

## Conformational Equilibrium Isotope Effects on Selectively Deuterated Cyclooctanone

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Conformational equilibrium isotope effects (CEIEs) are found in selectively deuterated cyclooctanone isotopomers (cyclooctanone-2-D, cyclooctanone-2,2-D<sub>2</sub>, cyclooctanone-2,8-D<sub>2</sub>, cyclooctanone-2,2,7,7-D<sub>4</sub>, and cyclooctanone-2,2,8-D<sub>3</sub>) by observing equilibrium NMR isotope shifts in <sup>13</sup>C spectra. The temperature dependence of the isotope shifts are included for the complete analysis of cyclooctanone conformation. Equilibrium constants and the changes in the free energies, enthalpies, and entropies are also reported for these cyclooctanone isotopomers. Molecular mechanics (MM2) calculations of steric interactions and molecular geometry strongly support the steric and hyperconjugative origin of the observed isotope shift results.

### Introduction

A systematic investigation of deuterated cycloalkane is needed to understand the origin of CEIEs of conformationally mobile ketones: There are few reports on CEIEs of unsymmetrically labeled cyclic ketones using isotopic splitting of <sup>13</sup>C signals, and the origin of these effects has not been clearly established.<sup>1</sup> The equilibrium NMR isotope shift in <sup>13</sup>C NMR spectroscopy is a very sensitive tool to study isotope effects, because <sup>13</sup>C NMR spectroscopy has a large spectral width and because the sharpness of the peaks in a <sup>1</sup>H-decoupled spectrum permits even a small isotopic splitting to be accurately observed when high field <sup>13</sup>C NMR is exploited. When there are <sup>13</sup>C signals which represent two or more carbons time-averaged to equivalence by a rapid degenerate equilibrium in an unlabeled compound, labeling can lead to splitting of the averaged resonances by removing the degeneracy. The signal splitting provides an accurate method for determining small CEIEs.

Conformational equilibrium isotope effects arising from the perturbation of hyperconjugation on 1,3-dioxane and N-methyl piperidine were reported.<sup>3</sup> In 5,5-dimethyl-1,3-dioxane-2-D<sub>1</sub>, deuterium preferred the equatorial position by 49.3 cal/mol. Forsyth and Henley reported on N-methyl piperidine, and the distribution of deuterium between equatorial and axial C-2 positions was found to be a 61 cal/mol preference for the equatorial position.<sup>4</sup> CEIEs were detected in several deuterated cyclopentanones and cyclohexanones by use of the temperature dependence of the circular dichroism spectra.<sup>5</sup> The preference of deuterium to be in the equatorial position in cyclopentanone-2-D was observed at room temperature and was understood within the concept of a "small size" for the heavier isotope. Although several CEIEs in conformationally mobile ketones have been observed, the origin of these effects was not clearly explained.

Selectively deuterated cyclooctanones provide good model systems to study CEIEs because rapid exchange between nonidentical environments in boat-chair conformations can cause isotopic splitting of <sup>13</sup>C signals. C-3 and C-7

of the boat-chair conformation of cyclooctanone do change environments in degenerate conformational equilibria, and unequal weighting of conformers due to isotopic labeling will cause separation of the signals for these two carbons:<sup>6</sup> (similar splitting is feasible for the C-2 and C-8 and also the C-4 and C-6 carbons.) In addition, the cyclooctanone model system enables the examination of various types of isotope effects systematically by comparing the effects originating from labeling at different positions: 1) Different steric isotope effects can be observed for the exchanging pair of C-3 and C-7 versus the pair of C-4 and C-6 since these carbons are located in positions which differ in extent of steric crowding; and 2) the hyperconjugative contribution can be evaluated by comparing isotope effects associated with C-2 and C-8 versus C-4 and C-6 because these carbons are situated at similar positions in the boat-chair cyclooctanone conformation although in different situations in regard to possible hyperconjugation with the carbonyl  $\pi$ -bond.

In this study, selectively deuterated cyclooctanone-2-D, cyclooctanone-2,2-D<sub>2</sub>, cyclooctanone-2,2,7,7-D<sub>4</sub>, cyclooctanone-2,8-D<sub>2</sub>, cyclooctanone-2,2,8-D<sub>3</sub> are investigated for their intrinsic and equilibrium NMR isotope shifts. These intrinsic and equilibrium isotope effects are discussed in relation to the preferred boat-chair conformation of cyclooctanone. The temperature dependence of the isotope shifts is also studied in order to better understand the origin of the isotope effects in cyclooctanone. Equilibrium constants for the perturbed equilibria between boat-chair conformers are calculated. The changes in the free energies, enthalpies, and entropies are also derived from the temperature dependence of the equilibrium isotope effects.

### Experimental

<sup>13</sup>C NMR spectra were recorded on Varian XL-300 NMR spectrometer equipped with a broad band probe at 75.4 MHz. NMR spectra measured with narrow spectral width to afford good digital resolution (*ca.* 0.001 ppm/point). Temperature was controlled during acquisition of spectra for the purpose

of determining isotope shifts : spectra recorded while temperature varied by more than  $\pm 1$  °C were discarded. All chemical shifts reported were referenced to Me<sub>4</sub>Si (0.00 ppm) either directly for <sup>1</sup>H NMR spectra or indirectly for <sup>13</sup>C NMR spectra by using solvent signals for reference: CDCl<sub>3</sub> (77.00 ppm) as a triplet, CF<sub>2</sub>Cl<sub>2</sub> (126.30 ppm) as a triplet, CFC<sub>3</sub> (115.67 ppm) as a doublet. <sup>13</sup>C NMR spectra of unlabeled and labeled cyclooctanone samples were recorded from 20 °C to -150 °C at every 20 °C interval and entire spectra were measured with a width of 20000 Hz and 65000 data points. <sup>13</sup>C NMR spectra of the deuterated and the mixture of deuterated and undeuterated cyclooctanones (2 : 1 ratio) were compared for signal assignments. The assignments of chemical shifts for methylene carbons above -90 °C is determined by replacing various protons with deuterium and observing the effect on the <sup>13</sup>C spectrum of cyclooctanone. The <sup>13</sup>C signals of the low temperature can be readily assigned by application of the  $\gamma$ -gauche and deuterium effect on chemical shifts.

MM2 calculations were carried out for quantitative conformational analysis of cyclooctanone, by use of the Allinger's MM2 force field method.<sup>7</sup> All geometrical optimizations are treated by minimizing the potential energy with respect to all geometrical variables. If a global minimum is desired to be found, it is necessary to repeated the calculation with different starting geometries, since the MM2 method will find local minima on the energy surface corresponding to different conformers separated by energy barriers.

**Derivation of Saunder's equation<sup>8</sup>.** The equilibrium constant is derived from  $\delta_{eq}$  by comparison with the maximum possible peak separation,  $\Delta$ , which is the chemical shift difference between exchanging nuclei in the absence of exchange. For cyclooctanone, the  $\Delta$  value for each pair of exchanging carbons was determined by the peak separation at -148 °C, where exchange is slow on the NMR time scale.

$$K = [B]/[A] = (\Delta + \delta_{eq})/(\Delta - \delta_{eq})$$

where A and B are concentrations of the two equilibrating species (here two boat-chair conformers of cyclooctanone),  $\delta_{eq}$  is the peak separation due to the perturbed equilibrium under conditions of rapid exchange, and  $\Delta$  is the maximum possible peak separation.

### Synthesis of cyclooctanone-2,2,7,7-D<sub>4</sub>

**Cycloheptanone-2,2,7,7-D<sub>4</sub>.** A solution of cycloheptanone (11.2 g, 0.100 mol), potassium carbonate (0.4 g), and D<sub>2</sub>O (9.3 g, 0.46 mol) was stirred at 75 °C for 2 days. The mixture was worked up and deuterium exchange was repeated. Distillation (bp 74-75 °C, at 10 mm) gave 9.24 g (83%) cycloheptanone-2,2,7,7-D<sub>4</sub>.

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 214.2 (s), 42.5 (p,  $J_{CD}$ =20 Hz, C<sub>2</sub>, C<sub>7</sub>), 29.8 (s), 23.6 ppm (s).

**1-(Dibromomethyl)-1-Cycloheptanol-2,2,7,7-D<sub>4</sub>.** Lithium diisopropylamine was made by addition of n-butyl lithium (16 mL, 2.6 M in hexane, 0.0416 mol) to dry isopropyl amine (6 mL, 0.0416 mol) in tetrahydrofuran at -78 °C under

N<sub>2</sub>. This solution of lithium diisopropyl amine was added to cycloheptanone-2,2,7,7-D<sub>4</sub> (2.34 g, 0.0208 mol) and dibromomethane (3 mL, 0.0416 mol) in tetrahydrofuran. The solution was stirred while monitoring the reaction progress by TLC, diluted with ice water, neutralized with 10% HCl (ph 7), and extracted with ether. After dry column flash chromatography, 3.1 g of 1-(dibromomethyl)cyclooctanol-2,2,7,7-D<sub>4</sub> (77%) were obtained.

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 77.31 (s, C<sub>1</sub>), 60.51 (s, -CHBr<sub>2</sub>), 36.12 (p,  $J_{CD}$ =20 Hz, C<sub>2</sub> or C<sub>8</sub>), 28.71, 22.36 ppm. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 5.68 (s, 1H), 2.51 (br s, 1H), 1.80-1.40 ppm (m, 8H)

**Cyclooctanone-2,2,7,7-D<sub>4</sub>.** To the solution of dibromide (2.3 g, 0.007 mol) in THF, n-BuLi (4.1 mL, 2.6 M in hexane, 0.0105 mol) was added dropwise at -78 °C under N<sub>2</sub>. This mixture was stirred with monitoring on TLC. After dry column flash chromatography 1.0 g of the desired product was collected (97%).

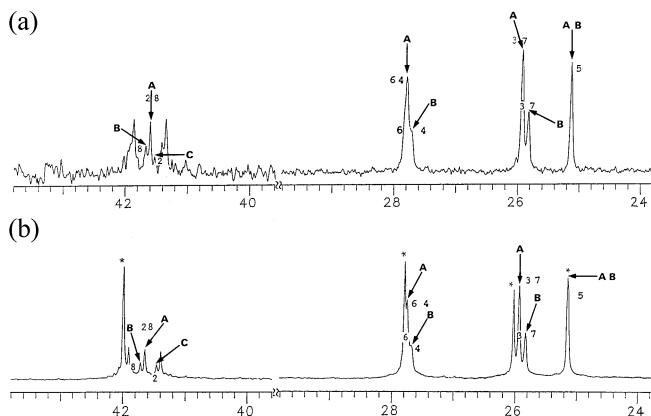
<sup>13</sup>C NMR (CDCl<sub>3</sub>): 217.45 (s, C<sub>1</sub>), 41.60 (s, C<sub>8</sub>), 41.19 (p,  $J_{CD}$ =19.39 Hz, C<sub>2</sub>), 26.78 (s, C<sub>4</sub> or C<sub>6</sub>), 25.40 (s, C<sub>3</sub>), 24.35 ppm (s, C<sub>5</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.42 (br s, 2H), 1.21-1.83 ppm (m, 8H).

### Synthesis of Cyclooctanone-2,8-D<sub>2</sub> and Cyclooctanone-2,2,8-D<sub>3</sub>

37 mg DTN dihydrochloride, 15 mg anhydrous K<sub>2</sub>CO<sub>3</sub>, and 23 mL D<sub>2</sub>O were added to cyclooctanone (4.2 g, 0.033 mol) in p-dioxane. The pD was adjusted to 8.65 using 20% DCl. The resulting solution was heated to 55 °C for 45 h, during which time the exchange was monitored by <sup>1</sup>H NMR spectroscopy. The reaction solution was allowed to cool and quenched by adding 5 drops of 20% DCl in D<sub>2</sub>O, then extracted with pentane. The combined pentane extracts were evaporated to give 2.4 g (56%) of the 3 : 10 : 10 mixture of cyclooctanone-2-D, tri-labeled cyclooctanone-2,2,8-D<sub>3</sub> and di-labeled cyclooctanone-2,8-D<sub>2</sub> after distillation (bp 138-145 °C, at 50 mm). The product ratio was identified by mass spectroscopy. <sup>13</sup>C NMR (CDCl<sub>3</sub>): 218.07 (s, C<sub>1</sub>), 41.35 (t, C<sub>2</sub>,  $J_{CD}$ =19.5 Hz), 26.89 (s, C<sub>4</sub> or C<sub>6</sub>), 25.32 (s, C<sub>3</sub> or C<sub>7</sub>), 24.28 ppm (s, C<sub>5</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.38 (m, 2H), 1.88 (m, 4H), 1.56 (m, 4H), 1.39 ppm (m, 2H). Mass Spectral Data (Electron Impact Nuclide 12-9DG 70 eV single focusing magnetic sector): 128.678 (M+3, 9.61), 127.781 (M+2, 10.06), 126.664 (M+1, 3.45), 99.735 (52.78), 84.810 (72.33), 57.006 (72.94), 55.964 (87.95), 54.932 (53.93), 43.031 (100.00), 41.998 (95.93), 41.231 (77.30), 28.216 (32.18), 27.174 (34.72).

## Results and Discussion

**Trans-Cyclooctanone-2,8-D<sub>2</sub> and Cyclooctanone-2,2,8-D<sub>3</sub>.** Specific deuteration aimed at preparation of the trans-2,8-D<sub>2</sub> isotopomer of cyclooctanone afforded the mixture of mono-deuterated (2-D), di-deuterated (2,8-D<sub>2</sub> and 2,2-D<sub>2</sub>), and tri-deuterated (2,2,8-D<sub>3</sub>) isotopomers in the ratio of 3 : 10 : 10 by analysis of electron impact mass spectroscopy. From analysis of <sup>13</sup>C NMR spectroscopy, there were three



**Figure 1.** (a)  $^{13}\text{C}$  NMR Spectrum of Cyclooctanone-2,8- $\text{D}_2$ (A), 2,2,8- $\text{D}_3$ (B) and 2-D (C) Isotopomers at 18.4 °C. (b)  $^{13}\text{C}$  NMR Spectrum of Mixture of Cyclooctanone-2,8- $\text{D}_2$  (A), 2,2,8- $\text{D}_3$  (B) and 2-D (C) Isotopomers and Cyclooctanone (Asterisks indicate peaks of unlabeled cyclooctanone).

sets of triplet peaks of C-2 and C-8 carbons, confirming the mass spectral data. These peaks appeared as having different chemical shifts and intensities, around 42 ppm, as shown in Figure 1. The  $^{13}\text{C}$  spectra of labeled and mixture of labeled and unlabeled cyclooctanone were compared and signals were assigned on the basis of chemical shift and signal intensity. The triplet peak at 41.61 ppm ( $J_{\text{CD}}=19.5$  Hz) was assigned to C-2 and C-8 carbon peaks in trans-2,8- $\text{D}_2$ , and the triplet at 41.69 ppm ( $J_{\text{CD}}=19.5$  Hz) was assigned to the C-8 peak in the 2,2,8- $\text{D}_3$  isotopomer.

The  $^{13}\text{C}$  signal assignments of cyclooctanone by deuterium substitution have been reported and agreed with those of Silverstein.<sup>9</sup> The chemical shifts of the four groups in the methylene region in Figure 1 correspond to the chemical shifts of C-5 and the averaged resonances for C-2 and C-8, C-3 and C-7, and C-4 and C-6. The structure of cyclooctanone on the NMR time scale at room temperature was known as a conformational average having net  $\text{C}_{2v}$  symmetry which has two planes and an axis of symmetry as in the planar representation of cyclooctanone.<sup>10</sup> The  $\text{C}_{2v}$  symmetry can be explained by any combination of rapidly interconverted conformers.

In the 2,8-di-deuterated isotopomer, there would be no equilibrium effects expected, because the equilibrium will remain degeneracy. The observed intrinsic isotope shift for C-2 of this isotopomer is 0.339 ppm, which is very similar to the derived intrinsic isotope shift for C-2 of cyclooctanone-2-D (0.356 ppm in Table 1).<sup>11</sup> This observed shift is also not temperature dependent, thus indicating that there is no equilibrium isotope effect observed for the 2,8- $\text{D}_2$  isotopomer. The unsymmetrically labeled 2,2,8- $\text{D}_3$  isotopomer affords a conformational equilibrium isotope effect since the degeneracy of equilibrium was removed by the unsymmetrical labeling, leading to a shift of equilibrium. Since the di-deuterated C-2 carbon peak was not visible in the spectrum, the equilibrium isotope shift was obtained from the difference between triplets of the 2,8- $\text{D}_2$  isotopomer and the 2,2,8- $\text{D}_3$  isotopomer. This can be done

**Table 1.** Observed Equilibrium and Intrinsic Isotope Shifts at Various Temperatures for Cyclooctanone-2-D

Temp. (°C)	Equilibrium Isotope Shifts		
	C-2,8	C-3,7	C-4,6
22.0	0.118	0.194	0.084
-20.5	0.130	0.278	0.096
-58.0	0.194	0.356	0.130
-92.0	0.357	0.145	0.064
Temp. (°C)	Intrinsic Isotope Shifts		
	C-2	C-3	C-4
22.0	0.356	0.081	0.038
-20.5	0.356	0.108	0.049
-58.0	0.356	0.129	0.049
-92.0	0.357	0.145	0.064

because the 2,8- $\text{D}_2$  isotopomer is affected only by the intrinsic isotope shift.

For the C-3 and C-7 methylene carbon region in the  $^{13}\text{C}$  NMR spectrum, there are two major peaks with different intensities as shown in Figure 1(a). When unlabeled cyclooctanone was added, a new peak around 26 ppm appeared in the most downfield position and was assigned to C-3 and C-7 methylene carbons of unlabeled cyclooctanone (Figure 1(b)). The middle peak belongs to C-3 and C-7 carbons of 2,8- $\text{D}_2$ , and also the C-3 carbon of the 2,2,8- $\text{D}_3$  isotopomers. The upfield peak was assigned to the C-7 carbon of the tri-deuterated isotopomer. The equilibrium isotope shift was calculated from difference between the C-3 and C-7 carbon peak of 2,8- $\text{D}_2$  and the C-7 carbon peak of the tri-deuterated isotopomer.

In the case of C-4 and C-6 carbons, the unlabeled methylene carbon peak was found in the most downfield position with strong intensity in Figure 1(b). The next most downfield peak beside the reference peak was assigned to the C-4 and C-6 of 2,8- $\text{D}_2$  isotopomer, and the most upfield peak to the C-4 carbon of 2,2,8- $\text{D}_3$  isotopomer. The observed chemical shift was the sum of one-half of the equilibrium isotope effect, plus the intrinsic isotope effect coming from di-deuteration at C-2 carbon. The intrinsic isotope shift for C-4 car-

**Table 2.** The Intrinsic Isotope shifts for Cyclooctanone-2,2,8,8- $\text{D}_4$

Temp. (°C)	Intrinsic Isotope Shifts (ppm)			
	C-2	C-3	C-4	C=O
18.5	0.512	0.194	0.094	-0.226
-20.0	0.518	0.194	0.097	-0.223
-58.4	0.519	0.190	0.090	-0.222
-90.2	0.501	0.194	0.093	-0.223

**Table 3.** The Equilibrium Constants and Free Energy Differences in Cyclooctanone-2,2,8-D<sub>3</sub>

Temp (°C)	Equilibrium Constants (K)				Free Energy Differences (cal/mol)			Enthalpy* $\Delta H^\circ$ (cal/mol)	Entropy* $\Delta S^\circ$ (cal/T)
	C-2,8	C-3,7	C-4,6	Ave.	$\Delta G^\circ$				
18.4	1.049	1.044	1.049	1.047	-27		-43±4	-0.06±0.00	
-20.5	1.056	1.053	1.058	1.056	-27				
-58.7	1.064	1.069	1.067	1.067	-28				
-90.3	1.097	1.091	1.100	1.096	-33		Corr. Coef.*=0.963		

\*From Van't Hoff plots

bon in 2,2,8-D<sub>3</sub> isotopomer was obtained from cyclooctanone-2,2,8,8-D<sub>4</sub> model compound (0.094 ppm in Table 2). Only intrinsic isotope shifts were observed for symmetrically deuterated cyclooctanone-2,2,8,8-D<sub>4</sub> isotopomer. The calculated equilibrium constants and the free energy differences are listed in Table 3. The relationship of equilibrium constants and inverse temperatures could provide the enthalpy and entropy differences. These differences were -43 cal/mol and -0.063 cal/K, respectively.

**Cyclooctanone-2,2,7,7-D<sub>4</sub>.** The chemical shifts of mixture of unlabeled cyclooctanone and labeled cyclooctanone-2,2,7,7-D<sub>4</sub> are listed in Table 4 at various temperatures. For the comparison of spectra of 2,2,7,7-D<sub>4</sub> and a 2 : 1 mixture 2,2,7,7-D<sub>4</sub> and unlabeled cyclooctanone, Figure 2(a) and (b) include the methylene carbon region at 18.5 °C. The peaks corresponding to peaks of unlabeled cyclooctanone are marked in Figure 2. Signals for C-2 and C-8 methylene carbons of unlabeled cyclooctanone overlapped with the signal for the C-8 methylene carbon of 2,2,7,7-D<sub>4</sub> at room temperature, but the peaks were separated at -90.3 °C. (see Figure 2(c)) C-2 and C-7 carbons of 2,2,7,7-D<sub>4</sub> do not show up in Figure 2 owing to complete deuteration on C-2 and C-7 carbons.

Intrinsic isotope shifts of the peaks for 2,2,7,7-D<sub>4</sub> can not be directly obtained from the <sup>13</sup>C NMR spectrum: (1) The directly deuterated C-2 and C-7 carbon peaks are not visible and only peaks for unlabeled cyclooctanone, and the corresponding C-3 and C-8 carbon peaks of 2,2,7,7-D<sub>4</sub> isotopomer are observable in the Figure 2(b). (2) Both C-4 and C-6 carbon peaks are shifted by intrinsic and equilibrium isotope shifts. Intrinsic isotope shifts were therefore obtained from average intrinsic isotope shifts of the model compounds in rapid exchange condition.

Model compounds were chosen which are only affected by intrinsic isotope shifts. Cyclooctanone-2,2,8,8-D<sub>4</sub> was chosen to obtain intrinsic isotope shifts of C-3 and C-4 carbons, because this isotopomer has a degenerate equilibrium, thus no equilibrium isotope shift occurs. Also, the C-3 carbon is two-bonds away from deuterium at the C-2 carbon in the tetra-deuterated cyclooctanone-2,2,8,8-D<sub>4</sub>, just like in cyclooctanone-2,2,7,7-D<sub>4</sub>. The intrinsic isotope shift of the C-3 carbon was obtained as 0.194 ppm from the room tem-

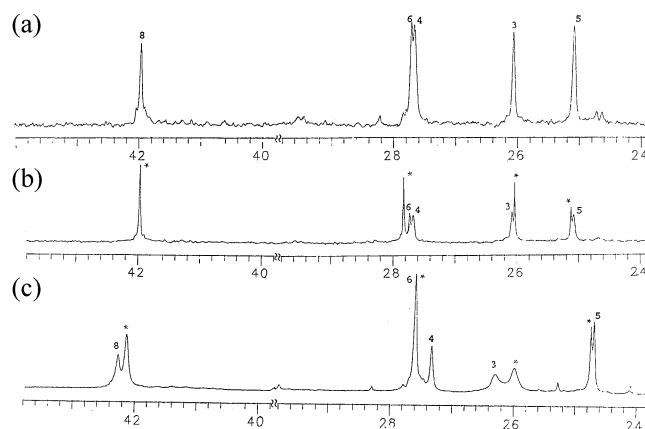
**Table 4.** The Chemical Shifts of 2 : 1 Mixture of Cyclooctanone-2,2,7,7-D<sub>4</sub> and Cyclooctanone

Temp. (°C)	Chemical Shifts (ppm)				
	C-2, 8 <sup>a</sup>	C-3, 7 <sup>a</sup>	C-4, 6	C-5	C=O
		26.07	*27.82	*25.18	*214.19
18.5	*42.04	*26.01	27.71	25.14	214.16
			27.66		
	42.19	26.26	*27.89	*25.11	*215.18
-18.2	*42.14	*26.15	27.83	25.05	215.05
			27.72		
	42.13	26.18	*27.67	*24.85	*215.92
-58.3	*42.06	*25.99	27.65	24.79	215.80
			27.45		
	42.26	26.29	*27.59	*24.76	*216.80
-90.3	*42.13	*25.98	27.33	24.70	216.66
	41.38				

\*Averaged methylene peaks for unlabeled cyclooctanone. <sup>a</sup>Chemical shifts of completely deuterated C-2 and C-7 carbon were not obtained.

perature spectrum of cyclooctanone-2,2,8,8-D<sub>4</sub>. (Table 2) The intrinsic isotope effect on the C-4 carbon in this isotopomer is influenced by two deuterium atoms at the C-2 position, but not by di-deuteration of C-7 due to greater bond separation. The intrinsic isotope shift of C-4 was obtained as 0.094 ppm from the room temperature spectrum of cyclooctanone-2,2,8,8-D<sub>4</sub>.

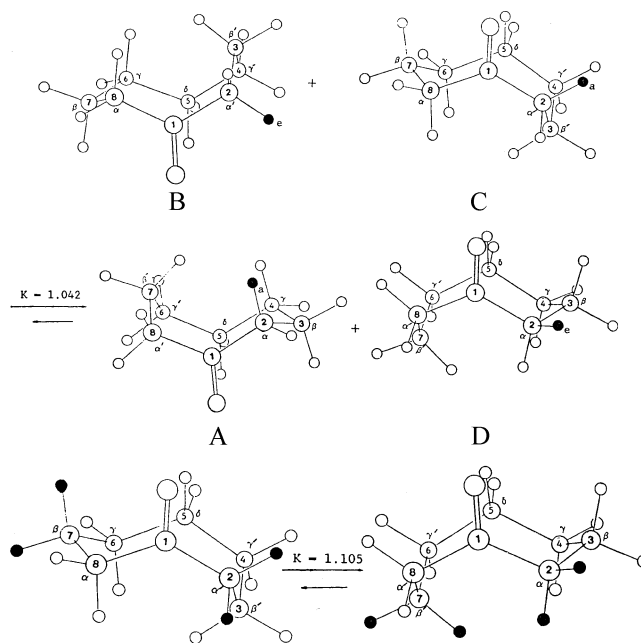
For the C-8 and C-6 carbons of cyclooctanone-2,2,7,7-D<sub>4</sub>, cyclooctanone-3,3-D<sub>2</sub> is chosen as a model compound, because the C-8 and C-6 carbons of this isotopomer are similarly located next to deuterium. The intrinsic isotope shift of the C-8 carbon is estimated as 0.130 ppm, from the C-2 position of cyclooctanone-3,3-D<sub>2</sub>.<sup>12</sup> For the isotope shift of C-6, an estimate is obtained as 0.188 ppm from the cyclooc-

**Figure 2.** (a) <sup>13</sup>C NMR Spectrum of Cyclooctanone-2,2,7,7-D<sub>4</sub> at 18.5 °C. (b) <sup>13</sup>C NMR Spectrum of 2:1 Mixture of Cyclooctanone-2,2,7,7-D<sub>4</sub> and Cyclooctanone at 18.5 °C. (c) <sup>13</sup>C NMR Spectrum of 2 : 1 Mixture of Cyclooctanone-2,2,7,7-D<sub>4</sub> and Cyclooctanone at -90.3 °C (Asterisks indicates peaks of unlabeled cyclooctanone).

tanone-3,3-D<sub>2</sub> isotopomer. Since the intrinsic isotope shift should remain approximately constant with changing temperature, the same values for the intrinsic isotope shifts were used for all the calculations of equilibrium isotope shifts to obtain equilibrium constants at various temperatures for 2,2,7,7-D<sub>4</sub> isotopomer.

The equilibrium isotope effects were observed from <sup>13</sup>C NMR data at several temperatures. The tendency of equilibrium isotope effects is to increase as temperature gets lower. This tendency is evident in Table 5 and Figure 2: In the case of C-8 and the reference methylene carbons, these two peaks overlap at room temperature, but the peaks were resolved at -90.3 °C in Figure 2(c). Similar increases in peak separations are seen for the other carbons also. From the observed chemical and intrinsic isotope shifts, equilibrium isotope shifts were calculated. The equilibrium constants and corresponding free energy differences are listed in Table 5, and the obtained enthalpy and entropy differences are -93 cal/mol and -0.122 cal/K, respectively, from the results of regression analysis of equilibrium constants versus inverse temperatures.

**Isotope Effects Related to Cyclooctanone Conformation.** The conformational equilibria that are being perturbed by isotopic substitution are the equilibria among the boat-chair conformers of cyclooctanone. The four conformers are shown in Figure 3 with all of the hydrogen positions indicated. Any particular hydrogen at C-2, C-3, or C-4 exchanges among four possible environments ( $\alpha$  or  $\alpha'$ , or  $\beta$ , or  $\beta'$ ,  $\gamma$  or  $\gamma'$  and axial or equatorial). If a single deuterium is substituted for a hydrogen at C-2, C-3, or C-4, the four conformers are diastereomeric and equilibrium isotope effects may occur in which each conformer contributes a different



**Figure 3.** The Shifts of Equilibrium in 2-D and 2,2,7,7,-D<sub>4</sub> Isotopomers.

amount to the equilibrium. However, since only two carbon environments can be distinguished, the apparent equilibrium will be between two pairs of conformers, *i.e.*,  $[1B + 1C] \rightleftharpoons [1A + 1D]$ . Each particular carbon has the same chemical shift in both 1A and 1D, *e.g.*, C-3 is in the environment in both 1A and 1D. Similarly, each carbon has the same chemical shift in the 1B and 1C, *e.g.*, C-3 is in the  $\beta'$  environment in both. The equilibrium isotope shifts in <sup>13</sup>C spectra can be used to detect the proportion of time C-3 is in each environment,  $\beta$  and  $\beta'$ , but cannot reveal the position of  $1B \rightleftharpoons 1C$  or  $1A \rightleftharpoons 1D$  equilibria. The situation is simpler if both hydrogens at a carbon are substituted by deuterium, as in the 2,2,7,7-D<sub>4</sub> isotopomer, because then the  $1B \rightleftharpoons 1C$  equilibrium is degenerate, the  $1A \rightleftharpoons 1D$  equilibrium is degenerate, and the observed equilibrium is between only two different conformers.

When equilibrium constants were derived from equilibrium isotope shifts using Saunders' equation, direction of the isotope effects were not indicated. The equilibrium constants were always expressed as values greater than unity,  $K > 1$ . The direction of the isotope effect can be determined by noting whether individual carbons are moved upfield or downfield by the equilibrium isotope shift. It was known that  $\alpha$ ,  $\beta'$ , and  $\gamma$  carbons appear upfield of the corresponding  $\alpha$ ,  $\beta'$ , and  $\gamma$  carbons due to the  $\gamma$ -gauche effect. Thus, for example, if C-3 is moved downfield and C-7 upfield by the isotope environment, it is clear that C-3 resides more of the time in the  $\beta$  environment, C-7 is correspondingly more in the  $\beta'$  environment, and the  $[1B + 1C] \rightleftharpoons [1A + 1D]$  equilibrium favors  $[1A + 1D]$ . If the isotope effect is in the opposite direction, the equilibrium constant for  $[1B + 1C] \rightleftharpoons [1A + 1D]$  will be inverse,  $K < 1$ . The results of the equilibrium isotope effect determinations are summarized in Table 6. This table gives

**Table 5.** Equilibrium Isotope Shifts on Cyclooctanone-2,2,7,7,-D<sub>4</sub> with Various Temperatures

Temp. Equilibrium Isotope Shifts							
(°C)	C-2,8	C-3,7	C-4,6				
18.5	0.336	0.474	0.177				
-18.2	0.384	0.608	0.226				
-58.3	0.436	0.782	0.313				
-90.3	0.534	1.004	0.380				
The Equilibrium Constants and Free Energy Differences in Cyclooctanone-2,2,7,7,-D <sub>4</sub>							
Temp. (°C)	Equilibrium Constants (K)				Free Energy Enthalpy* Entropy* Differences		
	C-2,8	C-3,7	C-4,6	Ave.	$\Delta G^\circ$ (cal/mol)	$\Delta H^\circ$ (cal/mol)	$\Delta S^\circ$ (cal/T)
18.5	1.120	1.100	1.095	1.105	-58	-93±6	-0.12±03
-18.2	1.123	1.130	1.123	1.126	-58		
-58.3	1.171	1.171	1.174	1.172	-66		
-90.3	1.200	1.224	1.215	1.213	-70		Corr. Coef.*=0.980

\*From Van't Hoff plots

**Table 6.** Equilibrium Constants and Free Energy Differences of Cyclooctanone Isotopomers

Isotopomers	Temp.	Keq [1B + 1C] $\rightleftharpoons$ [1A + 1D]	$\Delta G^\circ$ (cal/mol)
	( $^\circ\text{C}$ )		
2-D	22.0	1.042	-24 <sup>a</sup>
2,2,7,7-D <sub>4</sub>	18.5	1.105	-58
3,3-D <sub>2</sub>	20.2	0.988	7 <sup>b</sup>
2,2,8-D <sub>3</sub>	18.4	1.047	-27
2,2-D <sub>2</sub>	---	---	(-51) <sup>*</sup>
2,8-D <sub>2</sub>	22.0, 18.4	1.000	0
2,2,8,8-D <sub>4</sub>	18.5	1.000	0

<sup>\*</sup>Estimated value from other results, based on additivity of isotope effects. See text for explanation. <sup>a</sup>The obtained data from reference 11. <sup>b</sup>The obtained data from reference 12.

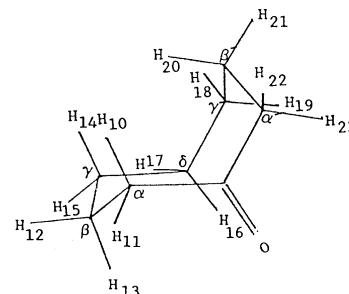
the equilibrium constants and derived free energy difference for the conformational equilibrium near room temperature. The magnitude of the conformational free energy difference in the 3,3-D<sub>2</sub> isotopomer<sup>12</sup> was smallest (7 cal/mol) and that of the 2,2,7,7-D<sub>4</sub> isotopomer was largest (-58 cal/mol). The isotope effect for the 2,2-D<sub>2</sub> isotopomer, which was not measured directly, can be estimated to be about -51 cal/mol by assuming additivity of isotope effects. Assuming additivity, the -58 cal/mol for the 2,2,7,7-D<sub>4</sub> isotopomer can be considered as the sum of -7 cal/mol from the 7,7-D<sub>2</sub> label (analogous to 3,3-D<sub>2</sub>) and -51 cal/mol from the 2,2-D<sub>2</sub> label. Alternatively, the -24 and -27 cal/mol for the 2-D and 2,2,8-D<sub>3</sub> isotopomers can be used also to obtain an estimate of -51 cal/mol for the 2,2-D<sub>2</sub> compound.

An MM2 calculation was carried out on the boat-chair conformation of cyclooctanone to assist in the interpretation of the NMR isotope shift results. This method enables one to find steric energy distributions and molecular geometry, *i.e.*, strain and energy of van der Waals interactions associated with calculated bond angles and distances. Geometrical optimization starting with a boat-chair conformation (BC-1) of cyclooctanone resulted in a BC-1 boat-chair conformation as the optimized structure. This conformation should be the lowest energy structure, as described in a previous study.<sup>13</sup> The results of the MM2 calculation are summarized in Table 7. Axial hydrogens at the  $\alpha$ ,  $\beta'$  and  $\gamma$  carbons have strong mutual steric interactions due to their close proximity in the boat-chair conformation. One indication of this steric effect in the MM2 calculations is the van der Waals interaction energies. Van der Waals repulsive interactions are seen for hydrogen atom pairs located on adjacent carbons in gauche alignment. In addition, there are mutual transannular interactions of H(20) with H(10) and H(14) on the  $\alpha$ ,  $\beta'$  and  $\gamma$  carbons. There is a near eclipsing interaction between H(15) and H(16) on the  $\gamma$  and  $\delta$  carbons. The sum of the van der Waals energies for the important steric interactions is given in the Table 7 for each hydrogen atom. For the purpose of discussing isotope effects, the important feature is the change in steric interactions as hydrogen atoms exchange

**Table 7.** Key Features of MM2 Geometry for Boat-chair Conformation of Cyclooctanone

Carbon	Atom Pair <sup>a</sup>	Interatomic Distance (Å)	Van der Waals Interaction Energy <sup>b</sup> (kcal/mol)	Total Van der Waals Energy
$\alpha$	H(10), H(12)	2.4237	0.1803	0.8069
	H(10), H(20)	2.3151	0.3808	
	H(10), C-8	2.6480	0.2458	
a	H(11), H(12)	2.3647	0.2760	0.7217
	H(11), H(13)	2.4140	0.1942	
	H(11), O	2.5732	0.2515	
b	H(12), H(11)	2.3647	0.2760	0.9839
	H(12), H(11)	2.4237	0.1803	
	H(12), H(14)	2.4211	0.1840	
b	H(12), H(15)	2.3313	0.3436	0.9839
	H(13), H(15)	2.3901	0.2314	
	H(13), C-1	2.7422	0.2217	
g	H(14), H(12)	2.4211	0.1840	0.9106
	H(14), H(20)	2.3949	0.2235	
	H(14),	2.6317	0.2717	
g	H(15), H(12)	2.3313	0.3436	1.3065
	H(15), H(13)	2.3901	0.2314	
	H(15), H(16)	2.2031	0.7315	
$\gamma$	H(18), H(20)	2.3739	0.2501	0.9606
	H(18), H(16)	2.2986	0.4216	
	H(18), H(21)	2.3626	0.2799	
$\gamma$	H(19), H(16)	2.4064	0.2055	0.7741
	H(19), H(17)	2.3541	0.2964	
	H(19), H(21)	2.3667	0.2722	
$\beta'$	H(20), H(10)	2.3151	0.3808	1.1715
	H(20), H(14)	2.3949	0.2235	
	H(20), H(18)	2.3739	0.2591	
$\beta'$	H(20), H(22)	2.4171	0.1896	1.1715
	H(20), C-1	2.8326	0.1185	
	H(21), H(18)	2.3626	0.2799	
$\alpha'$	H(21), H(19)	2.3667	0.2722	1.0341
	H(21), H(22)	2.3815	0.2458	
	H(21), H(23)	2.3872	0.2362	
$\alpha'$	H(22), H(20)	2.4171	0.1896	0.4354
	H(22), H(21)	2.3815	0.2458	
	H(23), H(21)	2.3872	0.2362	
	H(23), O	2.4853	0.4278	0.6640
Dihedral Atom	Dihedral Angle ( $\theta$ )		$\text{Cos}^2 \theta$	
H <sub>22</sub> - $\alpha'$ -C <sub>1</sub> -P <sub>orbital</sub>	16.51		0.919	
H <sub>23</sub> - $\alpha'$ -C <sub>1</sub> -P <sub>orbital</sub>	82.00		0.019	
H <sub>11</sub> - $\alpha$ -C <sub>1</sub> -P <sub>orbital</sub>	42.00		0.552	
H <sub>10</sub> - $\alpha$ -C <sub>1</sub> -P <sub>orbital</sub>	73.00		0.085	

<sup>a</sup>Numbering system for hydrogen atoms is shown below. <sup>b</sup>Only interactions greater than .01 kcal/mol are indicated



environments during the equilibration process between conformers. For example, hydrogens at the  $\alpha$  carbon (H10+H11) exchange into the  $\alpha'$  position (H22+H23). The calculations show that the  $\alpha$ -hydrogens would become less sterically crowded in becoming  $\alpha'$ -hydrogens, with the van der Waals energy decreasing by 0.43 kcal/mol. Hydrogens at the  $\beta$ -carbon become more crowded in exchanging into the  $\beta'$  position (+0.72 kcal/mol); this is the result of the uncrowded H(13) at  $\beta$  and the crowded H(20) at  $\beta'$ . Hydrogens at the  $\gamma$ -carbon become less crowded in exchanging into the  $\gamma'$ -position (-0.48 kcal/mol).

When deuterium is involved in such calculation of conformational equilibria, deuterium then tends to occupy more crowded positions due to this "steric isotope effect."<sup>14</sup> Introduction of deuterium would be expected to cause isotopic perturbation of the boat-chair equilibria by the steric isotope effect. Deuterium is expected to prefer the  $\alpha$ -position over  $\beta'$ , over  $\beta$ , and  $\gamma$  over  $\gamma'$ . The actual observations in Table 6 are consistent with the expectations.

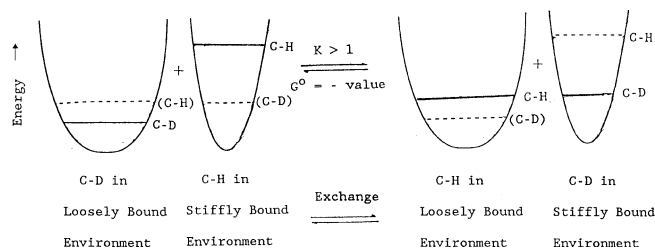
The free energy differences for the equilibria of mono-2-D, 2,2-D<sub>2</sub>, 3,3-D<sub>2</sub>, isotopomers and 2,2,7,7-D<sub>4</sub> were -24, -51, +7, -58 cal/mol, respectively, at room temperature. If the steric isotope effect alone were responsible for these free energy differences, the free energy differences for 3,3-D<sub>2</sub> would be larger than for 2,2-D<sub>2</sub>. But, the free energy differences for 2-D was larger than for the 3,3-D<sub>2</sub> isotopomer by 17 cal/mol. This discrepancy suggests strongly that another mechanism is needed to account for the relatively large free energy difference resulting from placement of the label at C-2. Hyperconjugation seems a likely candidate to be the major cause of the isotope effects for the 2-D, 2,2,8-D<sub>3</sub>, and 2,2,7,7-D<sub>4</sub> isotopomers. Hyperconjugation of  $\alpha$  or  $\alpha'$  C-H bonds with the carbonyl  $\Pi$ -bond would weaken and lengthen the hyperconjugating bonds. By creating a broader potential well (smaller force constants) for stretching and bending, hyperconjugation can be the origin of equilibrium isotope effects (see Figure 4). It is necessary, of course, that the extent of hyperconjugation differ between the two positions undergoing exchange ( $\alpha$  and  $\alpha'$ ).

In orbital terms, hyperconjugation is the release of electron density from a bonding C-H orbital into the  $\Pi$ -antibonding orbital of the carbonyl. Such orbital interactions are not included in molecular mechanics calculations. However, the angular dependence of hyperconjugation can be investigated from the MM2 results by examining the predicted molecular geometry, especially the dihedral angle between  $\alpha$

and  $\alpha'$  hydrogens and the p-orbital at the carbonyl carbon. The corresponding dihedral angle between H(22) and the p-orbital is 16.51°, and the angle between H(23) and the p-orbital is 82.00°, for the protons of the  $\alpha'$  carbon. The dihedral angles of protons H(10) and H(11) at the  $\alpha$  carbon are 73.00° and 42.00°, respectively. Sunko, Hehre, *et al.* suggested a  $\text{Cos}^2 \theta$  dependence of kinetic deuterium isotope effects of individual C-H(D) bonds, based on the angular dependence of hyperconjugative overlap, where the value  $\theta$  is the dihedral angle of the C-H(D) bond with respect to the p-orbital.<sup>15</sup> Calculated values of the  $\text{Cos}^2 \theta$  dependence for the individual C-H(D) bonds are listed at the bottom of Table 7.

The smaller the dihedral angle  $\theta$ , the better the alignment of the C-H bond for overlap with the p-orbital. Better overlap leads to increased hyperconjugation, as indicated by the  $\text{Cos}^2 \theta$  term. Hyperconjugation weakens the force constant for the C-H stretching vibration (and probably bending vibrations), hence the potential wells for C-H bonds. Thus, considering Figure 4, deuterium will be found preferentially in nonhyperconjugating positions in an equilibrium because such positions are the more stiffly bound positions. In cyclooctanone, the hyperconjugative interactions are not equal for all the  $\alpha$  and  $\alpha'$  hydrogens. For example, there are four possible conformers in the 2-D isotopomer (Figure 3), and the shift of equilibrium in this isotopomer is controlled by steric and hyperconjugative isotopic perturbation. H(22) (or H <sub>$\alpha'$ e</sub>) has the best alignment with p-orbital for hyperconjugation, and the steric interaction on this proton is smallest among the protons of  $\alpha$  and  $\alpha'$  carbons: the value of  $\text{Cos}^2 \theta$  on H(22) is 0.919, and the van der Waals energy is 0.435 kcal/mol. For both these reasons, deuterium is least likely to be found there. H(11) (or H <sub>$\alpha$ e</sub>) has the next best alignment ( $\text{Cos}^2 \theta = 0.552$ ) and the steric interaction is larger (0.772 Kcal/mol). H(10) (or H <sub>$\alpha$ e</sub>) and H(23) (or H <sub>$\alpha'$ e</sub>) both have very poor alignments for hyperconjugation, with  $\text{Cos}^2 \theta$  values of 0.019, respectively. Although the equilibrium was shifted by combined factors of steric and hyperconjugative interaction, the main factor of the comparatively large conformational energy difference for the 2-D isotopomer is expected to be the hyperconjugative interaction: The observable equilibrium  $[1B+1C] \rightleftharpoons [1A+1D]$  for the 2-D isotopomer is shifted by -24 cal/mol while the magnitude of the steric contribution is expected to be less than half the effect observed for the 3,3-D<sub>2</sub> isotopomer of 7 cal/mol. The sum of  $\text{Cos}^2 \theta$  values for 1B+1C = 0.919+0.019 = 0.938 while the sum for 1A+1D = 0.552+0.085 = 0.637, so it is clear that the tendency for deuterium to avoid the  $\alpha'$ e position (1B in Figure 3) because of its hyperconjugative interaction is the dominant influence on the equilibrium.

The temperature dependence of the CEIE is summarised in Table 3 and 5. As expected, equilibrium constants are larger at low temperatures. The same relative magnitudes of effects are maintained as at room temperature. The one somewhat disturbing feature of the results is the trend of  $\Delta G^\circ$  values toward larger magnitudes with lower temperature rather than remaining constant. The possible error for the  $\Delta H$  and  $\Delta S$  values from the  $\ln K$  versus  $1/T$  plots are simply the



**Figure 4.** Origin of Isotope Effect on Equilibria for Exchange between Stiffly and Loosely Bound Positions.

one standard deviation of these values from a simple linear regression analysis which did not include errors in the K or T measurements: two species the actual errors in  $\Delta H$  and  $\Delta S$  are expected to be larger. The source of the variation with temperature is not a systematic error in temperature measurement. The  $\Delta G^0$  value is relatively insensitive to errors in temperature (however,  $\Delta H$  and  $\Delta S$  are much more sensitive). The calibration of the thermocouple reading with actual sample temperature has been checked over a wide range of temperatures and found to vary from the actual temperature by no more than 3°, which is not sufficient to account for the variation. Another possible source of error arises from the assumptions involved in separating intrinsic and equilibrium isotope shifts. It is difficult to rule out these sources as contributing a systematic error because it was not possible to measure accurately intrinsic isotope shifts for each conformer at low temperature. However, the potential impact of these assumptions should be minimized by measuring equilibrium constants for each labeled compound from three independent sets of data, *i.e.*, from the three pairs of exchanging carbons.

The  $^{13}\text{C}$  chemical shifts of cyclooctanone are somewhat temperature dependent, including those of the carbonyl carbon and C-5 which are not affected by line shape changes due to boat-chair exchanges. Also, no temperature-dependent, equilibrium isotope shifts were detected for the symmetrically labeled 2,2,8,8- $\text{D}_4$  isotopomer, where the label cannot perturb equilibria among boat-chairs but could perturb an equilibrium between the boat-chairs and another type of conformer. The sensitivity of the technique depends not only on the magnitude of the equilibrium isotope effect (in cal/mol), but also on the chemical shifts differences between the species being rapidly equilibrated and the relative populations of the two species. The boat-chair form afforded a satisfactory explanation of the  $^{13}\text{C}$  NMR spectral data, and appears to be the lowest energy form of cyclooctanone con-

formation. The equilibrium isotope shifts provide good evidence of the origin of CEIEs in cyclooctanone, in which isotope labeling perturbs conformational equilibria by either isotope effects arising from hyperconjugative interactions or steric isotope effects.

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