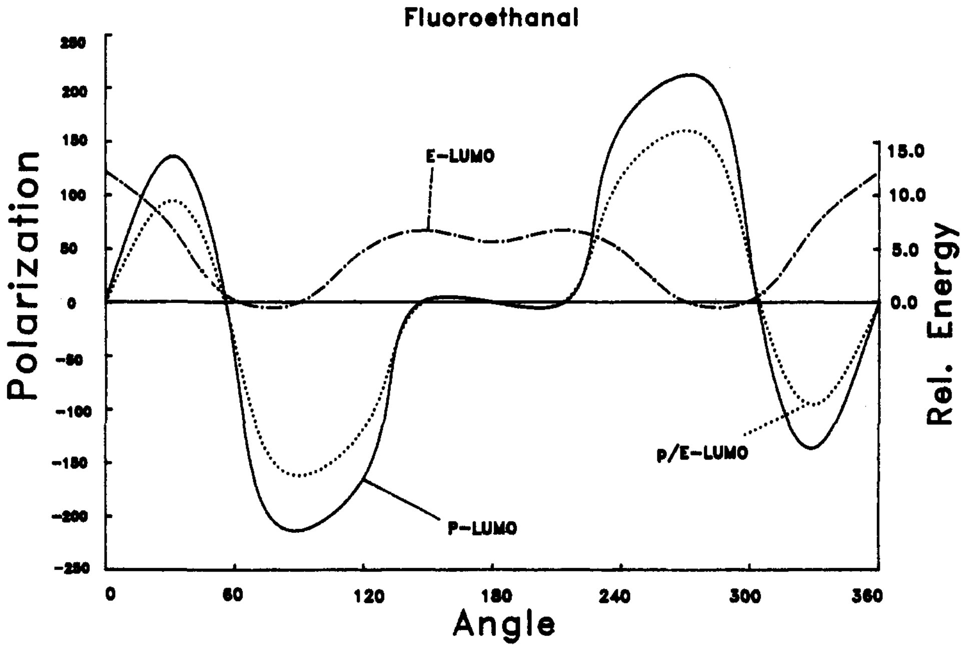

Figure 3. p, E^{LUMO}, and $10p/E^{\mathrm{LUMO}}$ plotted against OCCF dihedral angle for fluoroethanal.

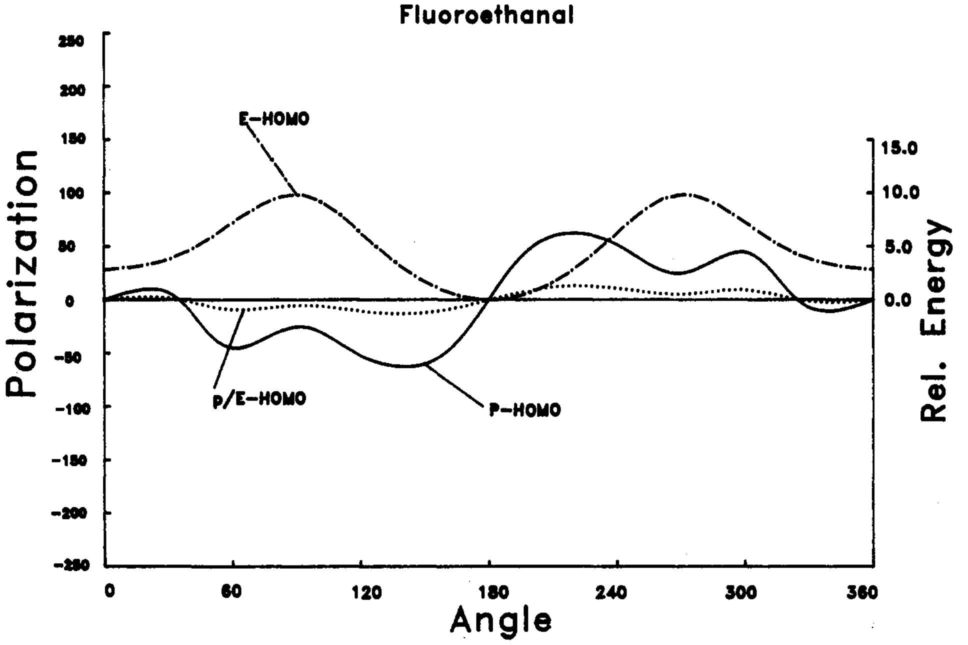

Figure 4. p, E^{HOMO}, and $-10p/E^{\mathrm{HOMO}}$ plotted against OCCF dihedral angle for fluoroethanal.

90, and 160 degrees) where PPFMO calculates the magnitude of p/E^{LUMO} to be greatest (see Figure 1).

For fluoroethanal, the polarization of the π^*-orbital (Figure 3) follows the qualitative pattern of that for propanal. However, the polarization of the π-orbital (Figure 4) differs somewhat from that of propanal in that it is polarized in the opposite direction for most torsional angles. The polarization of 2-fluoropropanal is shown in Figures 5–7. In the last figure, we compare it with the sum of the polarizations for propanal and fluoroethanal. For this figure, zero torsional angle corresponds to the C–F bond eclipsed with the carbonyl group. The polarization for propanal is added with the appropriate shift of 120 degrees. As can be seen, the polarization of the π^*-orbital is qualitatively additive, while that for the π-orbital is not. If we compare the PPFMO results with the calculated transition states reported by Frenking for the additions of LiH to chloroethanal and 2-chloropropanal,[9] all the selectivities agree with one exception. That exception is for a transition state for chloroethanal whose dihedral angle is –170 degrees. From Figure 3, the predicted polarization for fluoroethanal is close to zero but opposite to that calculated by Frenking. Since the polarization is predicted to be small and we are comparing fluoro and chloro derivatives, this difference does not seem to be important. Furthermore, one should note that the transition states optimized by Frenking include the effect of the Li^+, which is not considered in the PPFMO model. In addition, our PPFMO calculations are in apparent excellent agreement with the HF/3-21G calculations of Paddon-Row on the transition states for cyanide addition to propanal, fluoroethanal, and 2-fluoropropanal.[10] Exact comparison is not possible, as Paddon-Row does not give the torsional angles for his transition states.

Paddon-Row states that the best transition state (TS) for cyanide addition to propanal has the methyl in the "inside" position. Frenking's TS for the addition of LiH to the same compound has a dihedral angle (OCCC) of 29 degrees. These

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[10] Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456.

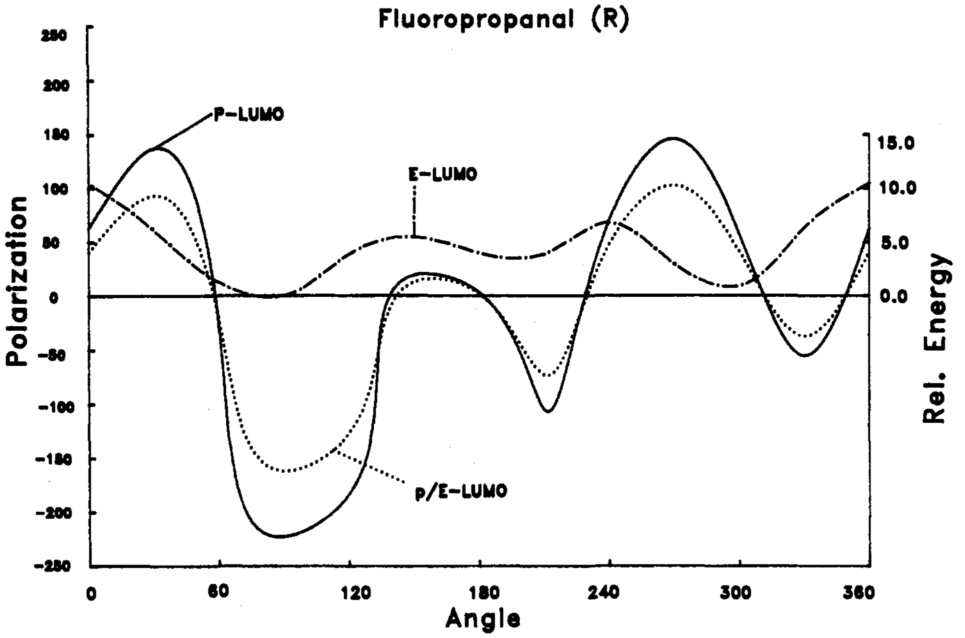

Figure 5. p, E^{LUMO}, and $10\mathrm{p}/E^{\mathrm{LUMO}}$ plotted against OCCF dihedral angle for 2-fluoropropanal.

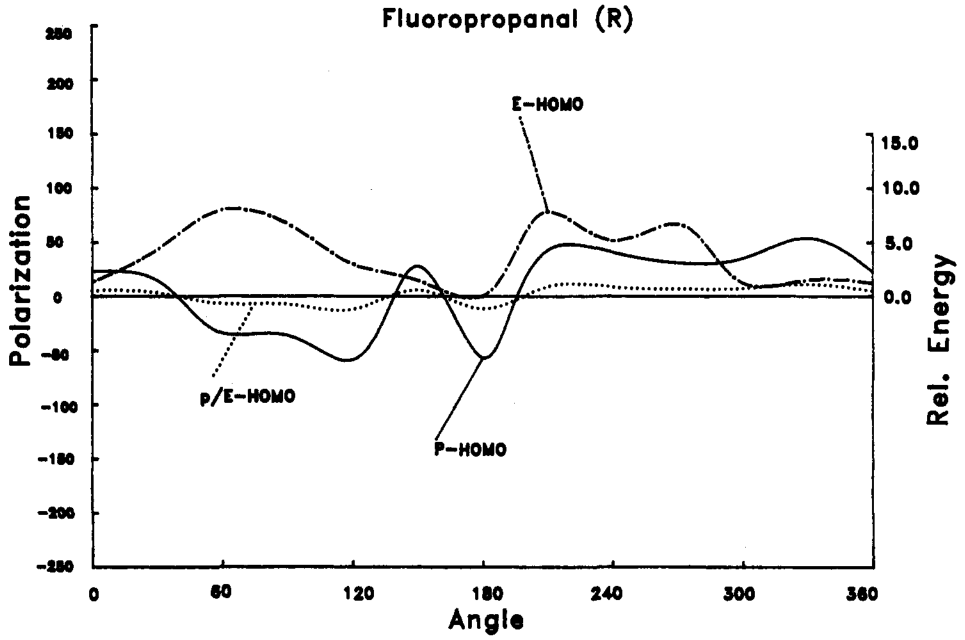

Figure 6. p, E^{HOMO}, and $-10\mathrm{p}/E^{\mathrm{HOMO}}$ plotted against OCCF dihedral angle for 2-fluoropropanal.

results are consistent with each other and with Figure 1, which shows $\mathrm{p}/E^{\mathrm{LUMO}}$ to be at a maximum in the syn direction at about 30 degrees.

For fluoroethanal, Paddon-Row finds the lowest TS to have the C–F bond antiperiplanar to the incipient C–C bond. This puts the OCCF dihedral in the range of −120–0 degrees. Frenking's TS for LiH addition to *chloro*ethanal (which is 0.3 kcal/mol less stable than that with a dihedral angle of 17 degrees) has a dihedral angle of 257° (-103°). Figure 3 shows that the magnitude of $\mathrm{p}/E^{\mathrm{LUMO}}$ at −103 degrees is very close to its maximum of about 90 degrees.

For 2-fluoropropanal, Paddon-Row reports the TS to have the C–F bond antiperiplanar and the methyl group "inside" (syn) to the incipient bond. The lowest TS for the addition of LiH to 2-*chloro*propanal by Frenking has an OOOCl dihedral of 84 degrees, similar to that for chloroethanal. Figure 5 indicates that the magnitude of $\mathrm{p}/E^{\mathrm{LUMO}}$ energy is near its maximum at this dihedral angle. The best TS leading to the diastereomeric product also has the C–F bond antiperiplanar to the incipient bond. Again taking the dihedral from Frenking's results for the addition of LiH, the OCCCl dihedral is −104° (256°), which Figure 5 again shows to be near a maximum in the magnitude of $\mathrm{p}/E^{\mathrm{LUMO}}$.[11]

Reaction of Grignard Reagents with Ortho Esters. In 1969, Eliel reported that the reaction of methoxydioxanes **IIIa–c** with Grignard reagents affords primarily trans product, presumably via attack on cationic intermediates **IVa–c**.[12] Despite the fact that this reaction is not a carbonyl reduction, we decided to include it in this study because of the evident similarities. PPFMO calculations on **IVa–c** indicate polarizations in the direction of

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(11) Comparisons to the literature are complicated by notational differences. Both Frenking and Paddon-Row inverted the chiral center rather than the side of attack in the halopropanal. Furthermore, each attacked from a different side so that (assuming F = Cl) they calculated enantiomeric transition states. We worked with the *R* enantiomer with anti attack in the dihedral range of 0–180° yielding one diastereomer, while anti attack in the range of 180–360° yields the other (syn attack would yield the opposite diastereomer in each range). Frenking's reported dihedrals of −84° and −104° must be modified to 84° and −104° (256°) for comparison with our results.

(12) Eliel, E. L.; Nader, F. *J. Am. Chem. Soc.* **1969**, *91*, 536.

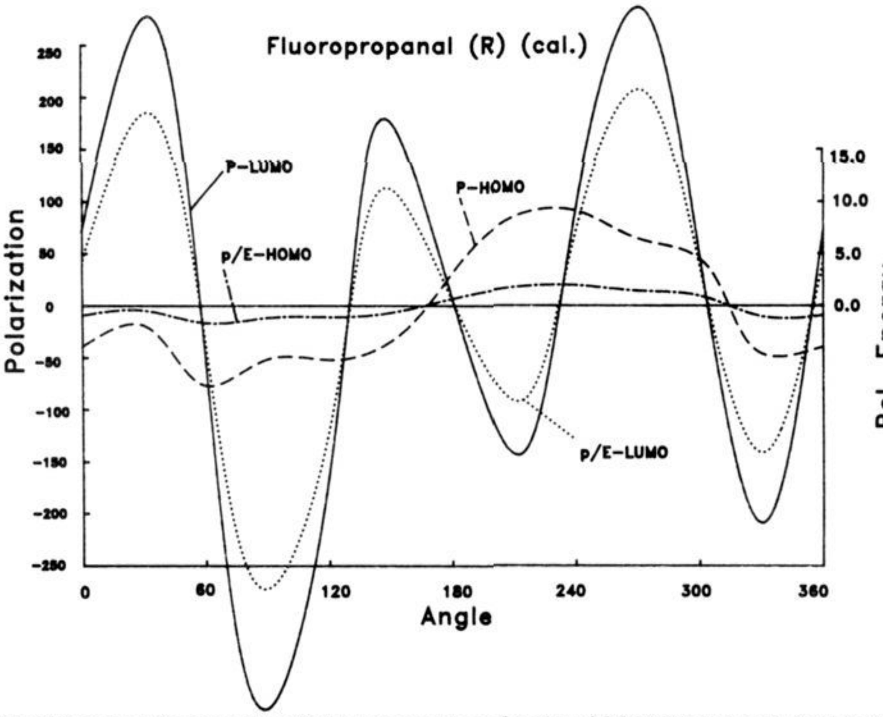
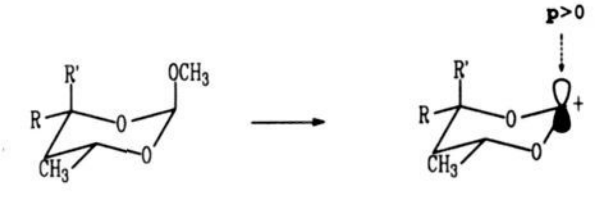


Figure 7. **p**(propanal) + **p**(fluoroethanal) compared to **p**(2-fluoropropanal) as a function of OCCF dihedral angle for both LUMO and HOMO. The OCCC angle for propanal is offset by 120 degrees for the comparison.



III

IV

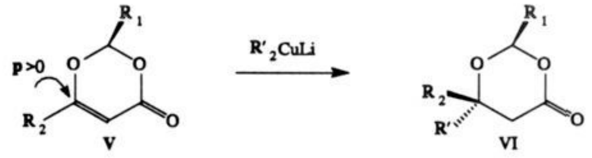
a: R=R'=H
b: R=CH$_3$; R'=H
c: R=R'=CH$_3$

Table III. Ortho Esters

compd	c_+	c_-	**p**	$2p^{\mathrm{LUMO}}$	E^{LUMO} (hartrees)	attack
IIIa	0.357	−0.299	0.058	0.654	−0.046	axial
IIIb	0.355	−0.315	0.040	0.647	−0.047	axial
IIIc	0.347	−0.321	0.027	0.648	−0.039	axial

axial attack leading to the observed product. We do not include $\mathbf{p}/E^{\mathrm{LUMO}}$ in Table III since (due to its cationic character) $E^{\mathrm{LUMO}} < 0$, making eq 6 of our earlier paper[1] (which assumes $E^{\mathrm{LUMO}} > 0$) inappropriate. Eliel also noted that the isomeric methoxydioxanes which are epimerized at the methoxy-substituted carbon were much less reactive. If one considers the loss of the methoxy group as a reaction equivalent to the reverse of attack on cationic intermediate **IV**, this observation is also consistent with the calculated polarizations.

Additions to 2,6-Disubstituted 1,3-Dioxin-4-ones. In 1988, Seebach reported that dialkyl-, allyl-, and phenyllithium cuprates add to 1,3-dioxin-4-ones **Va–c** stereospecifically to give *ul* (unlike) products **VIa–c**.[13] He attributed the stereoselectivity to a small amount of pyrimidalization about the π-system. We thought this a useful test for the PPFMO method for two reasons. First, the rationale presented for the observations is different from that presented for the reduction of ketones and aldehydes. Second, the reaction involves a conjugate addition to the π-system rather than a simple addition to a carbonyl. The data in Table IV show a clear polarization in the direction (negative) that gives the observed *ul* products (anti to R$_1$).



a: R$_1$=C(CH$_3$)$_3$; R$_2$=CH$_3$
b: R$_1$=C(CH$_3$)$_3$; R$_2$=CH$_2$CH$_3$
c: R$_1$=R$_2$=CH$_3$

Table IV. 2,6-Disubstituted 1,3-Dioxin-4-ones

compd	c_+	c_-	**p**	$2p^{\mathrm{LUMO}}$	E^{LUMO} (hartrees)	attack[13]	$\mathbf{p}/E^{\mathrm{LUMO}}$
Va	0.367	−0.600	−0.234	0.609	0.173	syn	−1.353
Vb	0.407	−0.598	−0.190	0.599	0.175	syn	−1.090
Vc	0.363	−0.606	−0.243	0.606	0.172	syn	−1.413

Substituted Norbornanones. Several experiments have been designed to evaluate the effects of purely electronic influences on the diastereofacial selectivities by designing experimental systems where other (i.e., steric, solvation) influences should be minimal. One of these systems involves substituted norbornanones **VIIa–e**.[14] Table V compares the calculated polarizations with the experimentally observed selectivities. The PPFMO results agree with the experimental observations in that the correct direction of attack is predicted in each case. This is true even for **VIIa**, where attack comes from the syn side, while all others undergo anti attack. In several cases, particularly **VIIa** and **VIIb**, the polarizations are quite small. In fact, **VIIa** gives the opposite polarization for some higher energy rotomers.

Reductions of Adamantanones. In a series of papers, le Noble has presented numerous results on the reductions of various

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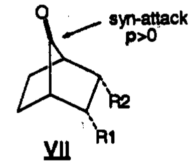


VII

a: R_1=R_2=$COOCH_3$
b: R_1=R_2=CH_2OCH_3
c: R_1=R_2=vinyl
d: R_1=vinyl, R_2=ethyl
e: R_1=R_2=ethyl

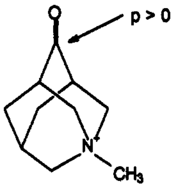
Table V. Norbornanones

compd	c_+	c_-	$\mathbf{p}$	$2p^{\mathrm{LUMO}}$	E^{LUMO} (hartrees)	attack[14]	$\mathbf{p}/E^{\mathrm{LUMO}}$
VIIa	0.745	–0.742	0.003	0.615	0.181	syn	0.018
VIIb	0.757	–0.761	–0.005	0.624	0.197	anti	–0.024
VIIc	0.722	–0.776	–0.054	0.619	0.196	anti	–0.275
VIId	0.740	–0.761	–0.021	0.620	0.198	anti	–0.106
VIIe	0.750	–0.770	–0.020	0.627	0.201	anti	–0.100

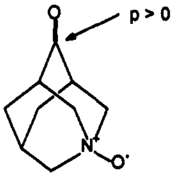
substituted adamantanones[15–18] and adamantyl radicals[19] in an attempt to separate the electronic and steric influences on diastereofacial selectivity. We have performed PPFMO calculations on virtually all of the relevant adamantanones that he has studied. The results are collected in Table VI. The PPFMO method successfully predicts the observed syn attack for all cases involving 5-azaadamantanones **VIII**, **IX**, and **X**. PPFMO, also, predicts polarizations that favor the observed syn attack in the cases of 5-substituted adamantyl derivatives **XIa–e**. For the series of para-substituted 5-phenyladamantanones **XIIa–e**, le Noble reported that the relative amount of syn attack could be related to the Hammett σ-constant for the substituents. The comparison with the calculated polarities and $\mathbf{p}/E^{\mathrm{LUMO}}$'s are included in Table V. The $\mathbf{p}/E^{\mathrm{LUMO}}$'s for **XIIa–e** are plotted against the σ-constants in Figure 8. The agreement is remarkably good for calculations made with so simple a theory as PPFMO. In the case of **XIId**, the polarization is quite sensitive to the dihedral angle the O–H makes with the phenyl ring. The values used are for the lowest energy rotomer, but $\mathbf{p}/E^{\mathrm{LUMO}}$ varies between 0.012 to 0.046 as a function of the dihedral.

The correspondence of the PPFMO polarizations $\mathbf{p}$ with the experimental and theoretical results that have been reported on the same systems is surprisingly qualitatively good. Quantitative agreement is much more difficult to attain. In this case, comparison should be made not with $\mathbf{p}$ but with either $\mathbf{p}/E^{\mathrm{LUMO}}$ or $\mathbf{p}/(E^{\mathrm{LUMO}} + k)$,[1] as PPFMO theory relates the relative activation energies to $E^{\mathrm{LUMO\text{-}HOMO}}$ as well as to $\mathbf{p}$. Here, the agreement is not as good, although the trends are often reproduced within groups of similar reactions (such as **XIIa–e**). This is not surprising since FMO theory takes neither the transition states nor the other reagent directly into account. Given the simplicity of the approach, the good qualitative agreement is all the more remarkable.

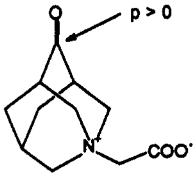
We are currently applying the PPFMO method to other kinds of reactions, such as electrophilic attacks.[20] Preliminary results show that the method is successful in predicting the experimentally observed facial selectivities in protonations of glycals.[21]



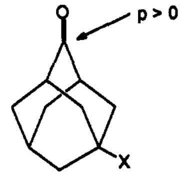
VIII



IX

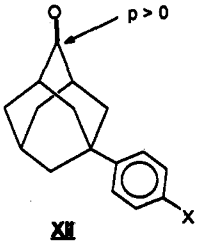


X



XI

a: X=F
b: X=CH_3
c: X =CF_3
d: X=Cl
e: X=t-butyl



XII

a: X=H
b: X=NO_2
c: X =CN
d: X=OH
e: X=NH_2

Table VI. Adamantanones

compd	c_+	c_-	$\mathbf{p}$	$2p^{\mathrm{LUMO}}$	E^{LUMO} (hartrees)	attack[a]	$\mathbf{p}/E^{\mathrm{LUMO}}$
VIII	0.784	–0.627	0.157	0.606	0.042	syn	3.701
IX	0.714	–0.703	0.011	0.633	0.175	syn	0.063
X	0.751	–0.666	0.085	0.624	0.146	syn	0.581
XIa	0.717	–0.711	0.006	0.635	0.190	syn	0.031
XIb	0.719	–0.718	0.001	0.636	0.197		0.007
XIc	0.719	–0.711	0.008	0.634	0.187	syn	0.042
XId	0.710	–0.712	–0.001	0.634	0.184	anti[b]	–0.008
XIe	0.717	–0.718	–0.001	0.637	0.198	anti[c]	–0.005
XIIa	0.723	–0.715	0.008	0.635	0.196	syn	0.041
XIIb	0.724	–0.714	0.010	0.633	0.187	syn	0.056
XIIc	0.723	–0.715	0.008	0.634	0.191	syn	0.043
XIId	0.721	–0.717	0.005	0.635	0.196	syn	0.023
XIIe	0.721	–0.718	0.003	0.635	0.198	syn	0.017

[a] References 15 and 18. [b] Reference 15 (earlier work reports syn). [c] Depending upon reaction conditions, either anti or no selectivity.[15]

The results presented here invite comparison with the predictions of the perturbational models of Anh[3] and Cieplak.[2] These, as well as several other models for explaining the facial selectivities observed in the reduction of cyclohexanones, have been critically discussed by le Noble in a recent review.[22] We have also discussed their relationships with FMO theory in a previous paper.[1] Several of the papers cited earlier have included discussions that are critical or supportive of one or the other of these models.

We have previously indicated that both of these models are based upon perturbation arguments that relate to stabilization of a bonding orbital by interaction with an antibonding orbital. Anh holds that the incipient bonding orbital is stabilized by an antibonding orbital of an antiperiplanar bond, while Cieplak claims that the bonding orbital of the antiperiplanar bond is stabilized by the incipient antibonding orbital. Neither of these models takes polarization of the π-orbitals directly into account. le Noble notes that the interactions involved in both models are potentially important and also, that their importance will vary in different directions as the transition state varies from early to late. We have come to similar conclusions using a different analysis than that by le Noble.[1]

Since the PPFMO method involves MO calculations, it should include the perturbations to the frontier orbitals that are operative in both the Anh and Cieplak formulations (as well as all other

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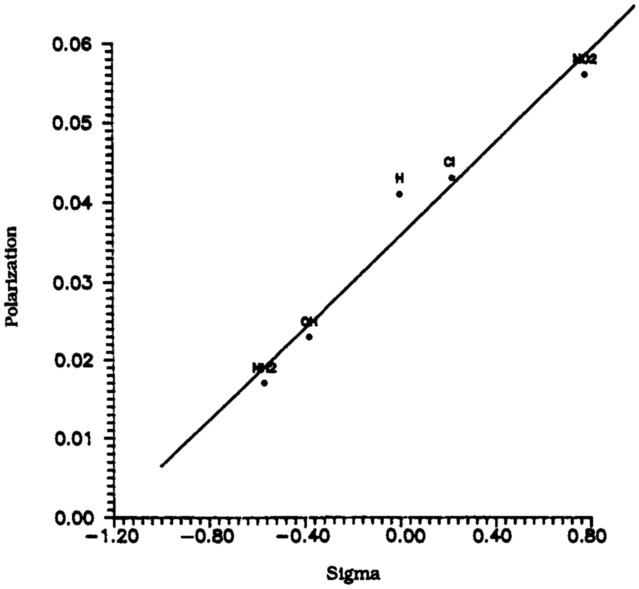

Figure 8. Plot of $\mathbf{p}/E^{\mathrm{LUMO}}$ versus Hammett σ for compounds **XIIa–e**.

orbital interactions in the reagents). These should be manifest in the energy of the LUMO, which will be the orbital involved in the incipient bond. In addition, the PPFMO method includes the effect of π-orbital polarization, which is absent from the Anh and Cieplak models. It is tempting to try to extend the Anh and Cieplak models to π-polarizations. Such extensions would require that the effects on the FMOs and **p** be qualitatively similar. However, examination of the data presented in this and a previous paper[1] illustrates the lack of correlation of substituent effects on **p** with those on the HOMO or LUMO energies.

Other groups have suggested procedures for qualitatively predicting the polarization of π-orbitals. However, the developments by Klein[6] and by Burgess and Liotta[23] are sufficiently different to lead to different polarizations from those obtained by PPFMO. This is largely because PPFMO employs an MO calculation to obtain the polarization, while the earlier methods rely upon perturbation techniques. Perturbation arguments require that one identify the dominant effect, which is not always an easy task. However, MO calculations must include all orbital interactions. They do not require the identification of the dominant effect. Thus, they have the advantage of properly describing the reagents, even where the dominating effects differ. The PPFMO results agree with Frenking's complete MO treatment of cyclohexanone[5] but require much less computer time and expertise.

In very recent papers, both Houk and Paddon-Row[24] and Chandrasekhar and Mehta[25] suggested that electrostatic control might be important in the stereoselectivities of nucleophilic additions to 7-norbornanones.[26] While their approaches are conceptionally different from ours, their results seem to be consistent with PPFMO. One expects the LUMO to be polarized in the direction of lower electron density (positive charge), as this is the first orbital that would be filled upon addition of an electron. Despite this, the recent results are taken to be in conflict with polarized orbitals.[25] It might be interesting to further compare the two analyses in the future.

Conclusions

The PPFMO method is capable of predicting diastereofacial selectivities in a wide range of approximately 50 different cases of nucleophilic attacks upon carbonyl compounds. It is particularly successful in predicting the polarizations of MOs that would arise from more complex analyses of the shapes of individual MOs as well as qualitatively predicting the relative energies of optimized transition states calculated by MO methods. It has qualitatively reproduced all of the experimental results discussed. Since the MO calculation on the reagent includes the influences of all substituents, one does not need to make qualitative judgments about their relative influences upon the diastereofacial selectivities.

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