Methyl–Halogen 1,3 Syn–Axial Interaction

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Abstract: The 1,3 syn–axial interaction between a methyl group and each of the halogen atoms has been examined through studies of *gem*-dimethylhalocyclohexanes. The conformational equilibrium constants for the 3,3- and 4,4-dimethylhalocyclohexanes were determined by the low-temperature nmr peak-area method. The free energy differences ($-\Delta G_{ae}°$) between axial and equatorial halogen for the 4,4-dimethyl systems are slightly but consistently smaller than those for the unsubstituted cases. For the 3,3-dimethyl systems, the free energy differences are substantially larger due to the syn–axial methyl–halogen interaction. The $-\Delta G_{ae}°$ values for I, Br, and Cl are greater than 1.5 kcal/mol; that for F is measured to be 0.64 kcal/mol, compared to 0.27 in the unsubstituted case and 0.18 in the 4,4-dimethyl system. Conformational calculations were performed for the 3,3-dimethylhalocyclohexanes using a static molecular model to determine the relative magnitudes of the 1,3 syn–axial methyl–halogen interactions. The variations are discussed in terms of the structural differences among the halides.

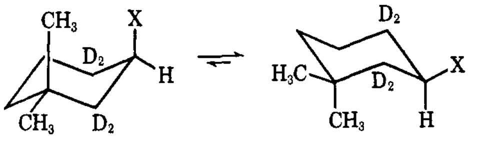
The "size" of a grouping of atoms has frequently been thought of in terms of the free energy difference (the *A* value) between axial and equatorial placement in a six-membered ring.[2,3] The data derived from the conformational analysis of monosubstituted six-membered rings have been of prime importance in studying the stereochemical and kinetic behavior of complex organic molecules. It would nonetheless be useful to have quantitative assessments of substituent sizes in sterically more and less demanding situations. Depending on the nature of the interactions involved, a given series of substituents might respond in a qualitatively different fashion from the well-known mode of the monosubstituted six-membered ring.

In the present study we have examined the effect of a 3-axial methyl group[4] on the conformational preference of halogen substituents. Interactions of this type tend to decrease the proportion of the axial isomer (Figure 1). The halogen atoms are used to probe this interaction because of their relatively small size in the *A* value sense. Furthermore, the monotonic nature of the halogen series with respect to van der Waals radius and bond length, the lack of specific solvation (as in acids, alcohols, or amines), the relative simplicity of preparation, and their central role in organic mechanistic studies make the halogens an important series to study. The halogens also lend themselves readily to quantitative calculations of the forces involved in molecular conformations.[2,5] We report herein experimental and computational assessments of the size of the halogen atoms in the presence of a 3-axial methyl substituent.

Methods and Results

The 3,3-dimethylhalocyclohexanes (**1**) were prepared in order to determine the magnitude of the 1,3 syn–axial methyl–halogen interaction. The 4,4-dimethylhalocyclohexanes (**2**) were included in order to have a general model for *gem*-dimethylcyclohexanes. Both series were ultimately derived from the corresponding cyclohexanones, which had been deuterated in the 2,6 positions (see Experimental Section). Deuteration was necessary to remove coupling between the 1 proton, to be observed, and the 2,6 protons.

For determination of the axial–equatorial equilibrium constants, we chose the low-temperature nmr integration method.[6] The sample is cooled to a temperature below the slow-exchange limit for ring reversal. Separate signals are observed for the 1 protons in the axial (**1a**-X or **2a**-X) and equatorial (**1e**-X or **2e**-X) isomers (eq 1), if both forms are appreciably populated.



1a-X **1e**-X (1)

The 1-proton signals may be integrated and the equilibrium constant calculated directly. The measured equilibrium constants, together with other pertinent data, are presented in Table I.

The isomeric purity of the dimethylhalocyclohexanes is of critical importance, especially in the 3,3-dimethyl series where a small amount of isomeric contaminant might be mistaken for the axial isomer (**1a**-X). The preparations of these compounds were planned with cognizance of this problem.[7,8]

Discussion

Conformational Equilibria. The 4,4-dimethylhalocyclohexane systems serve as a model to determine the effect of the *gem*-dimethyl group on ring conformation[9]

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Table I. Spectral Parameters and Calculated Equilibrium Data for *gem*-Dimethylhalocyclohexanes

Compound[a]	Temp, °C	Concn, *M*	$K^{b,c}$	% equatorial	$-\Delta G_{\mathrm{ae}}^{\circ}$, cal/mol	$\delta_{\mathrm{axial\ H}}$,[d] Hz	$\delta_{\mathrm{equa\ H}}$,[d] Hz
2-F	−85	1.63	1.63 ± 0.07	62.0 ± 1.0	183 ± 15	378	417
2-Cl	−80	2.01	3.06 ± 0.08	75.4 ± 0.3	429 ± 12	328	392
2-Br	−80	1.92	3.49 ± 0.08	77.8 ± 0.5	479 ± 10	344	403
2-I	−80	2.0	3.03 ± 0.15	75.3 ± 0.8	425 ± 19	353	429
1-F	−85	1.8	5.47 ± 0.31	84.5 ± 0.7	635 ± 21	401	425
1-Cl	−80	2.14			>1500	346	
1-Br	−80	1.74			>1500	363	
1-I	−80	2.0			>1500	382	

[a] The solvent is 95% CS_2–5% TMS in all cases. [b] K = (% equatorial halide)/(% axial halide). [c] Errors are average deviations of five or more determinations. [d] Chemical shifts downfield from TMS, measured at 90 MHz.

Table II. Summary of Conformational Energy Differences ($-\Delta G_{\mathrm{ae}}^{\circ}$, kcal/mol) in Halocyclohexanes

Substituent	Unmethylated[a]	4,4-Dimethyl	3,3-Dimethyl
F	0.27	0.18	0.64
Cl	0.53	0.43	>1.5
Br	0.48	0.48	>1.5
I	0.47	0.43	>1.5
OH	0.93	0.90[b]	>1.5[b]

[a] Reference 6. [b] Reference 10.

and on the rate of ring reversal. The average difference in free energy differences ($\delta\Delta G_{\mathrm{ae}}^{\circ}$) between the unsubstituted and the 4,4-dimethyl systems for the five substituents studied to date[10] (Table II) is about 50 cal/mol. This small difference obviates consideration of any major deformation as a result of introducing the *gem*-dimethyl grouping. The consistent direction of the effect toward an increased proportion of the axial conformer can be explained as a result of the symmetrization of the C–C–C bond angles about the C_4 atom, from about 111° in cyclohexane to about 109° in this quaternary system. The result of these minor bond angle alterations is a slight puckering of the 3,4,5 portion of the ring and a bending away of the 3,5-axial protons from the ring center. The 1-axial substituent thereby experiences reduced syn–axial repulsions, and the axial isomer becomes populated to a slightly greater extent. The observed coalescence temperatures (~ −50°) indicate that the barrier to ring reversal is little affected by the introduction of the *gem*-dimethyl grouping.

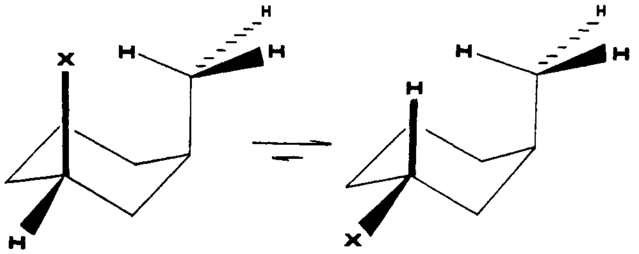

Figure 1. The axial (left) and equatorial conformers of the 3,3-dimethylhalocyclohexanes.

The small range of $-\Delta G_{\mathrm{ae}}^{\circ}$ values (Table II: 270–530 cal/mol) in the unmethylated systems has been explained in terms of opposing (and hence canceling) effects of bond length and van der Waals radius.[2,6,11] As the van der Waals radius of the halogen atom increases (fluorine to iodine) with an anticipated increase in nonbonded repulsions, the C–X bond length also increases, thereby placing the halogen atom a greater distance from the 3,5-axial hydrogens. The longer bond length also guarantees that a small bending of, *e.g.*, the C–C–I angle, by which the iodine atom would move away from the ring, can reduce the syn–axial repulsions with little expense in angle-deformation energy.[2]

In the 3,3-dimethyl series, however, the bond length and van der Waals radius operate in conjunction to increase the energy of the axial conformer. The distance between the axial 1-halogen atom and a hydrogen on the 3-axial methyl group changes by less than 0.5% at distances well within the sum of the van der Waals radii, whereas the axial–axial hydrogen–halogen distances in the unmethylated series change almost 10% at a distance roughly equal to the sum of the van der Waals radii. The 3,3-dimethyl series (**1-X**) therefore gives a more characteristic picture of the interaction between hydrogen and halogen at a constant internuclear distance.

The increased proportion of the equatorial conformer in **1-F** with respect to that in **2-F** (62 to 85%) reflects the more repulsive CH_3–F syn–axial interaction in comparison with the H–F interaction. The unobservably small amount (<5%) of axial coformer in the remainder of the series (**1-Cl**, **1-Br**, **1-I**) indicates substantially larger syn–axial interactions. The magnitude of these interactions is not available from the nmr experiment, but estimates may be obtained by empirical calculations (next section). It is interesting that the axial-fluorine conformer (**1a-F**) is appreciably populated at all. The net destabilization of the axial conformer in passing from the unsubstituted case to the 3,3-dimethyl case is only 370 cal/mol (Table II). This result points up the small magnitude of nonbonded H–F interactions, even at short distances.

There appear to be very few quantitative measurements involving 1,3 syn–axial interactions between a methyl group and monoatomic substituents. The bromine–methyl interaction has been studied in 5,6-dibromo steroids[12] and in 2-bromocyclohexanones.[13]

Conformational Calculations. Even though much of the 3,3-dimethyl series (**1-Cl**, **1-Br**, **1-I**) failed to exhibit a measurable amount of axial isomer, we nonetheless wanted some indication of the *relative* energies

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(10) We thank Professor C. H. Bushweller for communicating his data on the hydroxyl systems to us prior to their publication.

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Table III. Calculated Conformational Energies (kcal/mol) for 3,3-Dimethylhalocyclohexanes

Substituent	1,3-CH_3X[a]	Σ axial[b]	Σ equatorial[c]	ΔΣ[d]	Calcd[e]	Obsd[f]
H	−0.08	−0.40	−0.35	−0.13		
F	+0.29	−0.65	−0.57	+0.21	+0.34	+0.64
Cl	+7.96	−0.82	−0.97	+7.21	+7.34	
Br	+14.99	−0.73	−0.68	+14.94	+15.07	
I	+27.49	+0.45	−1.38	+28.24	+28.37	

[a] Interaction between the axial methyl group (C and H) and the substituent at the 1 position in the axial conformer. [b] The sum of all interactions for the 1-axial substituent except with the 3-methyl group. [c] The sum of all interactions for the 1-equatorial substituent. [d] The calculated free energy difference of the 1 substituent, neglecting the interactions of the 1 proton. [e] The calculated free energy difference ($-\Delta G_{ae}°$) including the interactions of the 1 proton. [f] The observed value of $-\Delta G_{ae}°$.

of these conformations. For this information, we had recourse to the computational method based on the Hill equation,[14] described in detail by Eliel, *et al.*,[2] and utilized extensively by Allinger,[15] Hendrickson,[16] and Wiberg.[17] All significant H–X and C–X interactions in the molecule were included in the computation. The calculated conformational energy differences for the 3,3-dimethylhalocyclohexanes are given in Table III.

The value of $-\Delta G_{ae}°$ calculated for **1**-F (0.34 kcal/mol) is very close to our experimental value (0.64). In this case, the calculation preceded the experiment. The large calculated free energy differences for the dimethylchloro-, -bromo-, and -iodocyclohexane equilibria (7, 15, and 28 kcal/mol, respectively) are consistent with the failure to observe axial contributions in the nmr spectrum. In fact, various twist boat conformations would be expected to have replaced the axial conformer as the second most stable form for these molecules. The order of stability (F > Cl > Br > I) now properly parallels the normal ordering of halogens according to van der Waals radius. The immense differential effect between fluorine and iodine is noteworthy. Whereas the syn–axial methyl group destabilizes an axial fluorine atom by less than 1 kcal/mol, the figure is enormous for the iodine atom, even though the two atoms have almost equivalent axial populations in the unmethylated system.

The calculated values undoubtedly are not accurate free energy differences, since the molecule can undergo bond and angle deformations, not included in our calculations, to reduce the interaction energies.[2,5,15–17] These calculations served primarily to order the conformational energies for the entire halogen series. A wide variety of other choices of interaction parameters[15,18] leads to substantially identical conclusions. We have refrained from a quantitative discussion of the calculations, but we find the qualitative conclusions most useful.

Summary. We have found that a 4,4-dimethyl grouping has the effect of slightly increasing the proportion of axial isomer for halocyclohexanes. The 3,3-dimethyl grouping, which gives rise to a syn–axial interaction, reduces (**1**-F) or nullifies (**1**-Cl, -Br, -I) the proportion of axial isomer. Calculations from the Hill equation show that the ordering of conformational energies in the 3,3-dimethyl series follows the van der Waals radius, whereas in the 4,4-dimethyl or the unmethylated series the lengthening of the C–X bond brings about a near equivalence of axial-isomer populations.

Experimental Section

Low-temperature nmr experiments were carried out on the Bruker HFX-10. The 1-proton resonances of the axial and equatorial isomers were integrated to obtain the conformational equilibrium constant. Care was exercised to avoid differential saturation of the signals.[6] In all cases several radiofrequency power settings were made; the values reported are those for which no change in equilibrium constant was observed with decreasing rf power. All samples were examined and found not to have any solute precipitation. The peak areas were integrated both by use of a polar planimeter and by cutting and weighing multiple copies of the nmr signals. The methods gave comparable results.[19] All reported equilibrium constants are the average of five or more separate determinations.

3-Methyl-2-cyclohexenone. Condensation of 2 mol of ethyl acetoacetate and 1 mol of formaldehyde, according to the method of Knoevenagel[20] and Rabe,[20] gave the "primary adduct," 2,4-dicarboethoxy-5-hydroxy-5-methylcyclohexanone, which was dehydrated, hydrolyzed, and decarboxylated in refluxing 10% H_2SO_4 for 20 hr to yield, after work-up, 43% of the desired product. The bp, ir, and nmr data agree with the reports of Dürr, *et al.*[21]

3,3-Dimethylcyclohexanone was obtained in 55% yield by the cupric iodide catalyzed addition of methyl magnesium iodide to 3-methyl-2-cyclohexenone following Kharasch and Tawny.[22] The bp and spectral data agree with those of Dürr, *et al.*[21]

4,4-Dimethylcyclohexanone. Condensation of methyl vinyl ketone and isobutyraldehyde with subsequent hydrogenation of the α,β-unsaturated ketone yielded 35% of the desired product.[23]

3,3- and 4,4-Dimethylcyclohexanol-*2,2,6,6-d*$_4$. The α protons in the ketones were exchanged in basic D_2O.[24] The extent of deuterium incorporation was 98% for the 3,3 isomer and 96% for the 4,4-dimethylcyclohexanone, as measured by nmr integration of the ring protons. The ketones were reduced with lithium aluminum hydride to the alcohols by standard procedures.

3,3-Dimethylfluorocyclohexane-*2,2,6,6-d*$_4$. The alkyl fluoride was prepared by the displacement of tosylate (from the alcohol) by fluoride ion following Edgell and Parts in a 4% yield.[25] The product was purified by preparative collection from a basic Carbowax 20 M gc column. The nmr spectrum showed the characteristic geminal H–F coupling constant of 48 Hz for the deuterium-broadened 1 proton. The major reaction pathway was elimination.

4,4-Dimethylfluorocyclohexane was prepared and purified in the above manner in 15% yield. The nmr spectrum showed the $^2J_{HF}$ of 49 Hz for the 1 proton.

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3,3-Dimethylchlorocyclohexane-*2,2,6,6-d*$_4$ was prepared from the alcohol by treatment with thionyl chloride in pyridine.[26] The product was separated from the alcohol and olefins by preparative gc. The mass spectrum (20 eV) showed parent peaks at *m/e* 150 ($C_8H_{11}D_4{}^{35}Cl$] and 152 ($C_8H_{11}D_4{}^{37}Cl$) in a 3:1 ratio, with intensities less than 1% of the base peak at *m/e* 99 (M − CH_2Cl).

4,4-Dimethylchlorocyclohexane-*2,2,6,6-d*$_4$ was prepared as given for the above chloride and purified by gc.

3,3-Dimethylbromocyclohexane-*2,2,6,6-d*$_4$ was prepared from the corresponding alcohol by reaction with $(C_6H_5)_3PBr_2$ following Wiley.[7] The reaction proceeded in substantially lower yield (20%) than is common with this reaction and large amounts of alcohol were recovered. The product was purified by gc.

4,4-Dimethylbromocyclohexane-*2,2,6,6-d*$_4$ was prepared in 80% yield and purified in a manner analogous to the 3,3 isomer. The mass spectrum of the purified product gave parent peaks at 196 ($C_8H_{11}D_4{}^{81}Br$) and 194 ($C_8H_{11}D_4{}^{79}Br$) in an approximate 1:1 ratio, with intensities less than 1% of the base peak at 115 (M − Br).

3,3-Dimethyliodocyclohexane-*2,2,6,6-d*$_4$ was prepared following Wiley[7] from the alcohol and $(C_6H_5)_3PI_2$. Again the yield was only 20%. The mass spectrum of the distilled product had a parent peak at *m/e* 242 ($C_8H_{11}D_4I$) with an intensity of 2% relative to the base peak at 115 (M − ^{127}I).

4,4-Dimethyliodocyclohexane-*2,2,6,6-d*$_4$ was prepared in 70% yield in a manner analogous to the 3,3-dimethyl isomer. The mass spectrum had a peak at *m/e* 242 with an intensity of 4% of the base peak at 115.

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Nitrous Acid Deamination of 2-(Aminomethyl)cyclohexanol. The Question of a 1,3-Hydride Shift or Two Consecutive 1,2-Hydride Shifts[1]

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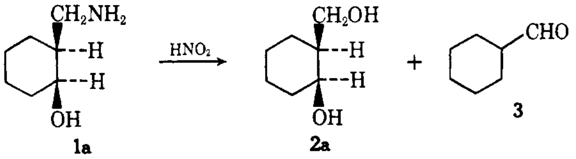
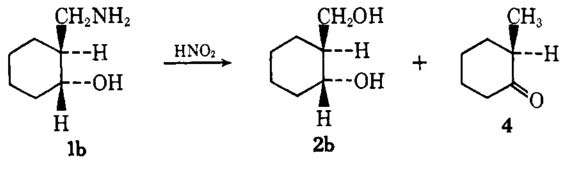
Abstract: The nitrous acid deamination of *cis*- and *trans*-2-(aminomethyl)cyclohexanol leads to the formation of the corresponding substitution products (*cis*- and *trans*-2-(hydroxymethyl)cyclohexanols, respectively), an elimination product (2-methylenecyclohexanol), and three rearrangement products (2-methylcyclohexanone and *cis*- and *trans*-2-methylcyclohexane-1,2-diol), albeit in different proportions from the two isomers. The differences are rationalized in terms of the reaction taking place from the most stable conformer and the subsequent reactions of the intermediate carbonium ions being more rapid than ring inversion. Contrary to an earlier claim, deuterium-labeling experiments indicate that 2-methylcyclohexanone arises from *trans*-2-(aminomethyl)cyclohexanol by way of two 1,2-hydride shifts rather than by a 1,3-hydride shift.

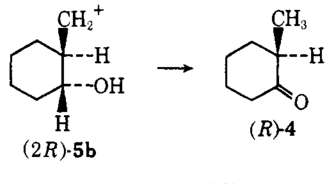
The nitrous acid deamination of 2-(aminomethyl)-cyclohexanol (**1**) has been described by Mousseron and coworkers.[3] The cis isomer **1a** was reported to give the corresponding diol, *cis*-2-(hydroxymethyl)-cyclohexanol (**2a**), and cyclohexanecarboxaldehyde (**3**) (eq 1). The latter was claimed to arise by a 1,3-alkyl shift. Likewise, from *trans*-2-(aminomethyl)-cyclohexanol (**1b**), *trans*-2-(hydroxymethyl)cyclohexanol (**2b**) was obtained, together with 2-methylcyclohexanone (**4**) as the only rearrangement product (eq 2). Furthermore, optically active **1b** was found to yield optically active **4**. It was argued that since **4** was optically active the asymmetric carbon was not touched during the reaction, and therefore a 1,3-hydride shift had occurred in carbonium ion **5b** (eq 3).[3c] However, this finding does not rule out a reaction path involving two consecutive 1,2-hydride shifts. Only if the configurational relationship between the reactant **1b** and the product **4** is known can a conclusion be drawn concerning the reaction mechanism. A 1,3-hydride shift would result in retention (eq 3), while two consecutive 1,2-hydride shifts would result in inversion at C-2 (eq 4).[4] Since this configurational relationship had not been established in the previous work, we decided to reinvestigate the nitrous acid deamination of **1b**.



1a **2a** **3** (1)



1b **2b** **4** (2)



(2*R*)-**5b** (*R*)-**4** (3)

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[1] This work was supported by a grant from the National Science Foundation (GP 9594).

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[4] This sequence implies that the intramolecular hydride migration in **6** is favored over proton elimination to give the enol, a process which would destroy the asymmetry.