

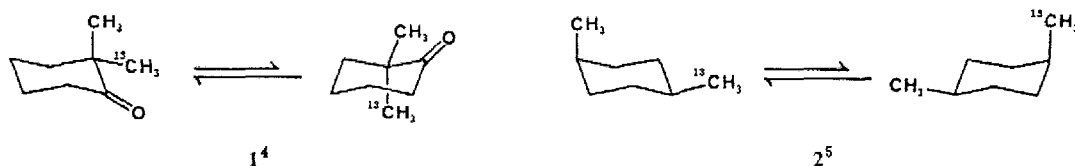
## THE ORIGIN OF CONFORMATIONAL EQUILIBRIUM ISOTOPE EFFECTS FOR CARBON

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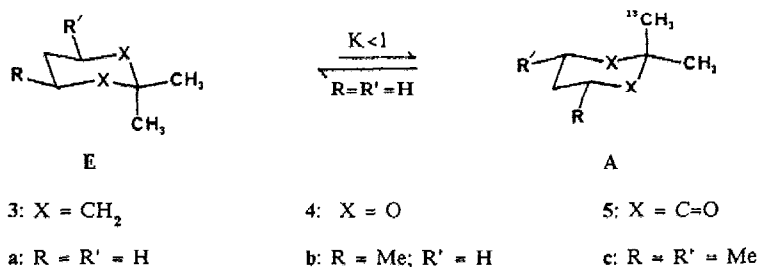
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**Abstract:** Conformational equilibrium isotope effects for carbon are dominated by orbital interactions between C-C bonds and strong acceptor (the  $\pi^*$  in C=O) or strong donor (the non-bonding electrons on O) groups, and show a small dependence upon solvent polarity.

Conformational equilibrium isotope effects (CEIEs) for hydrogen have several origins, depending upon the structure of the molecules concerned.<sup>1,2</sup> Steric effects are important for strongly hindered hydrogens but the anomeric effect<sup>3</sup> and long range analogues of it,<sup>1</sup> hyperconjugation,<sup>2</sup> and differences in polarity of C-<sup>1</sup>H and C-<sup>2</sup>H bonds (leading to solvent effects)<sup>1</sup> are usually more important in compounds with heteroatoms near the site of isotopic substitution for hydrogen. CEIEs for carbon are expected to be much smaller than for hydrogen and as yet successful measurements of such CEIEs have been reported for two systems only, **1**<sup>4</sup> and **2**,<sup>5</sup> in both of which <sup>12</sup>C preferred the *more* hindered axial position:



The CEIEs in **1** and **2** are not consistent with steric effects of non-bonded repulsions because the latter should be smaller for the *heavier* isotope<sup>6</sup> but no positive conclusions about their possible origins were drawn.<sup>4,5</sup> We now report carbon CEIEs and their solvent dependence in three widely differing systems, **3a-5a**. We conclude that orbital interactions involving *axial* C-C bonds as donors to the  $\pi^*$ -orbitals in carbonyl groups (in **1** and **5a**) or to axial (C-H)  $\sigma^*$  orbitals (in **2** and **3a**), or as acceptors for non-bonded electrons (in **4a**: the anomeric effect) are the most important factors in CEIEs for carbon.



The systems used in the present work, **3a-5a**, were selected for the following reasons. The measurement of CEIEs for carbon using <sup>13</sup>C chemical shifts involves a comparison of <sup>13</sup>C<sub>1</sub> and <sup>13</sup>C<sub>2</sub> isotopomers. One must choose either to use two widely separated sites for <sup>13</sup>C, in the hope that the intrinsic isotope effects (IIEs) on <sup>13</sup>C

chemical shifts may be neglected,<sup>5</sup> or two sites close enough for IIEs to be measurable. We have chosen the latter, using the geminal methyl groups in 3-5 as the sites for <sup>13</sup>C both for observation and for replacement of <sup>12</sup>C in order to generate a CEIE. The measurement of CEIEs for carbon, particularly in hydrocarbons,<sup>5</sup> is close to the practical limit because the changes in resonance frequencies may be much less than the line widths (see Table 1). The hydrocarbon 3a has significant steric strain for the axial methyl group and the CEIEs for hydrogen in methyl groups on cyclohexane rings are well known.<sup>7</sup> In 4a and 5a the presence of two perturbing groups (O or C=O) rather than one C=O as in 1 was expected to magnify the measured effects (but see below). Finally, it is necessary to have large chemical shift differences *D* between axial and equatorial 2-[<sup>13</sup>C]methyl groups in order to achieve adequate sensitivity.<sup>11</sup>

The carbon CEIEs in 3a-5a were estimated from the observed difference in chemical shifts, *d*<sub>obs</sub>, for the isotopically substituted sites in the <sup>13</sup>C<sub>1</sub> and <sup>13</sup>C<sub>2</sub> species, both of which give singlets,<sup>12</sup> and from the chemical shifts, and IIEs<sup>13</sup> thereon, of methyl groups in the dual series of model compounds<sup>14</sup> 3b,c-5b,c. In all three systems we expected that full use could be made of the dual model method<sup>14</sup> (using 3b,c-5b,c) for estimating both chemical shifts and intrinsic isotope effects on them in individual chair conformers of the mobile systems 3a-5a. In the model compounds 3b,c and 4b,c spin-spin coupling between *non*-equivalent <sup>13</sup>C sites in the geminal methyl groups in the <sup>13</sup>C<sub>2</sub>-isotopomers (4.8 Hz in 4b and 4c) ensures that the resonances for the <sup>13</sup>C<sub>1</sub> (singlets) and <sup>13</sup>C<sub>2</sub> isotopomers (AB quartets) are well separated with the result that even the very small IIEs in 3a may be measured with precision (see Table 1: the IIE of 0.60 ppb for I<sub>E</sub> in 3a in CCl<sub>4</sub> is equivalent to 0.038 Hz at 5.87 Tesla). Unfortunately the series 5a-c proved unsatisfactory in some respects that lead us to doubt whether there is a simple chair-chair equilibrium in 5a. For example, (i) the difference in chemical shifts for the geminal methyl groups in 5b and 5c was much more sensitive to solvent than is usual in anancomeric six-membered ring compounds with the result that the derived values of *D* for 5a differ by over 10% in different solvents, compared with less than 1% for 3a and 2% for 4a, and (ii) the observed averaged chemical shifts for the geminal methyl groups in 5a differ from values calculated<sup>11</sup> from 5b and 5c by as much as 0.1 ppm compared with about 0.005 ppm for 3a and 4a. A further difficulty is that spin-spin coupling could not be resolved (<sup>2</sup>J<sub>CC</sub> < 0.1Hz) in the <sup>13</sup>C<sub>2</sub> isotopomers of 5b and 5c with the result that the small IIEs, particularly I<sub>E</sub>, could not be estimated as reliably for 5a as for 3a and 4a.

The CEIEs were derived from equation 1:<sup>15</sup>

$$K = [D - 2d_{\text{obs}} + I_E + I_A] / [D + 2d_{\text{obs}} - I_E - I_A] \quad (1)$$

In all three systems 3a-5a, as in 1 and 2, the CEIEs are *inverse*, ie, opposite to those expected for steric interactions<sup>6</sup> in the axial methyl groups. In order to throw light on the possible origins of the CEIEs we have measured<sup>16</sup> the one bond carbon carbon coupling constants <sup>1</sup>J<sub>CC</sub> for the axial and equatorial C-Me bonds in the model compounds 3(A,E)b-5(A,E)b (Table 2). In all three series the coupling constants are larger for the equatorial than for the axial bonds, as would be expected from earlier measurements of <sup>1</sup>J<sub>CC</sub> constants in methylcyclohexane,<sup>17</sup> and ketones and amines.<sup>18</sup> Since it is known that values of <sup>1</sup>J<sub>CC</sub> correlate well with stretching force constants for C-C bonds<sup>19</sup> the lower coupling constants for *axial* C-C bonds is strong evidence that these bonds are weaker than the equatorial bonds. This is qualitatively the same as the weakening in *axial* (or equivalent) C-H bonds adjacent to groups with non-bonding electrons<sup>1</sup> or to π\* orbitals of carbonyl groups,<sup>2</sup> for which readily observable changes in stretching frequencies give direct evidence for bond weakening.<sup>20</sup> Accordingly we suggest that the carbon CEIEs in 3a-5a originate in, respectively, (weak) σ to σ\*, *n* to σ\*, and σ to π\* interactions.

Table 1. Conformational equilibrium isotope effects ( $\Delta G^\circ/J \text{ mol}^{-1}$ ) in **3a-5a** derived from equation 1, using  $d_{\text{obs}}$  for **3a-5a** and  $I_E$ ,  $I_A$ , and  $D$ , estimated by extrapolation from **3b,c-5b,c**

System (Temp.)	Solvent	$d_{\text{obs}}$ (/ppb) <sup>a</sup>	$I_E$ (/ppb) <sup>a</sup>	$I_A$ (/ppb) <sup>a</sup>	$D$ (/ppm)	$K$	$\Delta G^\circ$ (/J mol <sup>-1</sup> )
<b>3a</b> (345K)	CCl <sub>4</sub>	2.00	0.60	0.92	9.475	0.99948(8) <sup>b</sup>	1.5±0.2 <sup>c</sup>
	C <sub>6</sub> D <sub>6</sub>	2.32	0.86	0.84	9.545	0.99938	1.7
	CD <sub>3</sub> CN	2.35	0.78	1.00	9.517	0.99938	1.7
<b>4a</b> (304K)	CS <sub>2</sub>	11.38	1.99	2.42	11.327	0.99677(7) <sup>b</sup>	8.2±0.2 <sup>c</sup>
	C <sub>6</sub> D <sub>6</sub>	11.21	1.88	2.45	11.510	0.99861	7.9
	CD <sub>2</sub> Cl <sub>2</sub>	10.60	1.89	2.38	11.211	0.99698	7.6
	CD <sub>3</sub> CN	10.45	1.80	2.35	11.276	0.99703	7.5
	CD <sub>3</sub> OD	10.19	1.78	1.65	11.107	0.99698	7.6
<b>5a</b> (304K)	CS <sub>2</sub>	-10.51	-4.99	-8.16	-4.183	0.99624(16) <sup>b</sup>	9.5±1.0 <sup>c</sup>
	CDCl <sub>3</sub>	-10.22	[-7.06] <sup>e</sup>	-8.49	-4.152	0.99780	5.6±2.0 <sup>d</sup>
	CD <sub>2</sub> Cl <sub>2</sub>	-11.26	-4.93	-9.45	-4.825	0.99662	8.5±1.0
	CD <sub>3</sub> CN	-11.02	-6.09	-8.92	-4.819	0.99709(19)	7.3±1.0
	CD <sub>3</sub> OD	-11.40	[-6.81] <sup>e</sup>	-9.91	-4.86	0.99750	6.3±2.0

<sup>a</sup>Parts per billion. <sup>b</sup>Errors in the last figure(s) are given in parentheses and are derived from the precision of the data in the earlier columns. <sup>c</sup>Errors based on the estimated errors for  $K$ . <sup>d</sup>Errors include a (subjective) allowance for possible uncertainties about the conformational equilibria in **5a-c**. <sup>e</sup>These estimates are very uncertain because the resonances overlap badly for **5c**.

One other aspect of the data in Table 2 deserves comment. The values of  $^1J_{\text{CC}}$  for 2-C-CH<sub>3</sub> in **5Ab,c** and **5Eb,c** differ by little more than the values for 2,2,4-trimethylcyclohexanone<sup>11</sup> or indeed for *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone,<sup>18</sup> in each of which there is only one carbonyl group perturbing the axial C-Me bonds. This might be due either to increased distortion from perfect chair rings caused by two trigonal carbon atoms reducing the difference in orientation between the carbonyl  $\pi$ -orbitals and the two C(2)-Me bonds in the chair conformers or to the presence of twist conformers, in which the difference in environment for the diastereotopic C-Me bonds would be reduced compared with the chair conformers, in **5b,c**. We hope to be able to include a study of the additivity of substituent effects on  $^1J_{\text{CC}}$  in rigid adamantane ketones and diketones in a full paper.

Table 2. One bond C-C couplings ( $^1J_{\text{CC}}$ ) for the geminal methyl groups in **3b-5b** (ca. 1M in CDCl<sub>3</sub>) in relation to CEIEs in **3a-5a** and **1**.

Compound	$^1J_{\text{CC}}/\text{Hz}$ (eq-Me)	$^1J_{\text{CC}}/\text{Hz}$ (ax-Me)	Difference		Range of CEIEs (/J/mol <sup>-1</sup> )
<b>3b</b>	36.08	35.60	0.48	<b>3a</b>	1.5-1.7
<b>4b</b>	49.25	44.87	4.38	<b>4a</b>	7.5-8.2
<b>5b</b>	37.07	31.27	5.80	<b>5a</b>	7.3-9.5
- <sup>a</sup>	38.25	32.97	5.28	<b>1</b>	6.3 ( $\Delta H^\circ$ ) <sup>b</sup>

<sup>a</sup>2,2,4,6-tetramethylcyclohexanone. <sup>b</sup>Ref. 4.

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11. The chemical shift difference, estimated to be 0.5 ppm, for the *gem*-methyl groups in the chair conformers of **1** is too small to be used in measuring a carbon CEIE. We thank Mr. K.J. Holland for preparing compounds used to derive this estimate.
12. The identification of the <sup>13</sup>C<sub>2</sub> isotopomer of **4a** was confirmed using [2,2-(<sup>13</sup>C-*methyl*), 4-<sup>2</sup>H<sub>1</sub>]**4a** in which the <sup>2</sup>H removes the degeneracy of the chair-chair equilibrium and the C-2 methyl carbons give an AB quartet with <sup>2</sup>J<sub>CC</sub>=4.8 Hz, as in **4b** and **4c**.
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