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The Origin of the Relative Stability of Axial Conformers of Cyclohexane and Cyclohexanone Derivatives: Importance of the CH/n and CH/π Hydrogen Bonds

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Ab initio MO calculations were carried out at the MP2/6-311++G(d,p) level to investigate the Gibbs energy of conformational isomers of cyclohexanes *cyclo*-$C_6H_{11}X$ **3** and cyclohexanones *cyclo*-C_6H_9OX **4**. In **3**, it has been found that the conformer bearing an oxygen or halogen atom ($X = OCH_3$, F, Cl, and Br) at the axial orientation is relatively stable as compared to corresponding alkyl cyclohexanes; the result is consistent with documented experimental data. For X = CCH and CN, the axial conformer has been suggested to be slightly more stable. In **4**, the axial conformer has been found to be more stable than the equatorial conformer, except for X = OH. Short non-bond distances have been disclosed in every axial conformer of **3** and **4**, between axial CHs of the cyclohexane ring and X. The reason for the relative stability of the axial conformers has been sought in the context of the CH/n and CH/π hydrogen bonds. We suggest that a considerable part of the relative stability of the axial conformation is attributed to intramolecular CH/n and CH/π hydrogen bonds. Natural bonding orbital charges of the relevant atoms are consistent with the above suggestion.

Understanding of the factors influencing the conformational equilibrium of six-member cyclic compounds has long been a subject of controversy in stereochemistry. For instance, the difference in the Gibbs energies between axial and equatorial conformers of alkyl cyclohexanes C_6H_{11}–R ($-\Delta G_{\text{eq–ax}}$: *A*-value) is 1.74–4.9 kcal mol^{-1} (1 cal mol^{-1} = 4.184 J mol^{-1}), depending on the size of the alkyl group R.[1] The *A*-values for halogenated cyclohexanes C_6H_{11}–X (0.53–0.64 and 0.48–0.67 kcal mol^{-1} for X = Cl and Br, respectively) are smaller than might be expected from the size of X. This has been attributed to the longer length of the C–X bond as compared to that of the C–C bond; the unfavorable 1,3-diaxial interaction consequently decreases.[2]

Previously we reported that by high-level ab initio MO calculations, the Gibbs free energy of the axial conformers in 2-substituted oxanes **1** and 1,3-dioxanes **2** is smaller than that of the corresponding equatorial conformers, when the 2-substituent X is electron-withdrawing.[3,4] The interatomic distance between X and the axial C–H has been calculated to be shorter than the van der Waals distance. In view of the above finding, we suggested that the five-member CH/n hydrogen bond (n: lone pair electrons) plays an important role in stabilizing the axial conformation of **1** and **2** (Scheme 1).

1 **2**

Scheme 1. The axial conformer of 2-substituted oxanes **1** and 1,3-dioxanes **2** is stabilized by the five-member CH/X hydrogen bond.

To explore the generality of the above phenomenon, here we extended the study to examine the conformational equilibrium of a series of substituted cyclohexanes *cyclo*-$C_6H_{11}X$ **3** and cyclohexanones *cyclo*-C_6H_9OX **4** (Scheme 2, X = OH, OCH_3, F, Cl, Br, C≡CH, and C≡N).

Computational Methods

The Gaussian 03 program[5] was used. Electron correlation energies were calculated by applying the second-order Møller–Plesset (MP2) perturbation theory. The geometry of axial and equatorial conformers of substituted cyclohexanes **3** and cyclohexanones **4** was optimized at the MP2/6-311++G(d,p) level of approximation. Vibrational frequencies were calculated using the analytical second derivatives at the same level of the geometry optimization for each conformer. Using these results, the thermal energy corrections were added to the total Gibbs energy at 298.15 K and 1 atmosphere of pressure. Natural bond

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3 **4**

Scheme 2. The conformational equilibrium of substituted cyclohexanes and cyclohexanones.

Table 1. Conformational Gibbs Energies $-\Delta G_{\text{eq-ax}}$ (in kcal mol^{-1}) of Substituted Cyclohexanes *cyclo*-$C_6H_{11}X$ **3**, Calculated at the MP2/6-311++G(d,p) Level of Approximation

X	$-\Delta G_{\text{eq-ax}}$	*A*-value
OH	−0.28	0.29–0.37[a)]
OCH_3	0.22	0.6[b)]
F	0.18	0.17[c)]
Cl	0.49	0.26, 0.34[c)]
Br	0.69	0.7[c)]
C≡CH	−0.16	0.18, 0.41
C≡N	−0.39	0.15–0.25[c)]
CH_3	1.95	1.87–1.96[c)]

a) Ref. 2 (CH_2Cl_2, $CHCl_3$, CCl_4, $C_2H_4Br_2$, CS_2, acetone, xylene, toluene, benzene, and *n*-hexane). b) Ref. 2 (CCl_4). c) Ref. 2 (gas phase).

orbital (NBO) calculations were performed with the NBO code[6] included in Gaussian 03.

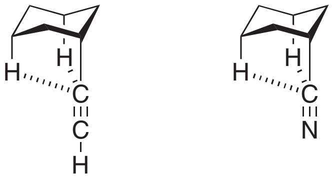
Results and Discussion

Conformational Gibbs Energy of Substituted Cyclohexanes. Table 1 lists the conformational Gibbs energy $\Delta G_{\text{eq-ax}}$ of substituted cyclohexanes *cyclo*-$C_6H_{11}X$ **3** (X = OH, OCH_3, F, Cl, Br, C≡CH, and C≡N). The data for methylcyclohexane (X = CH_3) are included for comparison.

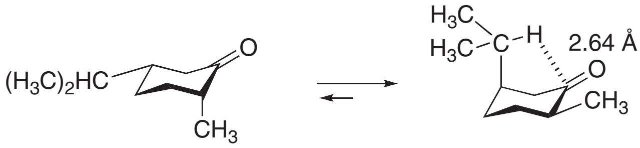
Table 1 shows that $-\Delta G_{\text{eq-ax}}$ for X = OCH_3, F, Cl, Br, and CH_3 does not significantly differ from the experimental data. Namely, the equatorial conformer is more stable than the axial conformer. The calculated negative $-\Delta G_{\text{eq-ax}}$ value for cyclohexanol (X = OH, −0.28 kcal mol^{-1}) is exceptional, which is at variance with the documented data (0.29–0.37 kcal mol^{-1}). We do not know at present the reason for this discrepancy, but the experimental values may reflect association by hydrogen bonds, which might favor the equatorial conformation. The calculated value, on the other hand, corresponds to the energy of a single molecule.

Another noteworthy feature is that the sign of $-\Delta G_{\text{eq-ax}}$ is negative for compounds bearing an sp π-group (C≡CH and C≡N); the axial conformer has been suggested to be more stable, though slightly, than the equatorial one. This however, does not agree with the documented experimental data ($-\Delta G_{\text{eq-ax}}$ 0.18[7] or 0.41[8] kcal mol^{-1} for X = CCH and 0.15–0.25 kcal mol^{-1} for X = CN[9]). It should be reminded that experimental values reflect the average conformation in solvents, while the calculated values correspond to the gas-phase data. Anyway, the discrepancy is insignificant but it is remarkable that the stability of the axial conformer bearing the π-groups is larger. We suggest that the above effect is a consequence of the CH/π hydrogen bond (Scheme 3).

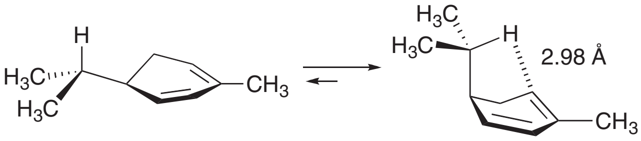
Experimentally, the effect of the CH/π hydrogen bond in stabilizing the folded conformations is well documented,[10–13] and the experimental evidence has been supported by MO calculations.[14] To cite an example from the chemistry of cyclohexane derivatives, it has long been known that the isopropyl-axial conformer in isocarvomenthone (=5-isopropyl-2-methylcyclohexanone) prevails in the equilibrium.[15] The experimental result has been reproduced by recent high-level ab initio calculations and this was interpreted on the basis of the CH/π(C=O) hydrogen bond (Scheme 4).[16]



Scheme 3. The axial conformer of **3** (X = CCH and CN) is stabilized by the CH/π hydrogen bond.



Scheme 4. Conformational equilibrium of isocarvomenthone.



Scheme 5. Conformational equilibrium of α-phellandrene.

In α-phellandrene, (*R*)-(−)-5-isopropyl-2-methyl-1,3-cyclohexadiene, the conformer bearing a quasi-axial isopropyl group has long been known to prevail in solution.[17] The result was reproduced by our MO study, and the result was interpreted on the basis of the CH/π hydrogen bond (Scheme 5).[18]

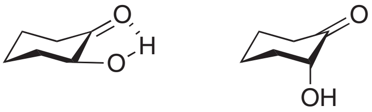
Conformational Gibbs Energy of Substituted Cyclohexanones. Table 2 summarizes the data for 2-substituted cyclohexanones *cyclo*-C_6H_9OX **4**. The values obtained for 2-substituted oxanes **1** and 1,3-dioxanes **2** are included for comparison. It is noted that $-\Delta G_{\text{eq-ax}}$ are negative in every case except for X = OH and CH_3.

Allinger et al.,[19,20] and Lehn and Ourisson[21] reported on the axial preference of halogen atoms in 2-halogenated cyclohexanones and discussed the results on the basis of the dipolar interactions. The present data are consistent with their conclusion. An interesting point is that $|-\Delta G_{\text{eq-ax}}|$ increases from X = F to Cl, and then to Br in every case for **4**, **1**, and **2**.

Table 2. Conformational Gibbs Energies $-\Delta G_{\text{eq–ax}}$ (in kcal mol^{-1}) of Substituted Cyclohexanones *cyclo*-C_6H_9OX **4**, 2-Substituted Oxanes **1**, and 1,3-Dioxanes **2**, Calculated at the MP2/6-311++G(d,p) Level of Approximation

X	4	1	2
OH	3.26		
OCH_3	−1.02		
F	−0.58	−2.47[a)]	−3.42[a)]
Cl	−1.20	−2.57[a)]	−4.31[a)]
Br	−1.52	−3.08[a)]	−5.45[a)]
C≡CH	−1.56	−0.68	−0.97
C≡N	−1.35	−1.22	−1.90
CH_3	1.51	3.27	5.22

a) Ref. 3.



Scheme 6. The intramolecular hydrogen bond can only be formed in the equatorial conformer of 2-hydroxycyclohexanone.

Scheme 7. CH/X hydrogen bonds stabilize the axial conformation.

In other words, the difference in the conformational free energy is maximal in the Br-derivatives. The electronegativity of X decreases in the above order. The above computational results might suggest that an effective negative charge of the halogen atom is built up around the axial proton. The above tendency may therefore be a consequence of the size of the ion radius: Br > Cl > F. In compounds with an sp-carbon (X: C≡CH and C≡N[22]), the axial conformer is suggested to be more stabilized.

The datum for X = OH is exceptional; in this case the equatorial conformer has been calculated to be more stable. This is consistent with the documented data[23] and is comprehensible since the stabilization by intramolecular hydrogen bonding is expected only for the equatorial conformation and not for the axial conformer (Scheme 6).

CH–X Interatomic Distance. In view of the above findings, we considered that five-membered intramolecular CH/n[24] and CH/π[25] hydrogen bonds play a role in bringing about the relatively stable axial conformation of **3** and **4**. To test this hypothesis, we examined the interatomic distances of the relevant C–H and X (Scheme 7). Table 3 lists the results.

Notice that in every axial conformer the CH/X distance is shorter than the sum of the van der Waals radii.[26,27] We think this suggests the effect of CH/n[28] and CH/π hydrogen bond. The decrease in the interatomic distance is most remarkable when X = CCH and CN (0.18–0.19 Å for **3** and 0.22–0.28 Å for **4**).

Table 3. Interatomic Distances (in Å) of Axial C–Hs and X

X	3	4		d_{vdW}[c)]
	$d_{X/H3} = d_{X/H5}$[a)]	$d_{X/H3}$[a)]	$d_{X/H5}$[b)]	
OH	2.60[d)] (0.11)	2.54 (0.18)	2.62 (0.10)	2.72
OCH_3	2.57 (0.11)	2.52 (0.20)	2.60 (0.12)	2.72
F	2.62 (0.05)	2.55 (0.12)	2.63 (0.04)	2.67
Cl	2.88 (0.07)	2.87 (0.08)	2.90 (0.05)	2.95
Br	2.97 (0.08)	3.01 (0.04)	2.98 (0.07)	3.05
C≡CH	2.73 (0.18)	2.72 (0.25)	2.75 (0.22)	2.97
C≡N	2.71 (0.19)	2.69 (0.28)	2.75 (0.22)	2.97

a) Distance between H^3 and X. b) Distance between H^5 and X. c) van der Waals distance. d) In the parentheses are differences (Δd) between $d_{X/H}$ and d_{vdW}.

Table 4. Natural Bonding Orbital Charges of (a) Hydrogens and (b) X, in the Axial and Equatorial Conformers of **3**

	X		NBO_{ax}	NBO_{eq}	$\Delta NBO_{\text{ax–eq}}$[a)]
(a)	OH	H^3	0.193	0.184	0.009
	OCH_3	H^3	0.192	0.182	0.010
	F	H^3	0.195	0.183	0.012
	Cl	H^3	0.197	0.184	0.013
	Br	H^3	0.198	0.184	0.014
	C≡CH	H^3	0.194	0.183	0.011
	C≡N	H^3	0.195	0.184	0.011
(b)	OH	O	−0.734	−0.717	−0.017
	OCH_3	O	−0.603	−0.591	−0.012
	F	F	−0.407	−0.396	−0.011
	Cl	Cl	−0.068	−0.052	−0.016
	Br	Br	−0.013	0.005	−0.018
	C≡CH	C[b)]	−0.003	0.007	−0.010
	C≡N	C	0.281	0.293	−0.012

a) NBO_{ax}–NBO_{eq}. b) The carbon attached to the cyclohexane ring is considered.

Table 5. Differences in the NBO Charges of X and Hydrogens in the Axial and Equatorial Conformers of **3** and **4**

X	3		4		
	ΔNBO_{H3}[a)]	ΔNBO_X[c)]	ΔNBO_{H3}[a)]	ΔNBO_{H5}[b)]	ΔNBO_X[c)]
OH	0.009	−0.017	0.016	0.008	0.002
OCH_3	0.010	−0.012	0.017	0.013	−0.012
F	0.012	−0.011	0.013	0.015	−0.021
Cl	0.013	−0.016	0.013	0.015	−0.030
Br	0.014	−0.018	0.014	0.016	−0.028
C≡CH[d)]	0.011	−0.010	0.012	0.013	−0.012
C≡N[d)]	0.011	−0.012	0.013	0.014	−0.015

a) NBO_{ax}–NBO_{eq} for H^3. b) NBO_{ax}–NBO_{eq} for H^5. c) NBO_{ax}–NBO_{eq} for X. d) The carbon attached to the cyclohexane ring is considered.

Natural Bonding Orbital Charge. Next, we examined the natural bonding orbital (NBO) charges of the relevant atoms, X and H, in the axial and equatorial conformers (Scheme 7). Table 4 lists the NBO data for **3**. Table 5 summarizes the difference in the NBO charges of hydrogens and X in the axial and equatorial conformers of **3** and **4**.

Note that the NBO charge, in every case, is more positive for H in the axial conformers than in the corresponding equatorial conformers. The inverse is true for the NBO data of electronegative atom X.[29] The result is consistent with our hypothesis that the CH/n or CH/π hydrogen bonds are contributing in stabilizing the axial conformation.

Conclusion

High-level ab initio MO calculations were carried out to investigate the Gibbs energy of conformational isomers of *cyclo*-$C_6H_{11}X$ **3** and *cyclo*-C_6H_9OX **4**. In **3**, the conformer bearing an axial alkyl substituent has been found relatively stable as compared to the parent cyclohexane compounds. In **4**, the axial conformation has been shown to be more stable than the equatorial conformer except for $X = OH$. In every case, short non-bond distances have been disclosed in the stable axial conformers, between CHs of the cyclohexane ring and substituent X. Inspection of the NBO charges of the relevant atoms gave results consistent with this conclusion. We suggest that the stability of the axial conformation is attributed to the five-member intramolecular CH/n and CH/π hydrogen bonds. The other effects such as the unfavorable steric effect and in the cases of **4**, delocalization of the electrons of the C=O double bond to the antibonding orbital of the C–X bond may also contribute.

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Supporting Information

Optimized geometries and natural charges of cyclohexanes *cyclo*-$C_6H_{11}X$ and cyclohexanones *cyclo*-C_6H_9OX ($X = OH$, OCH_3, F, Cl, Br, $C\equiv N$, and $C\equiv CH$) at the MP2/6-311++G(d,p) level of approximation are listed. This material is available free of charge on the Web at: http://www.csj.jp/journals/bcsj/.

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