Pergamon

Tetrahedron Letters, Vol. 38, No. 34, pp. 6095-6098, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01376-2

3-Halocyclohexanones. Torsion Angle Changes After Cation-Carbonyl Complexation Dictate the Facial Selectivity in Reactions with Nucleophiles: An ab initio Investigation

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Abstract: The geometrical changes that take place after complexation of the carbonyl oxygen of 3-halocyclohexanones with prototypical cations such as H^+ and Li^+ were calculated using ab initio MO methods at 6-31G level. The torsion angle changes interpret rationally the experimentally known axial preference of the 3-eq-derivatives and the axial preference (predicted from transition state calculations) of the 3-ax-species.

In a recent communication we reported on the facial selectivity of 3-oxa- and 3-thia-substituted cyclohexanones and demonstrated that the geometrical changes upon complexation of the carbonyl oxygen with representative cations such as H^+ and Li^+ served well to predict the prefered face for nucleophilic attack.[1] The geometrical changes upon complexation have their roots in stereoelectronic effects[2]. Our ab initio MO calculations predicted an enlarged empty p orbital on the carbonyl carbon, its orientation dependent upon the polarisation of the α, β-bond. The orbital is oriented orthogonal to the plane containing the bond when electron release is from C_α to C_β but antiperiplanar to it when the electron release is from C_β to C_α. Whereas the orthogonal arrangement required the p orbital to orient axial, the antiperiplanar arrangement had the same equatorially disposed. The selectivity of nucleophilic attack was, therefore, axial and equatorial, respectively.

In the present manuscript, we wish to comment on the π-facial selectivity of nucleophilic additions to 3-halocyclohexanones. The Cieplak model predicts axial attack irrespective of whether the halogen is axial or equatorial.[3] From transition state calculations using ab initio quantum chemical methods, Frenking *et al.* have predicted equatorial attack on 3-ax-fluorocyclohexanone and axial attack on the related 3-eq-species.[4] These authors have computed the equatorial attack on 3-ax-fluorocyclohexanone to be favored over the axial attack by 2.3 kcal mol^{-1}. Likewise, the axial attack on 3-eq-fluorocyclohexanone was computed to be favored over the equatorial attack by 2.7 kcal mol^{-1}. Whereas the prefered axial attack on cyclohexanones bearing equatorial electron-withdrawing substituents at position 3 is known[3b], Frenking's prediction of equatorial attack on 3-ax-fluorocyclohexanone has not been verified experimentally due to the conformational mobility of rings of compounds studied.

Huang and Dannenberg, in their application of the Polarized π-Frontier Molecular Orbital (PPFMO) method[5] to the description of diastereofacial selectivities in substituted cyclohexanones, observed discrepancy between the PPFMO and ab initio results for attack on 3-ax-fluorocyclohexanone.[6] In contrast to Frenking's ab initio results to favor equatorial attack, the PPFMO method predicted only axial addition. Whether this discrepancy was due to 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 was included in the ab initio calculation on transition state but not in the PPFMO calculation on the reagent was left to speculation. Houk has observed ring strain and electrostatic effects as the two most significant elements to contribute to facial selectivity.[7] However, the PPFMO method which does not take either of these two elements into consideration predicts still the same general trend. Huang and Dannenberg, therefore, concluded "at least some of the selectivity is already inherent in the reagent itself".

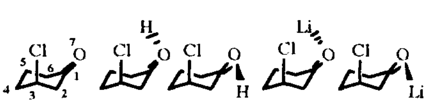
From electron density studies on monosubstituted cyclohexanones and heterocyclohexanones, Shi and Boyd have shown no significant difference in the extents of charge depletion on the two sides of the carbonyl plane.[8] This is in contradiction to the studies of Klein[9] as well as Frenking,[4] both having computed nonequivalent LUMO distributions on the two faces. Moreover, if the little difference in charge depletion had any significant effect, the 3- and 4-substituted cyclohexanones must exhibit slight preference for equatorial attack. This is, again, in contradiction to the experimentally observed preference for axial attack. It was, therefore, assumed that the extents of electron deficiency on both the faces were quite similar and that it did not play a significant role in diastereoselection. The selectivity was, therefore, considered to be controlled by the electrostatic field difference between the two sides of the carbonyl plane which was in agreement with the conclusions of Houk *et al.* [7]

We have stated in our earlier publication that a nucleophilic attack on a carbonyl carbon must generally be preceded by complexation of a cation with the carbonyl oxygen and that this complexation must occur in the carbonyl σ plane. This complexation will reduce the C=O bond order and, hence, affect the torsion angles of the carbonyl oxygen with the ring positions in the process of the ensued pyramidalization at the carbonyl carbon. This pyramidalization must be reflected in the torsion angle C2C1O7C6 (= D1) in the complexed species which must either increase or decrease in respect of that in the parent uncomplexed species. The changes in D1 on the axial face will translate into corresponding changes in the torsion angles O7C1C6C5 (= D2) and O7C1C2C3 (= D3). Alternatively, the increase or decrease in the torsion angles may be linked, respectively, to ring flattening or ring puckering at the carbonyl carbon. Since the magnitude of change in D1 (a measure of pyramidalization) is expected to be small, it may be more meaningful to focus on the changes in D2 and D3.

We have studied 3-chloro- and 3-fluorocyclohexanones.[10] The carbonyl oxygen was allowed to complex with H^+ and Li^+ in its σ plane. Because there are two distinct sites available for complexation, both were studied. In **Tables 1** and **2**, we have collected D1-D3 parameters for the 3-ax- and 3-eq-chlorocyclohexanones, respectively. The angles O7C1C6 (= A1) and O7C1C2 (= A2) are also given as these are the measures of further desymmetrization about the carbonyl carbon on complexation. The all round reductions in D1-D3 in **2** suggest equatorial attack. Although the changes in **4** and **5** are identical, the subtle decreases in all the three torsion angles support equatorial attack. Whereas the facial distinction from the changes in D2 and D3 in **3** is not so clear, the 1° reduction in D1 may be taken to favor, once again, equatorial attack. On the contrary, 3-eq-chlorocyclohexanone (**6**) must prefer axial attack. The torsion angles D2 and D3 are enlarged by > 10° in complexes with H^+ and > 6° in complexes with Li^+. D1 is also enlarged by 1.3-1.9°, its magnitude, though, is not as well pronounced as the changes in D2 and D3. It is interesting to note that the enhancements in D2 and D3 in the complexes of the 3-equatorial derivative are considerably larger than the reductions in the same in the

3-axial counterparts. Consequently, 3-eq-chlorocyclohexanone will be predicted to display improved π-facial selection in comparison to 3-ax-chlorocyclohexanone.

Table 1: 3-ax-chlorocyclohexanone

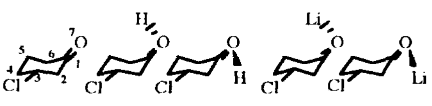


1 2 3 4 5

	1	**2**	**3**	**4**	**5**
D1	183.71	181.76	182.70	183.03	183.03
D2	138.27	135.62	140.71	138.16	138.16
D3	140.47	133.93	138.54	137.56	137.56
A1	122.15	117.21	122.71	121.42	121.42
A2	120.90	122.22	116.00	120.23	120.23

D1 = C2C1O7C6; D2 = O7C1C6C5; D3 = O7C1C2C3
A1 = O7C1C6; A2 = O7C1C2

Table 2: 3-eq-chlorocyclohexanone



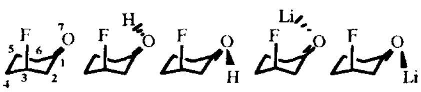
6 7 8 9 10

	6	**7**	**8**	**9**	**10**
D1	181.48	182.93	183.40	183.07	182.76
D2	134.18	144.89	148.04	141.82	140.74
D3	134.33	145.64	147.80	141.63	141.11
A1	122.32	122.27	116.34	121.07	121.12
A2	121.21	115.73	121.40	120.10	120.14

D1 = C2C1O7C6; D2 = O7C1C6C5; D3 = O7C1C2C3
A1 = O7C1C6; A2 = O7C1C2

Tables 3 and **4** comprise the results on 3-ax- and 3-eq-fluorocyclohexanones, respectively. Analysed on the patterns of 3-chlorocyclohexanones, 3-ax-fluorocyclohexanone must undergo equatorial attack and the 3-eq-fluorocyclohexanone axial attack. Looking at the magnitudes of the changes in the D1-D3 parameters, an axial fluorine atom at C3 will be predicted to be a better director for equatorial attack than an axial chlorine atom. A similar observation can be made for the two 3-eq-species where, again, the fluorine appears a better control element than chlorine. The present facial selectivity predictions are in excellent accord to the reported predictions of Frenking et al[4] which are based upon tenuous differential transition state energies. It is known from experiments that cyclohexanones bearing 3-equatorial electron-attracting substituents undergo attack by nucleophiles on the axial face.[3]

Table 3: 3-ax-fluorocyclohexanone

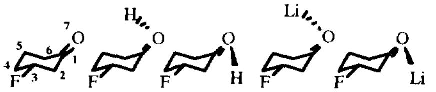


11 12 13 14 15

	11	**12**	**13**	**14**	**15**
D1	183.15	182.05	178.51	179.94	179.42
D2	138.07	139.44	127.88	130.94	129.38
D3	139.77	136.68	125.92	129.22	127.96
A1	122.08	122.73	117.50	121.77	121.78
A2	121.07	116.13	122.52	120.74	120.86

D1 = C2C1O7C6; D2 = O7C1C6C5; D3 = O7C1C2C3
A1 = O7C1C6; A2 = O7C1C2

Table 4: 3-eq-fluorocyclohexanone



16 17 18 19 20

	16	**17**	**18**	**19**	**20**
D1	180.96	182.86	182.81	182.48	183.07
D2	133.58	147.04	147.13	140.84	142.55
D3	134.59	149.67	149.71	142.26	144.50
A1	122.17	122.05	116.38	121.09	120.93
A2	121.44	115.67	121.39	120.24	120.13

D1 = C2C1O7C6; D2 = O7C1C6C5; D3 = O7C1C2C3
A1 = O7C1C6; A2 = O7C1C2

The axial attack on the 3-eq-species can be explained by stereoelectronic effects. The substituent imparts electron-withdrawing character into the C2-C3 bond which, in turn, controls the pyramidalization of the carbonyl carbon and ensures, as much as possible, the arrangement of the enlarged electron-depleted p orbital orthogonal to it. This amounts to axial disposition and, hence, the axial attack by a nucleophile. If these arguments were to hold for the 3-ax-species, as one may like to expect, only axial attack will be predicted. However, the axial orientation of the carbonyl p orbital will result in a 1,3-dipolar interaction with the axial substituent. It would, therefore, appear that this dipolar interaction is more important than the stereoelectronic effect arising from the electron-attracting axial substituent. This causes the carbonyl pyramidalization to orient the p orbital equatorial for capture of the nucleophile. Frenking has attributed this equatorial preference to a combination of (i) better interactions between a nucleophile approaching from equatorial side and 3-ax-halocyclohexanone than that in the axial approach and (ii) steric interactions between the 3-axial substituent and the attacking nucleophile in the alternate transition state for axial attack.[4] While we do not disagree with either of these, we believe that the above 1,3-dipolar interaction is even more significant.[11] The selectivity, therefore, is already inherent in the reagent itself, more so after cation complexation, as obseved by Huang and Dannenberg.[6]

In conclusion, we have demonstrated that a simple geometry calculation after cation complexation of the carbonyl oxygen in 3-halocyclohexanones suffices to reliably predict their diastereofacial selectivities. While we subscribe to steric interactions between the 3-ax-halogen and the nucleophile in the transition state for axial attack, we believe that the 1,3-dipolar interactions between the 3-ax-halogen and the axially oriented p orbital on the carbonyl carbon are of greater influence in the determination of the π-facial selectivity.

Acknowledgements: This work was supported by the Council of Scientific & Industrial Research, India. The authors wish to thank Dr. Arpita Yadav for helpful discussions and Mr. Nirmal Roberts of Computer Centre, IIT Kanpur for generous allocation of computer time on HP-9000 series mini supercomputers.

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(*Received in UK* 4 *June* 1997; *revised* 1 *July* 1997; *accepted* 4 *July* 1997)