# Quantitative evaluation of steric effects for π-facial stereoselection: π-plane-divided accessible space

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**A simple method for quantitative evaluation of steric effects in π-facial stereoselection has been described.**

Steric effects, defined as the exchange repulsion term between reactant molecules according to the Salem–Klopman equation,[1] often play a key role in stereochemical control of organic reactions. It is, however, commonly used only as a qualitative term. Nevertheless highly practical asymmetric syntheses have been designed through intuitive estimation of steric effects based on the size of substituents, such as *A* values[2] or van der Waals radii.[3] It is however often difficult to predict steric effects in π-facial selection[4] intuitively, in particular for substrates having complex substituents around the π-bond. A simple quantitative parameter of π-facial steric effects should provide a convenient means to gain clearer and more effective perception in designing organic syntheses. Herein we describe the first method that is useful for predicting π-facial steric effects for common organic unsaturated substrates.

The new method focuses on the three-dimensional space outside the van der Waals surface of a reactant molecule.[5] It is based on the simple assumption that the volume of the outer (exterior) space nearest to a reaction center should contain steric information of the reactant (substrate), since this volume precisely corresponds to the three-dimensional space available for a reagent to access the reaction center of the substrate. The exterior volume is calculated for the two faces of the π-plane separately. Fig. 1 illustrates the definition of the π-plane-divided accessible space (PDAS) as a reasonable quantitative measure of π-facial steric effects using formaldehyde as an example. The molecular surface is defined as an assembly of spherical atoms having the appropriate van der Waals radii.[3] Integration of exterior three-dimensional space for the PDAS of the carbonyl carbon is performed according to the following conditions. If a three-dimensional point P(*x*, *y*, *z*) outside the repulsive surface is the nearest to the surface of the carbonyl carbon (a reaction center on the *xz* plane) [*i.e.* if the distance between P and the van der Waals surface of the carbonyl carbon ($d_C$) is the shortest compared with the distances from P to the other atomic surfaces (two $d_H$ and one $d_O$)] and if the point is located above the carbonyl plane ($y > 0$), the space at this point is assigned to the above-space of the carbonyl carbon. The integration (summation) of such points is defined as the PDAS of the carbonyl carbon for the above-plane. For the sake of convenience, spatial integration is limited to 5 au (2.65 Å) from the molecular surface, where extension of an electronic wave function is negligible beyond this limit. In general, the carbonyl plane is defined as the plane which includes the two $sp^2$ atoms of the π-bond and which is parallel with the vector connecting the two atoms at the α-positions. The basic concept of the PDAS definition is readily extended to other π-facial steric effects in compounds containing a general double bond other than a carbonyl. The calculation procedure usually begins with structure optimization at the HF/6-31G(d) level using GAUSSIAN 94.[6] PDAS calculation is then performed according to the three-dimensional lattice method with a unit lattice volume of 0.008 au$^3$ ($1.18 \times 10^{-3}$ Å$^3$). The method has been successfully applied to a variety of unsaturated substrates. A few examples, for which facial stereoselection has been previously explained without invoking steric effects, will be described.

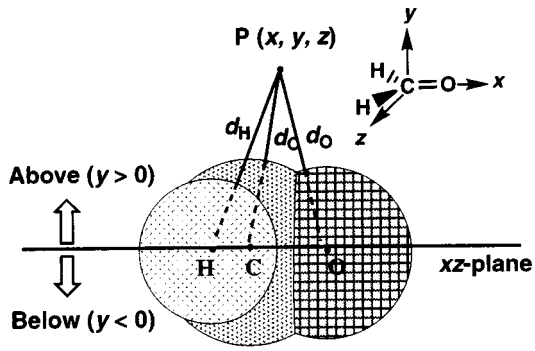


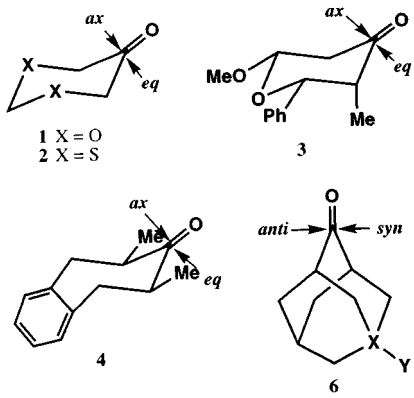

**Fig. 1** Definition of π-plane-divided accessible space (PDAS) for the case of formaldehyde.

Table 1 collects the PDAS data of four cyclic ketones (**1**–**4**) along with two cyclohexanones for comparison. The *ax*-face of cyclohexanone (19.4 au$^3$) is indeed more hindered than the *eq*-face (47.2 au$^3$), as it is for *tert*-butylcyclohexanone.[7] The stereochemistries of these two and other alkyl-substituted cyclohexanones have been successfully rationalized with the EFOE model (exterior frontier orbital extension model)[8] and are apparently orbital-controlled. The stereochemical reversal observed for 4-*eq*-phenyl-1,3-dioxan-5-one (**1**)[9] and its sulfur analog (**2**)[10] has been the subject of intense investigation.[11,12] Not only the nearly constant stereoselectivity irrespective of the bulkiness of the Grignard reagent employed (RMgI; R = Me, Et, Pr$^i$),[9,10] but also the PDAS values for **1** and **2** clearly indicate that steric effects should be mainly responsible for the face selection of the heterocyclic ketones. Exclusive attack of $LiEt_3BH$ from the *ax*-face of 2-*ax*-methyl-3-*eq*-phenyl-5-*eq*-methoxypyran-4-one **3**[4,13] can also be explained by the substantially reduced PDAS value in the *eq*-face (13.8 au$^3$) compared to the *ax*-face (22.4 au$^3$). As seen in Table 1, exclusive equatorial hydride attack at 2-*eq*, 7-*eq*-dimethyl **4**[14] can be readily rationalized by severe steric hindrance in the *ax*-face where the PDAS value is only 5.5 au$^3$. In all these examples, the peculiar stereochemical behavior can be ex-

**Table 1** π-Plane-divided accessible space (PDAS) for the carbonyl carbon of cyclic ketones and their observed π-facial stereoselectivity in nucleophilic additions[a]

| Compound | PDAS/au$^3$ *ax* | PDAS/au$^3$ *eq* | Observed *ax*:*eq* |
|---|---|---|---|
| Cyclohexanone | 19.4 | 47.2 | — |
| 4-eq-*tert*-butylcyclohexanone | 19.6 | 46.7 | 86:14[b] |
| **1** | 67.6 | 26.5 | 94–98:2–6[cd] |
| **2** | 17.9 | 55.4 | 7–15:85–93[cd] |
| **3** | 22.4 | 13.8 | 100:0[e] |
| **4** | 5.5 | 36.4 | 0:100[c] |

[a] HF/6-31G(d). [b] $NaBH_4$. [c] $LiAlH_4$. [d] RMgI (R = Me, Et, Pr$^i$. [e] $LiEt_3BH$.




plained simply using ground-state conformations without resorting to transition state effects.[11,15]

Another intriguing example is the 3-substituted cyclohexanone system **5**. A plot of the PDAS values for the *ax*-face of **5** (*ax*-PDAS)[16] against facial stereoselectivity [ln(*ax*/*eq*)] for the reaction of **5** with MeLi reported previously by Cieplak[17,18] for eight substituents indicated an excellent linear correlation ($r^2$ = 0.95), strongly suggesting that the conformations of **5** are sensitive to the electronic properties of these substituents. Four major explanations have appeared to date to rationalize the enhancement of *ax*-attack in the cyclohexanone system carrying an electron-withdrawing substituent at C3 relative to 4-*tert*-butylcyclohexanone.[12*a*,17–20] Our PDAS calculations clearly indicate that subtle ground-state conformational changes in the cyclohexanone moiety caused by an equatorial substituent at C3 are most likely to be responsible for the observed trend of facial selection of this system.

5-Substituted adamantan-2-ones **6** (X = C or N; Y = substituent) have been regarded as sterically unnbiased systems, where both π-faces are assumed to be sterically equivalent.[21] The parent adamantan-2-one is less reactive with hydride than cyclohexanone,[22] despite the theoretical observation that the transition state antiperiplanar effects are much greater than those in cyclohexanone.[23] Table 2 collects the PDAS data of **6**.[6] The PDAS values of adamantan-2-one are both 11.1 au$^3$. This is much smaller than the PDAS value for the *ax*-face of cyclohexanone (19.4 au$^3$), suggesting that adamantan-2-one is *much more sterically demanding* than cyclohexanone. This in turn suggests that subtle changes in steric environment around the carbonyl of **6** may cause significant variation in π-facial stereoselection. The data in Table 2 exhibits a good correlation between the facial stereoselectivity (*anti* : *syn*) and the facial difference in the PDAS value [$\omega$ = PDAS(*syn*) − PDAS(*anti*)] ($r^2$ = 0.68). Among 16 substituents examined, those which pefer *anti*-selectivity are limited to two bulky substituents ($SiMe_3$ and $SnMe_3$; $\omega < 0$). This strongly indicates that in the adamantan-2-one system, where facial differences in frontier orbital extension are marginal, subtle steric effects may be especially important for facial stereoselection in agreement with the recent report by Gung.[24]

**Table 2** π-Plane-divided accessible space (PDAS) of 5-substituted adamantan-2-ones **6**[a]

| | | PDAS/au$^3$ | | | |
|---|---|---|---|---|---|
| X | Y | *anti* | *syn* | $\omega$[b]/au$^3$ | Observed[c] anti : syn |
| C | H | 11.1 | 11.1 | 0.0 | 50 : 50 |
| C | Me | 10.7 | 11.2 | 0.5 | — |
| C | Bu$^t$ | 11.1 | 10.7 | −0.4 | 50 : 50[d] |
| C | Ph | 10.7 | 11.9 | 1.2 | 42 : 58 |
| C | F | 10.3 | 12.7 | 2.4 | 38 : 62 |
| C | Cl | 10.5 | 12.5 | 2.0 | 41 : 59 |
| C | Br[e] | 10.6 | 11.8 | 1.2 | 41 : 59 |
| C | I[f] | 10.9 | 11.5 | 0.6 | 36 : 64 |
| C | OH | 10.9 | 11.2 | 0.3 | 43 : 57 |
| C | $NH_2$ | 10.3 | 11.7 | 1.4 | 34 : 66 |
| C | $CO_2Me$ | 10.4 | 11.6 | 1.2 | 39 : 61 |
| C | $CF_3$ | 10.4 | 11.6 | 1.2 | 41 : 59 |
| C | $SiMe_3$ | 11.3 | 10.6 | −0.7 | 55 : 45 |
| C | $SnMe_3$[f] | 11.8 | 10.5 | −1.3 | 56.5 : 43.5 |
| N | — | 10.2 | 11.5 | 1.3 | 38 : 62 |
| $N^+$ | Me | 10.3 | 12.4 | 1.1 | 12 : 88 |
| $N^+$ | $O^-$ | 9.6 | 13.7 | 4.1 | 4 : 96 |

[a] HF/6-31G(d) unless otherwise noted. [b] $\omega$ = PDAS(*syn*) − PDAS(*anti*). [c] $NaBH_4$ in Pr$^i$OH or MeOH unless otherwise noted (ref. 21). [d] $LiAlH_4$ in $Et_2O$. [e] Huzinaga's 43321/4321/311(d) basis set for Br with 6-31(d) basis sets for C and H were used at the HF. [f] HF/3-21G*.

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