The Cation Complexation Model Predicts the Experimental π-Facial Selectivity of 2-ax- and 2-eq-Substituted Cyclohexanones. A Detailed Ab Initio MO Investigation

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Abstract—The geometrical changes on complexation of the carbonyl oxygen with prototypical cations such as H^+ and Li^+ are in tune with the polarity features of the C–X bonds in 2-ax-X-cyclohexanones (X=Cl, F, SR, OR; R=H, Me); the stereoelectronic effects apply. While the 2-ax-Cl- and 2-ax-SR-cyclohexanones are predicted to favor axial attacks, the 2-ax-OR- and 2-ax-F-cyclohexanones must capture a nucleophile predominantly from the eq-direction. The eq-selectivity of 2-ax-OR-cyclohexanone is in contradiction with the torsional model of Anh and Felkin. The Houk model will also fail due to the eminent steric interactions arising from the 2-ax-OMe function in the eq-TS. Neither the Anh–Felkin model nor the Cieplak model could be applied to 2-eq-MeO-cyclohexanone. The complexation model, however, predicts eq-selectivity in full agreement with experimental results. Second order perturbation theory analysis of the Fock matrix in NBO basis indicates that the role of the antiperiplanar effects is not as significant as perceived earlier by Cieplak and by Anh and Felkin. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The diastereofacial selection of substituted cyclohexanones is an area of current interest.[1] Several models have been proposed to explain the π-facial preferences. The Anh–Felkin model[2] considers the transition state (TS) to be electron-donating and, thus, a nucleophile is required to attack the carbonyl carbon from a direction that is antiperiplanar to an electron-attracting σ bond at the α carbon. In contrast, the Cieplak model[3] assumes the TS to be electron-attracting and, thus, a nucleophile is required to attack antiperiplanar to an electron-donating σ bond at the α carbon. These two models, thus, predict opposite selectivities for the same substituent type. Furthermore, despite being simple, these models have failed to adequately accommodate several experimental stereochemical results. The Houk model[4] is not general either because, for instance, an extrapolation of the true ax-selection of 2-ax-Cl-cyclohexanone to 2-ax-OR-cyclohexanone contradicts the experiments. The pictorial representations of these models are given in Fig. 1.

The orbital distortion model by Frenking[5] and the polarized π-frontier molecular orbital (PPFMO) model by Dannenberg[6] are less popular amongst organic chemists probably because their applications are tedious. The electrostatic control models by Chandrasekhar and Mehta[7a] and Houk[7b] are successful in many instances but fail at some. Tomoda[8] has developed an exterior frontier orbital extension (EFOE) model that relies on the total space available on both the faces of the carbonyl function. No results, however, have been published as yet on the selectivities of 2-ax- and 2-eq-X-cyclohexanones.

We have reasoned that the above failures are likely due to the ignorance of the experimentally well-documented cation complexation and/or chelation effects[9,10] and, hence, the consequent geometrical changes in the substrate. We ourselves have been attracted to the study of facial selectivities
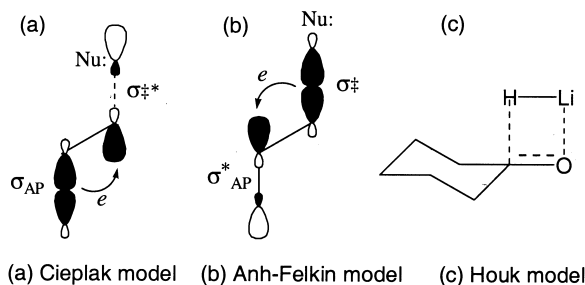

Figure 1. Pictorial representations of: (a) the Cieplak model; (b) the Anh–Felkin model; and (c) the Houk model for axial attack on cyclohexanone with LiH as the nucleophile. **Nu**=nucleophile.
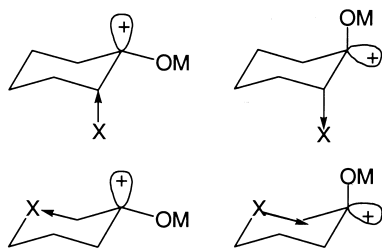
Figure 2. Stereoelectronically favored ax- and eq-orientations of $p_{C=O}$ on cation complexation. The head of the arrow indicates the direction of the electron-flow along the bond. M=cation and X=substituent.

of substituted cyclohexanones in reactions with nucleophiles by taking such effects into account. The geometrical changes arising from the complexation of the carbonyl oxygen with cations such as H^+ and Li^+ have predicted correctly the selectivities of 3-oxa-, 3-thia- and 3,5-dioxacyclohexanones.[11a] The selectivities of both the 3-ax- and 3-eq-Cl/F-cyclohexanones[11b] and also 4-substituted cyclohexanones[11c] have been reported from similar studies to conform to the experimental and/or theoretical results. This methodology has recently been applied successfully to 5-substituted-2-adamantanones as well.[11d]

In this manuscript, we report the results of the application of the cation complexation model to 2-ax- and 2-eq-substituted cyclohexanones and demonstrate that (a) the predicted selectivities are in excellent accord with the experiments, (b) in as much as the 2-substituted cyclohexanones are concerned, the model is general in its qualitative applicability; the selectivity is, respectively, axial and equatorial for electron-donating and electron-attracting 2-ax-substituents, (c) the predicted selectivity of 2-eq-MeO-cyclohexanone is in full accord with the experiments, and (d) the antiperiplanar effects are not as important as considered previously. A comparison of the performance of the complexation model with those of the Cieplak, Anh–Felkin, and Houk models is also presented to show that while the complexation model is consistently in agreement with the experiments at predicting the selectivities; other models may or may not apply.

Background

Cation complexation activates the carbonyl carbon for reaction with nucleophiles by increasing the coefficient of the p orbital on the carbonyl carbon (hereinafter referred to as $p_{C=O}$) and, thus, lowering the energy of activation for the reaction. That this complexation precedes the most actual nucleophilic attack[9] and that this occurs in the carbonyl σ plane[10] have constituted the two most significant fundamentals to motivate us to take up the ab initio MO investigations of the geometrical changes on such cation complexations.[11]

The complexation causes significant geometrical changes around the carbonyl carbon. These changes are such that the molecule achieves maximum possible conformational stability in accordance with the stereoelectronic effects.[12] An electron poor $p_{C=O}$ orients antiperiplanar to the more

electron-donating substituent on C_α. For 2-ax-substituted cyclohexanones, this translates into an axial $p_{C=O}$ orientation when the substituent is electron-donating and an equatorial $p_{C=O}$ orientation when the substituent is electron-attracting. These notions are depicted in Fig. 2. Since a nucleophilic reaction is essentially a consequence of the interactions of $p_{C=O}$ with a filled orbital on the nucleophile, the axial and equatorial $p_{C=O}$ orientations result, therefore, in ax- and eq-preferences, respectively, in the absence of other control elements including the steric effects.

The notion that an electron-donating bond that is antiperiplanar to an electron-attracting bond constitutes a stereoelectronically favored prospect can be gleaned easily from, for instance, the transition states for E1cB and E2 reactions as shown in Equations 1 and 2, respectively. It is important to note that the six-ring geometry is very likely to limit somewhat the geometrical changes caused upon a cation complexation.
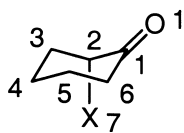

$$(1)$$

$$(2)$$
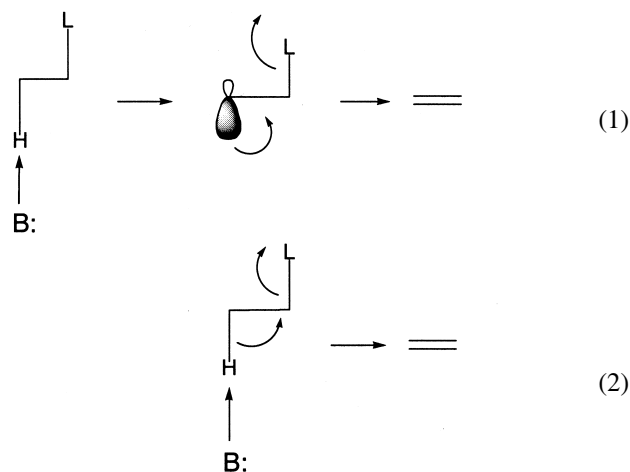
L=electron withdrawing leaving group, B=base

The geometrical consequence of an ax-like $p_{C=O}$ orientation is an increased flattening at the carbonyl carbon. This results in an increase, on the axial face, of the absolute torsion angles $D1$ (=O1–C1–C2–C3) and $D2$ (=O1–C1–C6–C5). Likewise, an eq-like $p_{C=O}$ orientation results in the decrease of these torsion angles and the ring is puckered. These geometrical changes are also reflected in the torsion angles $D3$ (=C3–C2–C1–C6) and $D4$ (=C5–C6–C1–C2) that will decrease when $D1$ and $D2$ increase, and increase when $D1$ and $D2$ decrease. Thus, an increase or decrease in these torsion angles predicts an ax- or eq-selectivity, respectively. On complexation with a cation, the bond angles $A1$ (=O1–C1–C2) and $A2$ (=O1–C1–C6) will also change as a consequence of the ensuing carbonyl pyramidalization.

Computational Methods

All the calculations were performed using the GAUSSIAN 94 program.[13] The stationary points (energy minima, all positive eigenvalues of the Hessian matrix, and transition states, one negative eigenvalue of the Hessian matrix and one single imaginary frequency) on the potential energy surface were fully optimized using the HF and MP2 methods. The

Table 1. Selected torsion angles (degree) and bond angles (degree) in 2-X-cyclohexanones (X=Cl, F, OH, SH, MeO) and their cation-complexed derivatives. $D1$=O1–C1–C2–C3, $D2$=O1–C1–C6–C5, $D3$=C3–C2–C1–C6, $D4$=C5–C6–C1–C2, $A1$=O1–C1–C2, $A2$=O1–C1–C6 (entries at 1(b), 4 and 7–9 are from Becke3LYP/6-31G(d) calculations; all other entries are from MP2/6-31G(d) calculations)

1(a)	Cyclohexanone
	$D1$=−126.65, $D2$=126.65, $D3$=52.05, $D4$=−52.05, $A1$=122.52, $A2$=122.52
(b)	$D1$=−131.04, $D2$=131.04, $D3$=48.97, $D4$=−48.97, $A1$=122.44, $A2$=122.44
2	2-ax-Cl-Cyclohexanone
	$D1$=−124.62; $D2$=123.09; $D3$=51.49; $D4$=−52.87; $A1$=120.53; $A2$=123.79
	2-ax-Cl-Cyclohexanone; protonated *anti* to C2 (E=−768.1954408)
	$D1$=−129.78; $D2$=126.99; $D3$=47.11; $D4$=−49.62; $A1$=115.07; $A2$=123.76
	2-ax-Cl-Cyclohexanone; protonated *syn* to C2 (E=−768.1941566)
	$D1$=−134.25; $D2$=131.99; $D3$=44.35; $D4$=−46.66; $A1$=121.56; $A2$=117.22
3	2-ax-F-Cyclohexanone
	$D1$=−114.76; $D2$=116.53; $D3$=59.63; $D4$=−57.65; $A1$=121.44; $A2$=124.68
	2-ax-F-Cyclohexanone; protonated *anti* to C2 (E=− 408.1816713)
	$D1$=−102.28; $D2$=104.59; $D3$=66.72; $D4$=−63.28; $A1$=115.68; $A2$=125.02
	2-ax-F-Cyclohexanone; protonated *syn* to C2 (E=−408.1798428)
	$D1$=−101.57; $D2$=105.25; $D3$=66.48; $D4$=−63.24; $A1$=122.10; $A2$=118.56
4	2-ax-F-Cyclohexanone
	$D1$=−118.64; $D2$=120.38; $D3$=57.41; $D4$=−55.53; $A1$=121.57; $A2$=124.62
	2-ax-F-Cyclohexanone; protonated *anti* to C2 (E=−409.4412842)
	$D1$=−105.16; $D2$=107.88; $D3$=64.96; $D4$=−61.28; $A1$=116.02; $A2$=124.86
	2-ax-F-Cyclohexanone; protonated *syn* to C2 (E=−409.4397727)
	$D1$=−105.02; $D2$=108.89; $D3$=64.47; $D4$=−60.96; $A1$=122.10; $A2$=118.76
5	2-ax-SH-Cyclohexanone
	$D1$=−136.52; $D2$=134.05; $D3$=44.45; $D4$=−44.45; $A1$=120.48; $A2$=122.82
	2-ax-SH-Cyclohexanone; protonated *anti* to C2 (E=−706.8053846)
	$D1$=−147.58; $D2$=142.60; $D3$=29.82; $D4$=−34.64; $A1$=115.37; $A2$=121.71
	2-ax-SH-Cyclohexanone; protonated *syn* to C2 (E=−706.8018067)
	$D1$=−142.29; $D2$=139.21; $D3$=37.43; $D4$=−40.52; $A1$=122.10; $A2$=115.68
6	2-ax-OH-Cyclohexanone
	$D1$=−125.74; $D2$=126.02; $D3$=53.86; $D4$=−53.57; $A1$=121.55; $A2$=123.80
	2-ax-OH-Cyclohexanone; protonated *anti* to C2 (E=−384.2008903)
	$D1$=− 102.79; $D2$=104.89; $D3$=66.74; $D4$=−63.38; $A1$=115.89; $A2$=124.45
	2-ax-OH-Cyclohexanone; protonated *syn* to C2 (E=−384.1990536)
	$D1$=−100.50; $D2$=104.05; $D3$=67.36; $D4$=−64.34; $A1$=122.31; $A2$=117.94
7	2-ax-MeO-Cyclohexanone
	$D1$=−126.28; $D2$=126.36; $D3$=53.16; $D4$=−53.07; $A1$=121.82; $A2$=123.64
	2-ax-MeO-Cyclohexanone; Li$^+$ *anti* to C2
	$D1$=−117.94; $D2$=119.31; $D3$=58.22; $D4$=−56.78; $A1$=121.06; $A2$=122.72
8	2-eq-OMe-Cyclohexanone
	$D1$=−125.41; $D2$=125.21; $D3$=53.16; $D4$=−53.38; $A1$=122.69; $A2$=122.82
	2-eq-OMe-Cyclohexanone; Li$^+$ *syn* to C2
	$D1$=−122.92; $D2$=124.05; $D3$=54.02; $D4$=−52.78; $A1$=120.13; $A2$=123.31
9	2-eq-OMe-Cyclohexanone; *syn* to C2 complex with BH$_3$
	$D1$=−112.60; $D2$=113.41; $D3$=60.69; $D4$=−60.54; $A1$=127.49; $A2$=118.26

Becke3LYP method was used to calculate the geometries of 2-ax-F-, 2-ax-OMe- and 2-eq-OMe-cyclohexanones and their complexes. The basis set 6-31G(d) was used throughout. The HF/6-31G(d) geometry was used as the initial guess for calculations at the MP2 and Becke3LYP levels.

Results and Discussion

Diastereofacial selectivity of 2-ax-X-cyclohexanone (X=Cl, F)

The geometrical data on the relevant torsion and bond angles and the total energies are collected in Table 1 (entries 2 and 3). We have used H$^+$ to mimic cation complexation. In a few cases we have used Li$^+$ as well. The extents of the geometrical changes on complexation with Li$^+$ were, however, lower than those with H$^+$. These changes, in fact, ought to be dependent on the rigidity of complexation. A tighter complex will cause larger geometrical changes through a greater polarization of the carbonyl π bond and, thus, influence the selectivity more than a weaker complex. Indeed, the ax/eq selectivity is known to vary from 7.7:1 to 16:1 to >25:1 in reactions of a 3,5-dioxacyclohexanone derivative with LAH, DIBAL-H, and RMgX, respectively.[14] The rigidity of the complexation will be expected to

Table 2. NBO atomic charges on selected atoms in 2-ax-X-cyclohexanones (X=Cl, F, OH, SH, MeO) and their cation-complexed derivatives (Ha$^+$ and Hs$^+$ indicate, respectively, carbonyl protonation *anti* and *syn* to C2. The C6–H$_a$ and C6–H$_e$ indicate, respectively, the axial and equatorial hydrogens on C6. The results on 2-ax-MeO-cyclohexanone and its complex with Li$^+$ (the last two entries) are at Becke3LYP/6-31G(d) level. All other charges were computed at MP2/6-31G(d) level)

X7	Charges (*e*)						
	O1	C1	C2	C6	C6–H$_a$	C6–H$_e$	X7
Cl	−0.6135	0.6665	−0.2824	−0.5341	0.2493	0.2543	−0.0891
Cl (+Ha$^+$)	−0.6486	0.8519	−0.3178	−0.5812	0.3149	0.2688	0.0155
F	−0.6196	0.6447	0.1915	−0.5345	0.2484	0.2508	−0.4458
F (+Ha$^+$)	−0.6572	0.8287	0.1827	−0.5821	0.3134	0.2723	−0.4072
SH	−0.6343	0.6723	−0.4519	−0.5336	0.2506	0.2527	−0.0235
SH (+Ha$^+$)	−0.6809	0.7808	−0.4481	−0.5618	0.3068	0.2690	0.1058
SH (+Hs$^+$)	−0.6632	0.8253	−0.4906	−0.5574	0.3052	0.2918	0.1002
OH	−0.6314	0.6539	0.0640	−0.5336	0.2466	0.2480	−0.8081
OH (+Ha$^+$)	−0.6602	0.8572	0.0526	−0.5804	0.3175	0.2671	−0.8012
MeO	−0.5338	0.5628	0.0120	−0.5548	0.2571	0.2571	−0.5827
MeO (+Li$^+$)	−0.7943	0.6709	0.0153	−0.5624	0.2930	0.2661	−0.5682

improve in that order. Further, the ax/eq selectivity remained at >25:1 when the nucleophile was varied from Me$^-$ to Bu$^-$ to Ph$^-$ derived from the respective Grignard species (RMgX).

From the total energy data, it is clear that a complexation of the oxygen electron pair that is *anti* to C2 is somewhat favored over the alternate arrangement in which the other electron pair is allowed to complex. The differences in the bond angles *A*1 (=O1–C1–C2) and *A*2 (=O1–C1–C6) show the increased desymmetrization of the molecule on such complexations. The enlargements in the torsion angles *D*1–*D*3 in the Cl-derivatives indicate preference for ax-attack. This is in accord with experiments.[15] The same torsion angles for the F-derivatives have, however, reduced considerably to less than a tetrahedral value to allow for eq-attack. Since these ground state structures after cation complexation lead to the TS structures,[16] the substantially reduced *D*1 and *D*2 in the protonated 2-ax-F-cyclohexanone leave little room for a nucleophile to enter from the ax-direction. Along with the reductions in *D*1 and *D*2, *D*3 has also reduced.

Assuming that the angle of attack[17] is, at least, 90°, the trajectory of attack on the ax-face in protonated 2-ax-F-cyclohexanone will be, at best, some 12–15° away from C3 and C5. The reaction trajectory will, therefore, pass very close to C3 and C5 and even closer to the axial hydrogens on these positions culminating in a large torsional strain. Conversely, the increased exposure of the eq-face will appear to ensure the very minimal torsional strain in the eq-TS. The eq-attack, therefore, must predominate. The genesis of the differential facial preferences of 2-ax-Cl- and 2-ax-F-cyclohexanones is present in the uncomplexed species as well. *D*1 and *D*2 in 2-ax-F-cyclohexanone are 7–10° smaller than those in 2-ax-Cl-cyclohexanone. The selectivity of 2-ax-F-cyclohexanone has not yet been reported to allow us match our prediction. The following details, however, also support the eq-selectivity.

(a) We have attempted the calculation of Houk's TS on 2-ax-F-cyclohexanone at HF/6-31G(d) level. Despite our several attempts, the ax-TS could not be located as it always converged onto the ground state LiH-complexed species. This is expected given the small values of *D*1

and *D*2 that culminate into high steric interactions between the approaching nucleophile and the axial hydrogens on C3 and C5. The eq-TS[18] was, however, located with relative ease.
(b) We have probed the facial preference of 2-ax-F-cyclo-hexanone at Becke3LYP level[19] as well (Table 1, entry 4). These parameters are somewhat overestimated over those computed from the MP2 method. It can, however, be clearly seen that the overall qualitative result that favored eq-selectivity remains unchanged.

Table 2 lists the natural bond orbital (NBO) charges on selected atoms in both the uncomplexed and complexed species. These charges are of much significance as they could be used meaningfully to rationalize the molecular geometry on cation complexation and, thus, predict the facial preference. A close inspection reveals the following:

(a) Whereas the C2 in the 2-ax-Cl-derivatives is sufficiently electron-rich, the Cl atom itself bears only a slight negative charge in the unprotonated species and a slight positive charge in the protonated derivative to indicate, in agreement with a recent report from Alkorta,[20] electron release from the Cl atom. This will help p$_{C=O}$ orient axial. An axial nucleophilic attack, therefore, is observed.
(b) The C2 in the 2-ax-F-derivatives is moderately positively charged and the attached F sufficiently negatively charged. This suggests electron withdrawal from C2 to F and, hence, stereoelectronic destabilization of an ax-oriented p$_{C=O}$. Consequently, the geometrical changes take a course that is opposite to that in the related Cl-derivative and p$_{C=O}$ develops predominantly on the eq-face to allow for eq-attacks.
(c) Though the positive charges on both the ax- and eq-hydrogens on C6 increase on carbonyl protonation, this is more prevalent for the ax-H than that for the eq-H. This indicates greater interaction of an axial C–H bond over that of an equatorial C–H with the carbonyl function. This is not surprising given the fact that an axial C–H bond orbital is parallel to the carbonyl p orbitals. Thus, all axial C–X bonds on C$_\alpha$ will influence the chemistry of the carbonyl function. This is in accord with the literature.[21] The α-substitution of Cl, Br, OH, and OAc in saturated cyclic ketones have been shown to exhibit marked effects on the absorption characteristics. The λ$_{max}$ of the

parent compound is reduced by 5–10 nm when the substituent is equatorial. However, a bathochromic shift of 10–30 nm occurs when the substituent is axial. This interaction becomes more important after the cation complexation because the $p_{C=O}$ coefficient is enlarged and it requires greater electron-donation to it. It is most certainly this additional electron requirement that forces $p_{C=O}$ orient axial or equatorial, depending upon the electronic nature of the substituent(s) on the adjacent carbon(s).

Diastereofacial selectivity of 2-ax-X-cyclohexanone (X=SH, OR; R=H, Me)

The geometrical and energy parameters are given in Table 1 (entries 5–7). The torsion angles $D1$ and $D2$ are enlarged by 8–11° on protonation in favor of ax-attack to 2-ax-SH-cyclohexanone. This is in full accord with a recent experimental study on 2-ax-SMe-cyclohexanone that underwent exclusive ax-attack on reduction with hydrides.[22] In contrast, the torsion angles $D1$ and $D2$ in 2-ax-OH-cyclohexanone are reduced by 21–23° on protonation allowing us to predict predominant eq-attack. This is also in full accord with the experiments. The reaction of *trans*-4-*t*-butyl-2-MeO-cyclohexanone with allylindium produced the axial alcohol predominantly in solvents such as THF, H$_2$O and a mixture of THF and H$_2$O.[23] Allylchromium in THF was also highly selective for the formation of the axial alcohol.[23] The results of Becke3LYP calculations on 2-ax-MeO-cyclohexanone and its complex with Li$^+$ ion are also given in Table 1 (entry 7). The geometrical changes favor eq-attack.

The torsion angles $D1$ and $D2$ in the protonated 2-ax-OH-cyclohexanone are, in magnitude, almost the same as those in the protonated 2-ax-F-cyclohexanone. If only such protonated (or cation complexed) species were to participate in reactions, the level of selectivity expected from both must match closely. The eq-attack in 2-ax-X-cyclohexanones (X=OR, F) may be additionally enhanced through a chelation-controlled eq-delivery of the nucleophile. However, such a chelation will be more effective with an oxygen substituent than with a fluorine atom since oxygen carries a larger negative charge than fluorine atom.

It could be argued that the change in the diastereoselectivity of 2-ax-SR-cyclohexanones (R=Me) is primarily due to the large bulk of the S atom and, hence, the significant steric interactions in the eq-TS. This, however, does not find support in view of the fact that the related 2-ax-MeO-cyclohexanone exhibits very high eq-selectivity. Paquette's above observations[23] in highly cation chelating solvents such as THF and water indicate clearly that the observed eq-selectivity of *trans*-4-*t*-butyl-2-methoxycyclohexanone is primarily electronic in origin and that the chelation has little to contribute.

Table 2 lists the NBO charges on selected atoms in both the uncomplexed and the complexed species. The following points emerge:

(a) A close comparison with the data on 2-ax-Cl-cyclohexanone reveals a somewhat comparable behavior of both the S and Cl atoms. Like Cl, S is very slightly nega-

tively charged, if at all, in the unprotonated species. This atom acquires relatively significant positive character on carbonyl protonation, indicating electron-release from sulfur. In consequence, C2 is appreciably electron-rich and $p_{C=O}$ orients axially for the capture of nucleophiles. (b) Whether protonated or not, the change in the charge on the carbinol oxygen in 2-ax-OH-cyclohexanone is negligible. This oxygen bears substantial negative charge and the C2 a slight positive charge. The electron-withdrawal by the carbinol oxygen is, therefore, obvious. In consequence, $p_{C=O}$ orients equatorial. The geometrical parameters on 2-ax-MeO-cyclohexanone and its complex with Li$^+$ present a very similar picture and an eq-attack is expected.

Diastereofacial selectivity of 2-eq-OMe-cyclohexanone

Since high eq-selectivity has been observed for *cis*-4-*t*-butyl-2-methoxycyclohexanone in reactions with allyl nucleophiles derived from various sources such as allylindium, allylmagnesium, allylcerium and allylchromium,[23] it was felt pertinent to study this system as well. We have computed 2-eq-MeO-cyclohexanone by the Becke3LYP method, both before and after complexation with Li$^+$. Here, complexation with Li$^+$ *syn* to C2 was considered beneficial because this is likely to allow the Li$^+$ to complex with the methoxy oxygen as well as resulting in a geometrically rigid bicyclo[4.3.0] system. Significantly, HF/6-31G(d) optimization of 2-eq-MeO-cyclohexanone that was deliberately complexed with Li$^+$ *anti* to C2 had also converged onto the above system *syn* to C2 with Li$^+$ complexed.

The significant geometrical parameters are collected in Table 1 (entry 8). In the uncomplexed molecule, the Me group is on the equatorial side of the carbonyl plane (Me-O7–C2–C1=73.85°, O7–C2–C1–O1=−4.68°). The geometrical changes on complexation are such that both the C2–O7 and O7–Me bonds are more or less in the $\sigma_{C=O}$ plane (Me-O7–C2–C1=168.60°, O7–C2–C1–O1=1.08°). The Li$^+$ ion is almost equidistant from both the oxygen atoms (1.86–1.88 Å). The torsion angles $D1$ and $D2$ have also decreased somewhat. The decrease in the torsion angles, the bicyclic geometry after cation chelation and the near co-planarity of the Me–O7 bond with that of the newly constructed Li$^+$-containing five-ring system make the eq-face highly accessible for nucleophilic additions. Additionally, the eq-face is devoid of any meaningful steric interference to the approach of a nucleophile because: (a) it is the convex face of the bicyclic species and (b) the Me substituent is away from the carbonyl and in the plane of the above Li$^+$-containing five-ring system.

The 3D structures of 2-eq-MeO-cyclohexanone and its complex with Li$^+$ are given in Fig. 3.[24,25] It is important to note that the orientation of the methyl substituent on the equatorial side of the carbonyl in the uncomplexed species will make Houk's eq-TS sterically congested. The Houk model will, therefore, predict ax-selection that contradicts experiments. The Anh–Felkin and Cieplak models cannot be applied in a straightforward manner as they are applied to the axially substituted cyclohexanones.
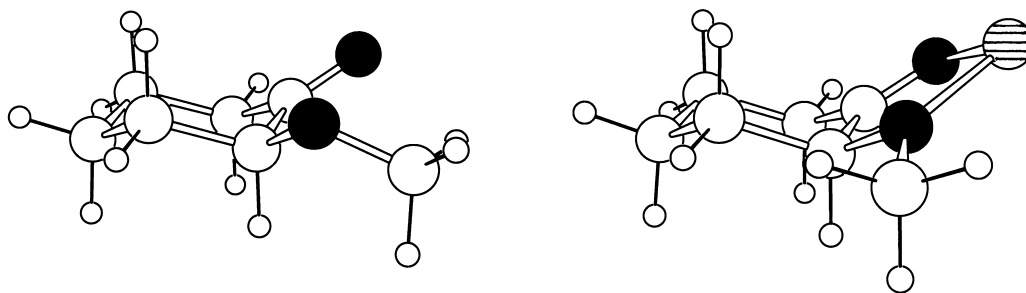
Figure 3. Becke3LYP/6-31G* 3D structures of 2-eq-OMe-cyclohexanone and its complex with Li$^+$ ion. The black and striped circles represent oxygen and lithium atoms, respectively.

It is not only cations that are used for the purposes of complexation with the carbonyl oxygen. In reductions with boranes, for instance, such cations are absent. To deal with such situations, we have calculated the complex of 2-eq-MeO-cyclohexanone with BH$_3$. The geometrical parameters are collected in Table 1 (entry 9). The torsion angles *D*1 and *D*2 have reduced considerably to suggest a preference for eq-attack. *Unlike the complex with Li$^+$ wherein the cation is almost equidistant from both the oxygen atoms and the complex itself is a rigid bicyclic structure, the boron atom is tightly bound to the carbonyl oxygen only (B–O=1.66 Å) as it is a significant 3.13 Å away from the methoxy oxygen.* The methoxy oxygen itself being located on the equatorial side of the carbonyl group [O7–C2–C1–O1=9.18°] is likely to complex with another molecule of BH$_3$ and, thus, direct an intramolecular delivery of a hydride ion to the eq-face of the carbonyl function.

Consequence of protonation on the geometry of simple α-X-acetaldehyde (X-CH$_2$CHO; X=Cl, SH, F, OMe)

The above heteroatom-controlled geometrical changes on cation complexation are general and also applicable to acyclic systems. We have computed α-Cl-, α-SH-, α-F-, and α-MeO-substituted acetaldehydes, both before and after protonation. In the initial model for each unprotonated species, the C–X bond was kept orthogonal to the σ$_{C=O}$ plane. The torsion angle of the heteroatom with the carbonyl oxygen across the intervening σ bonds changed from 162.53 to 103.40° for X=Cl and from 127.45 to 102.98° for X=SH on protonation. Both the changes are in tune with stereoelectronic arguments and indicate the participation of the C–Cl and C–S bonds in the stabilization of the protonated carbonyl function through electron-donation. This is

rendered facile by making these bonds antiperiplanar to p$_{C=O}$. Again, both the Cl and S atoms in the unprotonated species are almost electoneutral and the carbons to which they are attached are significantly negatively charged. Both the heteroatoms acquire moderate positive charge on carbonyl protonation (Table 3) just as observed above in 2-ax-X-cyclohexanones (X=Cl, SH).

For X=F and OMe, the torsion angle of the heteroatom with the carbonyl oxygen changed little and was 180° in both. This shows the orthogonal arrangement of these electron-attracting bonds with p$_{C=O}$. The carbon bearing the F is near electroneutral and F itself bears significant negative charge in both the unprotonated and the protonated species. Likewise, the methoxy oxygen in 2-MeO-acetaldehyde carries significant negative charge that changed negligibly on carbonyl protonation. These charge distributions and the relative stereodispositions are clear indications of the strong electron-attracting nature of both the C–F and C–O bonds as opposed to those of the C–Cl and C–S bonds.

Further Discussions

The predictions from the complexation model may appear to parallel the predictions from the Cieplak model for 2-ax-X-cyclohexanones. The two, however, approach the problem differently. The Cieplak model, for instance, envisions electron donation from a more electron-rich C2-substituent to the σ* orbital associated with the bond under construction and, hence, predicts eq-attack for the 2-ax-Cl-, 2-ax-F- and 2-ax-OR-cyclohexanones due to the electron-withdrawing nature of these substituents. The predicted eq-selectivity of 2-ax-Cl-cyclohexanone clearly contradicted the experimental ax-selectivity. The complexation model, however, performs consistently well in predicting the correct selectivity of all these species. This model has also led us to discover the C–Cl bond in 2-ax-Cl-cyclohexanone as electron donating overall. This bond has traditionally been considered electron-attracting. Furthermore, whereas the complexation model can be easily applied to cyclohexanones bearing 2-eq-substituents, the Cieplak and Anh–Felkin models do not apply.

Table 4 lists the antiperiplanar interactions of C2–C3, C5–C6, C2–X and C6–H$_{ax}$ with π*$_{C=O}$ in 2-ax-X-cyclohexanones (X=Cl, F, OH and SH) and the protonated derivatives from a second order perturbation theory analysis of the Fock matrix in NBO basis. We concentrate only on these

Table 3. NBO atomic charges on selected atoms in XCH$_2$CHO (X=Cl, F, SH, MeO) and their protonated derivatives at MP2/6-31G(d) level (H$^+$ indicates carbonyl protonation *anti* to C$_\alpha$)

X	Charges (*e*)			
	O (C=O)	C (C=O)	C$_\alpha$	X
Cl	−0.5999	0.4941	−0.5173	−0.0752
Cl (+H$^+$)	−0.6393	0.6361	−0.5213	0.0678
SH	−0.6033	0.4974	−0.6806	0.0019
SH (+H$^+$)	−0.7070	0.3704	−0.5734	0.2988
F	−0.6106	0.4647	−0.0099	−0.4321
F (+H$^+$)	−0.6423	0.6669	−0.0397	−0.3833
MeO	−0.6216	0.4989	−0.1483	−0.6490
MeO (+H$^+$)	−0.6485	0.7018	−0.1820	−0.6442

Table 4. The antiperiplanar effects from second order perturbation theory analysis of the Fock matrix in NBO basis for 2-ax-X-cyclohexanones (X=Cl, F, OH, SH) and their protonated derivatives

Donor NBO (i)	Acceptor NBO (j)	E (2) (kcal/mol)
2-ax-Cl-cyclohexanone		
σ_{C2-C3}	$\pi^*_{C=O}$	02.05
σ_{C5-C6}	$\pi^*_{C=O}$	03.22
σ_{C2-Cl}	$\pi^*_{C=O}$	04.43
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	07.64
2-ax-Cl-Cyclohexanone; protonated *anti* to C2		
σ_{C2-C3}	$\pi^*_{C=O}$	02.59
σ_{C5-C6}	$\pi^*_{C=O}$	05.75
σ_{C2-Cl}	$\pi^*_{C=O}$	11.47
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	15.38
2-ax-F-Cyclohexanone		
σ_{C2-C3}	$\pi^*_{C=O}$	03.07
σ_{C5-C6}	$\pi^*_{C=O}$	04.28
σ_{C2-F}	$\pi^*_{C=O}$	01.73
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	06.77
2-ax-F-cyclohexanone; protonated *anti* to C2		
σ_{C2-C3}	$\pi^*_{C=O}$	04.98
σ_{C5-C6}	$\pi^*_{C=O}$	07.51
σ_{C2-F}	$\pi^*_{C=O}$	02.91
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	12.75
2-ax-OH-Cyclohexanone		
σ_{C2-C3}	$\pi^*_{C=O}$	02.43
σ_{C5-C6}	$\pi^*_{C=O}$	03.41
σ_{C2-O7}	$\pi^*_{C=O}$	02.42
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	07.58
2-ax-OH-Cyclohexanone; protonated *anti* to C2		
σ_{C2-C3}	$\pi^*_{C=O}$	06.03
σ_{C5-C6}	$\pi^*_{C=O}$	08.18
σ_{C2-O7}	$\pi^*_{C=O}$	03.63
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	12.50
2-ax-SH-Cyclohexanone		
σ_{C2-C3}	$\pi^*_{C=O}$	01.63
σ_{C5-C6}	$\pi^*_{C=O}$	02.28
σ_{C2-S}	$\pi^*_{C=O}$	06.94
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	08.57
2-ax-SH-cyclohexanone; protonated *syn* to C2		
σ_{C2-C3}	$\pi^*_{C=O}$	02.31
σ_{C5-C6}	$\pi^*_{C=O}$	04.56
σ_{C2-S}	$\pi^*_{C=O}$	22.52
$\sigma_{C6-H_{ax}}$	$\pi^*_{C=O}$	13.95

interactions because it is the $\pi^*_{C=O}$ that is under attack during reaction.

In 2-ax-Cl-cyclohexanone, both σ_{C-Cl} and $\sigma_{C6-H_{ax}}$ donate to $\pi^*_{C=O}$ by 4.43 and 7.64 kcal mol^{-1}, respectively. These donations improve to 11.47 and 15.38 kcal mol^{-1}, respectively, on carbonyl protonation. This situation is somewhat different in 2-ax-F-cyclohexanone. Whereas the σ_{C-F} has negligible interaction with $\pi^*_{C=O}$, the $\sigma_{C6-H_{ax}}$ interacts with it to the extent of 6.77 kcal mol^{-1} and this improves to 12.75 kcal mol^{-1} on protonation. The situation with 2-ax-OH-cyclohexanone is similar to that of 2-ax-F-cyclohexanone. The interaction of $\sigma_{C6-H_{ax}}$ with $\pi^*_{C=O}$ increases from 7.58 kcal mol^{-1} to 12.50 kcal mol^{-1} on protonation. Finally, 2-ax-SH-cyclohexanone possesses interactions of σ_{C-S} and $\sigma_{C6-H_{ax}}$ with $\pi^*_{C=O}$ to the extent of 6.94 and 8.57 kcal mol^{-1} that improve to 22.52 and 13.95 kcal mol^{-1}, respectively, on protonation.

The total antiperiplanar effects in the axial direction that

arise from the C2-X and C6–H$_{ax}$ bonds are 12.07, 8.07, 10.00 and 15.51 kcal mol^{-1} and these improve on protonation to 26.85, 15.66, 16.13 and 36.57 kcal mol^{-1} in 2-ax-Cl-, 2-ax-F-, 2-ax-OH- and 2-ax-SH-cyclohexanones, respectively. The total antiperiplanar effects in the equatorial direction that arise from the C2–C3 and C5–C6 bonds are less significant and improve, on protonation, from 5.27 to 8.34, 7.35 to 12.49, 5.84 to 14.21 and 3.91 to 6.87 kcal mol^{-1} in 2-ax-Cl-, 2-ax-F-, 2-ax-OH- and 2-ax-SH-cyclohexanones, respectively. If one has to rely only on the antiperiplanar effects and, hence, electron donation from the σ bonds on C2 and C6 to the incipient bond, all of the above species will be expected to favor ax-selection. However, the results are to the contrary. While the 2-ax-Cl- and 2-ax-SR-cyclohexanones display predominantly ax-selectivity, the 2-ax-F- and 2-ax-OR-cyclohexanones vie for eq-selectivity. There are, therefore, effects other than the antiperiplanar effects that influence the facial selectivity. These observations are in agreement with those of Tomoda[8] who has argued the antiperiplanar effects involving the incipient bond to be less significant as a control factor for π-facial selection.

If one has to rely only on the total space available on either side of the carbonyl group in the uncomplexed ground state like the EFOE model, the opposite results from cyclohexanone (ax-selective) and 2-ax-OH-cyclohexanone (eq-selective) appear difficult to explain. The $D1$ and $D2$ angles being very similar (Table 1, entries 1(a) and 6), both the molecules will integrate for very much the same space on the ax-side. The eq-side, however, will be expected to integrate for less space due to the bulk of the ax-OH function. This will predict ax-attack for 2-ax-OH-cyclohexanone. This situation, however, changes somewhat when one compares the Becke3LYP geometrical data for 2-ax-MeO-cyclohexanone (Table 1, entry 7) with similar data for cyclohexanone (Table 1, entry 1(b)). The angles $D1$ and $D2$ in 2-ax-MeO-cyclohexanone are ~5° smaller than those in cyclohexanone. This means the space available on the ax-face of 2-ax-MeO-cyclohexanone is less than that available in cyclohexanone. However, the space available on the eq-face of 2-ax-MeO-cyclohexanone will also not be much due to the large bulk of the MeO substituent. It is significant to remember that the Me group projects to the equatorial face and, hence, covers substantial space. Since the EFOE model has not yet been applied to 2-ax-X-cyclohexanones, its efficacy cannot be compared with that of the cation complexation model.

The steric interactions arising from the ax-MeO substituent will be expected to favor Houk's ax-TS over the alternative eq-TS. The Houk model, therefore, is also unable to adequately accommodate the observed eq-selectivity of 2-ax-MeO-cyclohexanone.

Conclusions

The results from the cation complexation model are collected together with the results from other models and the experiments in Table 5. An inspection of Table 5 is revealing. Whereas the 2-ax-Cl- and 2-ax-SR-cyclohexanones were predicted for ax-attack, the 2-ax-OMe- and

Table 5. A comparison of the diastereoselectivities of 2-X-cyclohexanones predicted from different models and the experiments (a blank (−) indicates that the requisite results are not available)

Substituent	ax/eq-Diastereoselectivity from						Ref.
	Experiment	Anh–Felkin	Cieplak	Houk	EFOE	Cation-complexation	
2-ax-Cl	ax	eq	ax	ax	−	ax	15
2-ax-F	−	ax	eq	eq	−	eq	5
2-ax-SR	ax	eq	ax	ax	−	ax	22
2-ax-OR	eq	ax	eq	ax	−	eq	23
2-eq-OR	eq	na	na	ax	−	eq	23

2-eq-OMe-cyclohexanones were predicted for eq-attack; all in full accord with the experiments. Furthermore, whereas the predicted eq-preference of 2-ax-F-cyclohexanone must await experimental verification, it falls very well in line with the observed eq-selectivity of 2-ax-OR-cyclohexanone. All these results are to be contrasted with the predictions from the Anh–Felkin model.

The complexation model performed well in predicting the correct eq-selectivity for 2-eq-OMe-cyclohexanone. The Anh–Felkin and Cieplak models do not apply. For the steric interactions with the equatorially disposed methyl group in the uncomplexed species, Houk's eq-TS is very likely to be of higher energy than the corresponding ax-TS. The Houk model, therefore, appears unsuitable for correctly predicting the diastereoselectivity of 2-eq-MeO-cyclohexanone.

The complexation model has a general qualitative applicability in as much as the electron-donating and electron-attracting effects of the substituent atoms or groups are clearly defined. It predicts ax- and eq-attacks to cyclohexanones bearing, respectively, an axial electron-donating and an electron-attracting substituent. Although not reported herein, the same qualitative predictions are made from the significantly less time-consuming HF/6-31G(d) calculations as well. The complexation model should prove of significant value for large systems and for systems that have more than one substituent at either the same carbon or at different carbons.[26]

Supplementary material: Cartesian coordinates of the geometries of 2-ax-Cl-, 2-ax-F-, 2-ax-OH- and 2-ax-SH-cyclohexanones and their *anti-* and *syn*-protonated derivatives optimized at MP2/6-31G(d) level, 2-ax-MeO- and 2-eq-MeO-cyclohexanones and their complexes with Li^+ optimized at Becke3LYP/6-31G(d) level, the complex of 2-eq-MeO-cyclohexanone with BH_3 optimized at Becke3LYP/6-31G(d) level and the Houk's eq-TS for 2-ax-F-cyclohexanone optimized at HF/6-31G(d) level (9 pages).

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