The Directional Changes in Torsion Angles Alone After Complexation of the Carbonyl Oxygen with a Prototypical Cation such as H+ Predict the Facial Selectivity of Substituted Cyclohexanones. An ab initio Investigation

Duraiswamy A. Jeyaraj, Arpita Yadav, Veejendra K. Yadav*

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Abstract: H+ was taken as a prototypical cation for complexation with the carbonyl oxygen of 3-oxa-, 3,5-dioxa-, and 3-thiacyclohexanones. The geometries of the complexes were fully optimized using ab initio MO calculations with 6-31G basis set. The complexation desymmetrizes the molecular geometry further to an extent that the torsion angle changes on the axial face can be rationally used for the prediction of the facial selectivity in reactions with nucleophiles. The torsion angle changes are sensitive to the nature, position, and orientation of the substituents. © 1997 Published by Elsevier Science Ltd.

The desymmetrization of the two faces of a planar carbonyl group is a fundamental paradigm of stereoselective synthesis. The failure of the Felkin-Anh model[1] to explain the observed diastereoselectivity in nucleophilic additions to certain substituted cyclohexanones and the alternative rationale based on the Cieplak model [2] are of much current interest.[3] Based on a detailed experimental study, Cieplak could show that in 3-substituted cyclohexanones the relative proportion of axial attack increases when the substituent becomes more electronegative. The stereochemical control was attributed to electron donation from the occupied orbitals of the ring into the vacant σ^* orbital associated with the bond being formed. This explanation has been considered based on a rather "paradoxical assumption" and even "dubious".[3a]

In this communication, we wish to report a conceptually simple approach to the assessment of facial selection in nucleophilic additions to heteroatom-containing cyclohexanones. A simple argument to consider is the geometrical changes in the substrate due to complexation with a cation before the actual attack of the nucleophile. This premise is based on the very fact that such a complexation constitutes the initial step of the reaction profile.[4] This complexation will reduce the C=O bond order and alter the torsion angles of the carbonyl oxygen with the ring positions. An increase in the torsion angles on the axial face will predict preferential axial attack. Likewise, a reduction in the torsion angles will indicate equatorial attack. Since these torsion angle changes are expected to depend on the nature, orientation, and relative position from the carbonyl function of a ring substituent, they are likely to constitute valuable tools for diastereoface determination in substituted cyclohexanones.

From the theory of stereoelectronic effects, a situation entailing an electron pair orbital antiparallel to a polar electron-attracting σ-bond on an adjacent atom is more stable than a situation where the same spatial relationship cannot be held. The higher stability is ascribed to a donor-acceptor kind of interaction between the two. The interaction is the greatest when the two participating orbitals are antiperiplanar and the least when the same are orthogonal. If we extend this notion to the relative orientations of an electron attracting polar σ-orbital and an

empty p-orbital on a carbonyl carbon, both must be orthogonal. The empty p-orbital, however, will orient antiperiplanar to an electron releasing σ-bond. The orthogonal situation must be expected to prevail in 3-oxacyclohexanones and the antiperiplanar situation in 3-thiacyclohexanones. This is so because the C-O bond is electron-attracting from C to O and the S-C bond electron-donating from S to C. This orientational preference must be heightened on complexation of the carbonyl oxygen with a cation; the overall easy-to-observe effect being on the torsion angles. The torsion angles on the axial face will enlarge and shrink, respectively, in 3-oxa- and 3-thiacyclohexanones. Consequently, while 3-oxacyclohexanone will undergo a prefered axial attack, 3-thiacyclohexanone must embrace the nucleophile from an equatorial trajectory. We present below an ab initio MO computational evidence[5] for these predicted torsion angle changes on complexation with a prototypical cation H$^+$. The choice of H$^+$ as cation was due to the computational simplicity.
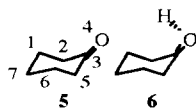
Table 1
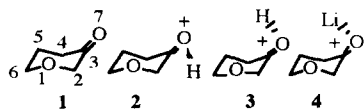
	1	2	3	4
D1	147.66	157.05	159.97	150.22
D2	147.22	153.56	156.41	147.51
A1	122.11	116.72	122.43	121.40
A2	120.42	121.64	115.33	119.83

D1 = O7C3C4C5, D2 = O7C3C2O1
A1 = O7C3C4, A2 = O7C3C2

Table 2

	5	6
D1	132.22	132.96
D2	132.09	132.94
A1	121.89	122.36
A2	121.90	116.74

D1 = O4C3C2C1, D2 = O4C3C5C6
A1 = O4C3C2, A2 = O4C3C5

Table 3
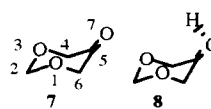
	7	8
D1	160.20	165.63
D2	160.10	165.21
A1	120.62	122.40
A2	120.64	115.82

D1 = O7C5C4O3, D2 = O7C5C6O1
A1 = O7C5C4, A2 = O7C5C6

The relevant parameters of significance obtained from calculations on 3-oxacyclohexanone (1) are given in **Table 1**. The two torsion angles, D1 and D2, represent the angles on the axial face, their signs have therefore, been omited. Because the electron pair orbitals on the carbonyl oxygen are in the carbonyl σ plane, only the in-plane complexation was considered. The site-selectivity of complexation was also considered and, hence, the pair 2/3 emerged. The energy difference of the pair is very small (0.8 kcal mol^{-1}). A comparison of 2 and 3 with 1 brings out the following points: (a) the differential changes in the two designated angles A1 and A2 signify further desymmetrization of the carbonyl and (b) the increase in the torsion angles D1 and D2 indicate empty p-orbital on the carbonyl carbon tending to orient axial and, thus, pushing the C-O bond equatorial. An attacking nucleophile shall naturally be electrostatically drawn to the axial face of the carbonyl as is indeed found from experiments to happen.[2] **Table 2** lists parameters for cyclohexanones for comparison.

Table 3 shows data on 3,5--dioxacyclohexanone 7 and its protonated derivative 8. The combined effect of the two ring oxygens must be the even more pronounced equatorial orientation of the carbonyl C-O bond than that in 3-oxacyclohexanone. The torsion angles D1 and D2 will, therefore, be larger and lead to a further enhanced preference for axial attack. These stereoelectronic arguments are in excellent accord with the results. The dioxa species 7 itself shows ~13° large the torsion angles D1 and D2 than in the monoxa species 1. The experimental observations are in full accord with the computational predictions. The dioxa species exhibit greater axial preference than the monoxa species.[6] Further, the higher Lewis acid strength of a cation will be expected to contribute to.the observed face selection through a greater polarization and, hence, enhanced desymmetrization of the carbonyl. Conversely, the cation remaining the same, the selectivity must not vary

significantly for the small changes in the steric requirement of the actual nucleophile. In agreement with this, the ax:eq selectivity varies from 7.7:1 to 16:1 to >25:1 in reactions of a 3,5-dioxacyclohexanone derivative with LAH, DIBAL and a Grignard, respectively. The quality of the complexation will be expected to improve in that order. Moreover, in keeping with expectation, the diastereoselectivity remained at >25:1 when the nucleophile was varied from Me^- to $n-Bu^-$ to Ph^- derived from the respective Grignard reagents.[6a]

In the event of the cation possessing poor complexing ability, the level of selection must be low for the reasons of less carbonyl polarization and, hence, less defined ax/eq disposition of the carbonyl C-O bond. A comparision of **3** and **4** (**Table** 1) brings out these features very clearly. In the complex with Li^+, the enhancement in the torsion angles D1 and D2 is 9-10° less than those in the complex with H^+. In parallel to this, the relative yield of the equatorial approach of AlH_4^- is 10% in the presence of Li^+ and 15% in the presence of tri-n-octyl-n-propylammonium ion.[6b] Though the high 88% and 80.5% equatorial selectivity observed in the reduction of 4-methylcyclohexanone by, respectively, K-selectride and Li-selectride is necessarily due to the very high steric interactions involved in the transition state for axial attack, the marginally higher equatorial selectivity observed with K-selectride may be due to the inferior complexing capability of K^+ over that of Li^+.[6c]

In calculations of the transition state energies for nucleophilic attack, both Houk[7] and Frenking[3a] have opted for LiH to mimic the nucleophilic species which, from fundamental standpoint, is less realistic; LiH is little known to act in the capacity of a nucleophile. Further, the transition states considered by these authors and also by Frenking et al[3a] entail the placement of Li-H in parallel to the carbonyl σ-plane and, thus, its direct attack on the π-bond. This ignores in-σ-plane complexation of Li^+ with the carbonyl oxygen. Our own calculations on 1-Li^+ show very similar axial attack tendency irrespective of the relative position of Li^+, whether or not in carbonyl σ-plane. In sharp contrast to this, in calculations where we wished to place H^+ above and below the σ-plane, the geometry converged always onto the in-plane complex counterpart. The Li-O bond was computed at 1.74 Å which is rather large and appears to show probably only the electrostatic attraction between the two constituent atoms. The complexation being the first step, it also appears that a minimum of two molecules of simple nucleophiles such as RMgX, RLi and the likes shall be required in the transition state. The polymeric forms of these reagents are well known.

Table 4

	9	10	11	12	13
D1	122.69	105.30	102.21	126.14	151.45
D2	122.91	111.86	107.52	121.71	146.23
A1	120.96	116.46	122.72	118.03	111.59
A2	121.73	122.60	116.46	123.53	122.90

D1 = O7C3C2S1, D2 = O7C3C4C5, A1 = O7C3C2, A2 =O7C3C4

Finally, we take up 3-thiacyclohexanone **9** (**Table** 4) and see how does the present approach account for the observed equatorial preference of attack by nucleophiles.[2] The stereoelectronic effects and the electron donating nature of a S-C bond would require the empty orbital on the carbonyl carbon to orient antiperiplanar (i.e. equatorial) to the S-C bond to constitute an arrangement which will be prefered over the one which has

them orthogonal (i.e. axial). This line of argument is fully supported by the substantial lowering (11-20°) of the torsion angles D1 and D2 on protonation as in **10** and **11**. To reaffirm these observations, we considered imparting electron-withdrawing character to the S-C bond by complexation of S with H^+ as in **12** and studied the effect of complexation of carbonyl oxygen with H^+ on D1 and D2. Sure enough, both the torsion angles enlarged considerably (24-27°). This behaviour is similar to that of 3-oxacyclohexanone.

In summary , we have shown by ab initio MO calculations that a simple application of stereoelectronics theory provides reliable predictive clues about the facial selectivity of substituted cyclohexanones in reactions with nucleophiles. Our results also indicate that in any modelling of the transition states of these reactions, complexation of the carbonyl oxygen with a cation is a must for a realistic reaction profile.[8]

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