Deuterium Isotope Effects on the ^{13}C Chemical Shifts of Cyclooctanone-2-D

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The intrinsic and equilibrium isotope effects on the ^{13}C NMR chemical shift of the cyclooctanone-2-D were investigated. Equilibrium constants and changes in the free energies, enthalpy, entropy, which are derived from the temperature dependence of the isotope shifts, are reported for this isotopomer.

Introduction

Deuterium isotope effects on ^{13}C NMR chemical shifts and the causes of the isotope shifts are currently under intensive study.[1,2] The ^{13}C shielding changes associated with deuterium substitution arise from either intrinsic or a combination of intrinsic and equilibrium isotope effects.[3] When there are ^{13}C signals which represent two or more carbons time averaged to equilibrium in the unlabeled compound, labeling can lead to splitting of the averaged resonances by removing the degeneracy. The splitting of the signals provides an accurate method for determining small equilibrium isotope effects.

Selectively deuterated cyclooctanone-2-D was synthesized and investigated for intrinsic and equilibrium NMR isotope shifts. These intrinsic and equilibrium isotope effects are discussed in relation to the preferred boat-chair conformation of cyclooctanone.[4] The temperature dependence of the isotope shifts were 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 were calculated, and changes in the free energies, enthalpy and entropy were derived from the temperature dependence of the equilibrium isotope effects.

Experimental

Deuterium labelled compounds were mostly prepared with acid- or base- catalyzed H-D exchange reaction of the starting materials. Details were given in a previous paper.[5] ^{13}C NMR Spectra were recorded on a Varian XL-300 NMR spectrometer equipped with a broad band probe at 75.4 MHz. ^{1}H NMR spectra were obtained on a Varian XL-300 NMR at 300 MHz. The ^{13}C and ^{1}H spectra were 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 ± 1 °C were discarded. ^{13}C NMR spectra of unlabeled and labeled cyclooctanone samples were recorded from 22 °C to − 148.5 °C at every 20 °C interval and the entire spectra were measured with a width of 20000 Hz and 65000 data points. ^{13}C NMR spectra of the labeled and the mixture of labeled and unlabeled cyclooctanones (2 : 1 ratio) were compared for signal assignments.

Results and Discussion

Signal Assignments of Cyclooctanone-2-D. ^{13}C NMR isotope shifts for cyclooctanone-2-D mixture were measured in ^{13}C spectra of a mixture of cyclooctanone isotopomers containing predominately cyclooctanone-2-D. In the mixture, the mole ratio of unlabled cyclooctanone to cyclooctanone-2-D to cyclooctanone-2,8-D_2 is approximately 0.39 : 1.00 : 0.12. The alkyl region of the ^{13}C spectrum at 22 °C is shown in Figures 1(a) for this mixture. Figure 1(b) shows the ^{13}C spectrum of a mixture to which more unlabeled cyclooctanone has been added to bring the more ratio to approximately 1.10 : 1.00 : 0.12. The peaks of the methylene carbons of unlabeled cyclooctanone are easily distinguished by comparison of Figure 1(a) and (b). When unlabeled cyclooctanone was added to the labeled cyclooctanone mixture, some of the peaks were increased. One peak increased in each of four groups of peaks in the alkyl portion of the spectrum. The chemical shifts of the four groups 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 increased peaks could be assigned to the averaged methylene carbons of unlabeled cyclooctanone and are indicated by an asterisk in Figures 1(a) and (b). These peaks will serve as reference peaks for the determination of isotope shifts. The remaining major peaks in Figure 1(a) arise from the methylene carbons of cyclooctanone-2-D. Some peaks appear upfield and some appear downfield of the reference peaks. The signals are shifted from the reference positions by a combination of equilibrium and intrinsic isotope effects.

Deuterium substitution in a compound equilibrating rapidly on an NMR time scale between a number of degenerate species can give rise to a splitting of an averaged resonance which is observed in unlabeled compound. This equilibrium isotope effect occurs when an energy surface has two or more minima seperated by low energy barriers. The magnitude of the isotope induced splitting depends in part on the relative stability of species within these minima.[6] The isotope effect on an equlibrium constant is reflected in different average environments and different average shieldings for nuclei which would be averaged to equivalence in an unlabeled compound. On the other hand, the isotope substitution in a static species involves only small intrinsic deuterium isotope shifts because isotopic substitution in a single structure perturbs only vibrational motion which relates

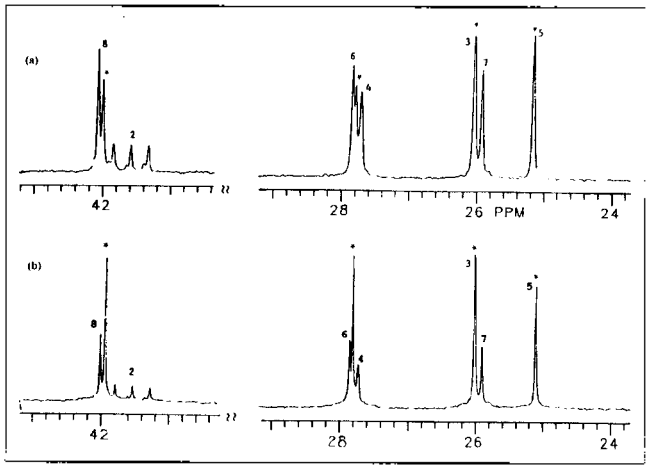

Figure 1. (a) Labeled ^{13}C NMR Spectrum of a Mixture Containing Predominately Cyclooctanone-2-D at 22 °C. (b) ^{13}C NMR Spectrum of the Mixture of Cyclooctanone-2-D and Cyclooctanone at 22 °C. (Asterisks indicate peaks of unlabeled cyclooctanone; numbers indicate the signal assignments to particular carbon atoms)

to average nuclear shielding. These shifts are the small changes in the chemical shifts which occur on a single minimum energy surface.[7]

^{13}C NMR spectra are obtained at various temperatures from 22 °C to − 148.5 °C in order to find the chemical shift at the temperature at which the dynamic process can be "frozen out" on the NMR time scale and cyclooctanone-2-D can be observed as a stable conformation. Both the ring conversion and pseudorotational processes must be "frozen out" in order to see separate resonances for all eight carbons in cyclooctanone. In contrast to ^{1}H spectra, slow down of the ring inversion process has only no apparent effect on the ^{13}C spectra because exchange of environments within the pairs of methylene carbons can still occur by the pseudorotational process. The carbon atom environment in this system will be given a Greek letter designaton of α or α', β or β', γ or γ', or δ. Hydrogen or deuterium environments can be denoted by combinations of Greek letter and axial-equatorial designator, such as $D_{\beta a}$, $D_{\beta a'}$, $D_{\beta e}$, or $D_{\beta e'}$. (Figure 2)

The assignment between the ^{13}C signals of methylene carbon pairs in cyclooctanone at low temperature can be done by application of the γ substituent effect (γ-gauche effect). The γ-gauche relationship was observed in the boat-chair conformation of cyclooctanone: this effect is closely associated with the geometrical features of cyclooctanone conformation in terms of the repulsive forces between closely spaced atoms. The most downfield peak in the alkyl region was assigned to the α' carbon since this position had a γ relationship only with the δ (C-5) carbon while the α carbon had a γ-gauche relationship with β' and δ carbons in the boat-chair conformation (see Figure 2). Therefore, the α carbon (C-2) was more shielded than α' (C-8) carbon. Consequently, each of the equivalent methylene pairs can be assigned by matching γ-gauche relationship. α', β and γ carbons are expected to be less shielded than the corresponding α, β' and γ' carbons which have more γ-gauche interactions.

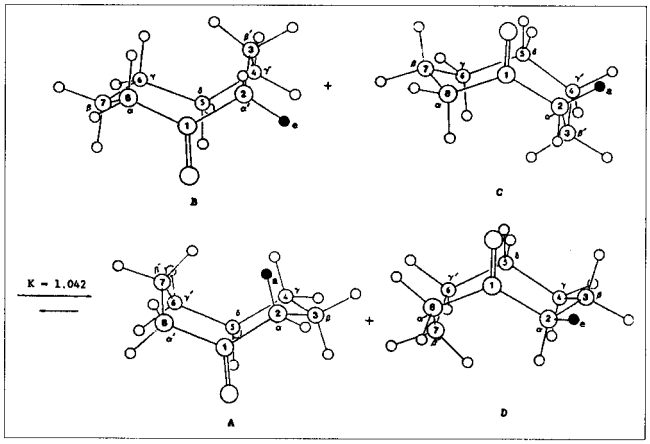

Figure 2. Designation and the Shift of Equilibrium in Cyclooctanone-2-D.

Assumption to Analyze the ^{13}C NMR Spectrum. For a pair of methylene carbons, a symmetric separation or "splitting" of the signals about the reference position would occur if the only effect were a perturbed equilibrium between boat-chair conformers. The "splitting" will be symmetrical only if the intrinsic isotope shifts are equivalent at both carbons in the pair. Each carbon signal could be shifted relative to the reference by an additional intrinsic isotope effect which is unlikely to be the same for both carbons in an exchanging pair. The difference in the anharmonicities between the C-H and C-D bonds produce averaged bond-length changes in the NMR time scale. The time-averaged position of the C-D bonding electron should be different from that of the C-H bonding electron. The former will be nearer to the carbon atom than the latter. The D-labelled carbon would be more shielded than the unlabeled carbon. This intrinsic effect is expected to be larger for the carbon nearer the deuteriation site; the effect may be negligible at the more remote site and is assumed to be so in our analysis. This is a reasonable assumption because the intrinsic isotope shift decreases rapidly with increase in the number of intervening bonds.

However, one difficulty remains. An observed, unsymmetrical separation of signals about the reference signal of the unlabeled compound (see Figure 3(a)) can arise in two ways, but the actual way cannot be determined a priori. One suitable type of information is the presence of spin-spin coupling to deuterium which results in a multiplet appearance of one of the resonances. Carbons close enough to the site of deuteriation to show coupling will also experience an isotope shift. Here, it is obvious that Case 1 for C-2 and C-8 applies because the upfield peak is a 1 : 1 : 1 triplet. The other information that can permit between Case 1 and Case 2 is consistency in the values of the equilibrium constant derived from observed peak seperations: Case 1 is chosen for C-2 and C-8 as well as C-4 and C-6, and Case 2 for C-3 and C-7 in the 2-D isotopomer. If an equilibrium is perturbed, equilibrium isotope shifts may be observed for more than one resonance in the ^{13}C spectrum. If Case 1 and Case 2 assumptions are separately applied in analysis of data for each affected carbon atom, two possible equilibrium constants will be derived from the two possible δ_{eq} values for each carbon. For example, when Case 1 and 2 as-

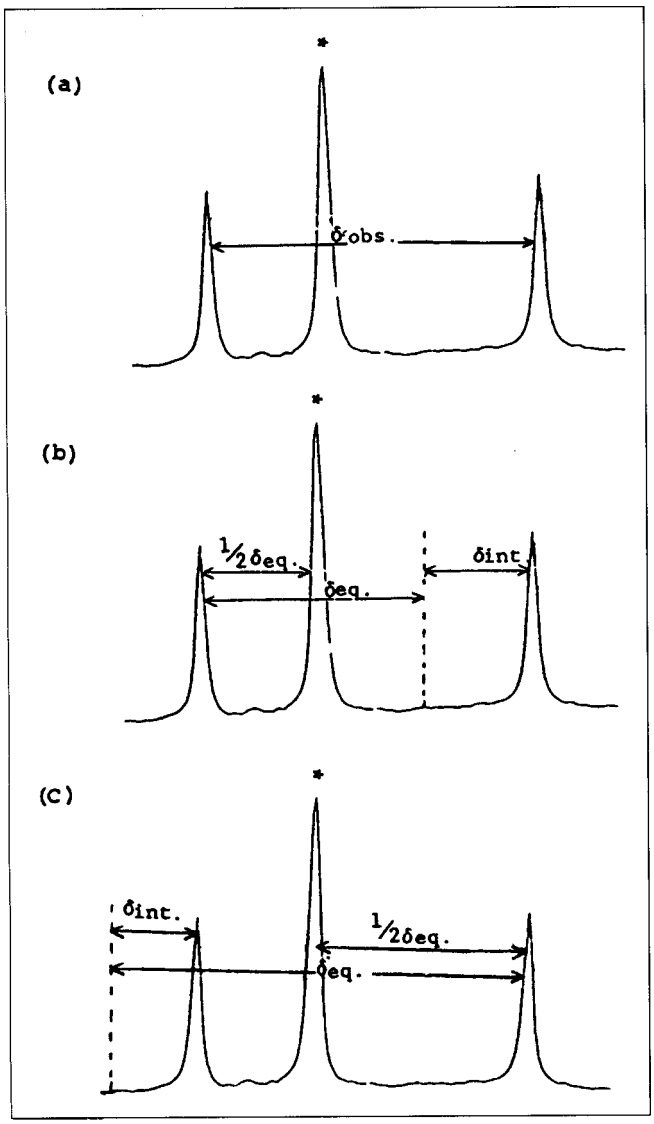

Figure 3. Assumption to Analyze the ^{13}C NMR Spectrum of Cyclooctanone-2-D. (a) An observed, unsymmetrical separation of signals about the reference position (b) Case 1. $\delta_{obs}=\delta_{eq}+\delta_{int}$, upfield peak is shifted further upfield by intrinsic isotope shift (c) Case 2. $\delta_{obs}=\delta_{eq}-\delta_{int}$, downfield peak is shifted upfield by intrinsic isotope shift

sumptions were applied in C-2 and C-8 carbons of cyclooctanone-2-D at 22 °C, the obtained equilibrium constants were 1.041 and 1.280, respectively. In the case of C-3 and C-7 carbons, equilibrium constants were 1.012 and 1.041 for the Case 1 and Case 2, respectively. Finally, the equilibrium constants C-4 and C-6 carbons were 1.044 and 1.086 for the Case 1 and Case 2, respectively. Which analysis is correct for each carbon is determined by the requirement that the same equilibrium constant (within experimental error) must be found from each data set. Thus, the choice of a derived equilibrium constant is made so as to obtain a constant result.

In Case 1, the observed separation, δ_{obs}, is the sum of the separation (δ_{eq}) due to the eqilibrium isotope effect and additional upfield shift (δ_{int}) due to intrinsic effect. In case 1, Figure 3(b), δ_{eq} can be determined by doubling the shift difference between the reference and the downfield peak, and then $\delta_{int}=\delta_{obs}-\delta_{eq}$. In Case 2 , Figure 3(c), less shielded carbon is additionally shifted by the intrinsic effect and $\delta_{obs}=\delta_{eq}-\delta_{int}$.

Table 1. Chemical Shifts for Cyclooctanone-2-D at Various Temperatures

Temp. (°C)	Chemical Shift (ppm)				
	C-2, 8	C-3, 7	C-4, 6	C-5	C=0
22.00	42.05	26.02	27.83		*214.45
	*41.99	*26.01	*27.79	*25.18	214.40
	41.58	25.91	27.71		
-20.50	42.02	26.01	27.78		*214.40
	*41.98	*25.98	*27.73	*24.88	214.34
	41.50	25.84	27.63		
-58.00	42.10	26.01	27.72		*215.28
	*42.00	*25.96	*27.66	*24.78	215.23
	41.55	25.78	27.55		
-92.00	42.28	26.12	27.66		*216.85
	*42.15	*26.01	*27.58	*24.76	216.79
	41.66	25.75	27.44		

*Averaged methylene peaks for unlabeled cyclooctanone.

Measurement of the Equilibrium Constants. ^{13}C chemical shifts are listed in Table 1 by various temperatures. The ^{1}H- decoupled ^{13}C spectrum of cyclooctanone-2-D above -58 °C has sharp singlet signals, shows broadening at -92 °C, has broad signals at -125 °C, and finally has eight sharp resonance signals at -148.5 °C (Figure 4) Equilibrium isotope shifts should be temperature dependent because the position of the the equilibrium will shift with temperature. Measurement of the equilibrium constants at different temperatures allows determination of enthalpy and entropy differences for the equilibrium reaction. The equilibrium constant is derived from δ_{eq} by comparison with the maximum possible peak seperation value for each pair of exchanging carbons which was determined by the peak seperation at -148.5 °C. Applying the case 1 assumption, the equilibrium isotope shifts for C-4 and C-6 carbon peaks was obtained from the low temperature ^{13}C NMR spectrum (Figure 5), the maximum peak separation between C-4 and C-6 at -148.5 °C was observed to be 3.88 ppm. The observed chemical shift difference between C-4 and C-6 peaks of the 2-D isotopomer at 22 °C was 0.122 ppm. The difference between the downfield and the upfield chemical shifts from the reference unlabeled carbon peak afforded the intrinsic isotope shift, 0.038 ppm. The equilibrium isotope shift (0.084 ppm) was obtained by subtracting the intrinsic isotope shift from the observed separation (0.122 ppm-0.038 ppm=0.084 ppm), since the observed separation, δ_{obs}, includes both equilibrium and intrinsic isotope shifts. Using Saunders' equation,[3] the calculated equilibrium constant K was 1.044 and free energy difference between conformers was -25 cal/mol at 22 °C.

Similarly, the eqilibrium isotope shifts on the carbons C-3 and C-7 were obtains using the Case 2 assumption. Introduction of deuterium would be expected to cause isotopic perturbation of the boat-chair equilibria by the steric isotope effect.[1,3] The observed isotope effects for the boat-chair conformation would lead to the conclusion that la-

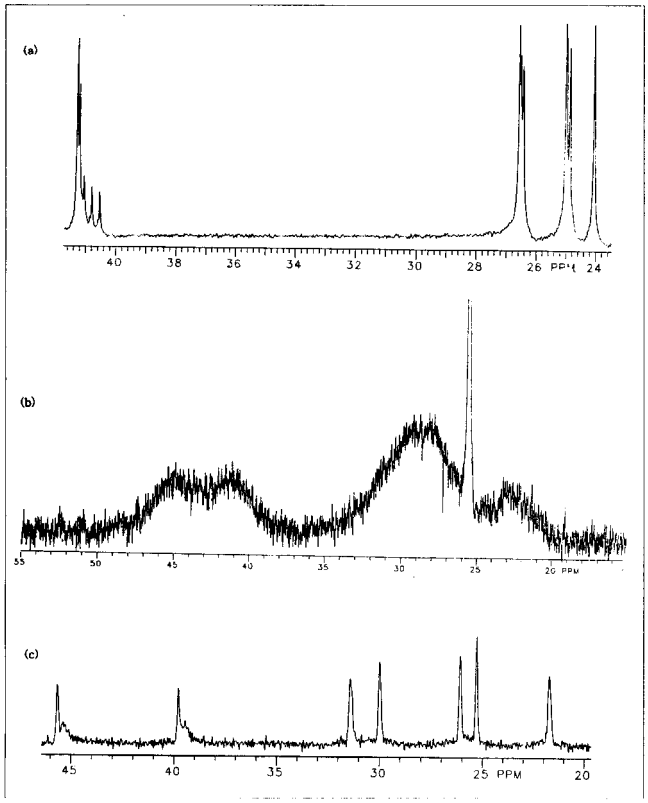

Figure 4. (a) Labeled ^{13}C NMR Spectrum of a Mixture Containing Predominately Cyclooctanone-2-D at 22 °C (only the ^{13}C peaks in the alkyl region are shown). (b) Methylene Carbons are broadened except Carbonyl and C-5 Carbons at −125 °C. (c) 7 Carbon Peaks in the Alkyl Region are well resolved since Exchange is slow enough at −148.5 °C.

beled methylene groups indeed prefer the sterically crowded positions. The actual observations are consistent with the expectations. Thus, it is reasonable that Case 2 can be applied for C-3 and C-7. The equilibrium isotope shift was equivalent to the chemical shift difference between C-3 and C-7 carbons plus the intrinsic isotope effect. The intrinsic isotope shift was calculated based on the difference between the following two chemical shift separations: the separation between the downfield chemical shift and reference peak, and the separation between the upfield peak and the reference peak. Because C-3 carbon is located at two-bonds distance to deuterium at C-2 carbon while C-7 carbon is four-bonds away from the deuterium, the intrinsic effect should be negligible at C-7. The calculated intrinsic isotope shift was 0.081 ppm, while the observed chemical shift difference of C-3 and C-7 carbons was 0.113 ppm at 22 °C. The equilibrium isotope shift was thus 0.194 ppm which was the sum of observed chemical shift difference (0.113 ppm) and the intrinsic isotope shift (0.081 ppm). The maximum isotopic splitting, that is, the difference of chenical shifts of C-3 and C-7 carbons at −148.5 °C, was 9.69 ppm. In the same way, the calculated equilibrium constant was 1.041 for these carbons at 22 °C. In the case of C-2 and C-8, it was clear from the 1 : 1 : 1 triplet signal for the C-2 carbon, which was directly substituted by one deuterium, that Case 1 condition applies for this position. The equilibrium

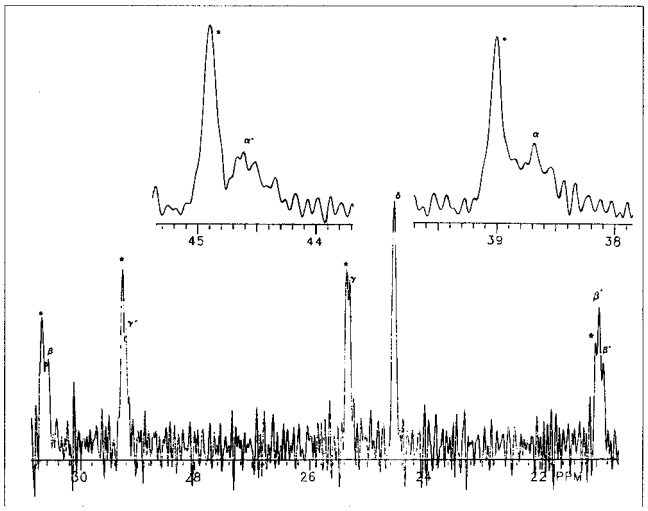

Figure 5. Low Temperature ^{13}C NMR Spectrum of Cyclooctanone-2-D Containing Some Unlabeled Cyclooctanone. (Asterisks indicate peaks of unlabeled cyclooctanone; numbers indicate the signal assignments to particular carbon atoms)

constant and free energy barrier were calculated, following the general approach described above.

NMR isotope shifts which are of the equilibrium type, *i.e.*, not intrinsic but instead arise from perturbed equilibria, are expected to be temperature dependent. As temperature went lower, the equilibrium isotope shifts started to increase as shown in Table 2. The results of equilibrium constants and free energy differences calculated from data for C-2 and C-8, C-3 and C-7, and C-4 and C-6 carbons with varying temperature are also listed in Table 3. A linear relationship between equilibrium constants and inverse temperature provided the enthalpy and entropy differences for the equilibrium from the equation. The value for the enthalpy and entropy differences are −48 cal/mol and −0.0802 cal/K. respectively.

The conformational equilibria that are being perturbed by

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

Temp.	Equilibrium Isotope Shifts					
(°C)	C-2, 8	C-3, 7	C-4, 6	C-2	C-3	C-4
22.0	0.118	0.194	0.084	0.356	0.081	0.038
−20.5	0.130	0.278	0.096	0.356	0.108	0.049
−58.0	0.194	0.356	0.130	0.356	0.129	0.049
−92.0	0.258	0.518	0.162	0.357	0.145	0.064

Table 3. Calculated Equilibrium Constants and Free Energy Diffrernces for Cyclooctanone-2-D

Temp.	Equilibrium Constants (K)				Free
(°C)	C-2, 8	C-3, 7	C-4, 6	Ave.	ΔG°
22.0	1.041	1.041	1.044	1.042	−24
−20.5	1.056	1.059	1.051	1.056	−27
−58.0	1.068	1.079	1.069	1.072	−30
−92.0	1.091	1.113	1.087	1.097	−33

isotopic substitution are the equilibria among the boat-chair conformers of unsymmetrically deuterated cyclooctanone-2-D. Any particular hydrogen at C-2, C-3 or C-4 exchanges among four possible environments (α or α', β or β', or γ or γ', and axial or equatorial). If a single deuterium is substituted for a hydrogen at C-2, the four conformers are diastereomeric and equilibrium isotope effects may occur in which each comformer contributes a different 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]$\rightleftarrows$[1A + 1D] as shown in Figure 2. The equilibrium isotope shifts in ^{13}C spectra can be used to detect the proportion of time C-2 is in each environment, α and α', but cannot reveal the position of 1B$\rightleftarrows$1C or 1A$\rightleftarrows$1D equilibria. The situation is simpler if both hydrogens at a carbon are substituted by deuterium, because then the 1B$\rightleftarrows$1C equilibrium is degenerate, the 1A$\rightleftarrows$1D equilibrium is degenerate and the observed equilibrium is between only two different conformers.

When equilibrium constants were derived from equilibrium isotope shifts using Saunder's equation, 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 move toward upfield or downfield by the equilibrium isotope shift. It was shown that α, β', and γ carbons appear upfield of the corresponding α', β, and γ' carbons. If C-2 is moved upfield and C-8 downfield by the isotope effect, it is clear that C-2 resides more of time in the α environment, C-8 is correspondingly more in the α' environment. The average environment for C-2 and C-8 would differ, with C-2 shifted upfield of the reference peak and C-8 shifted downfield by an equal amount. Deuterium labeling at C-2 position in a cyclooctanone causes the intrinsic and equilibrium isotope effects by causing deviations in the relative populations of B+C and A+D involved in the equilibrium.

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Studies of the Pyrrhotite Depression Mechanism with Diethylenetriamine

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The mechanism by which pyrrhotite is depressed by diethylenetriamine (DETA) during pentlandite flotation has been studied. Amyl xanthate is observed to adsorb on pyrrhotite to form both dixanthogen and iron xanthate. In the presence of DETA, the amount of xanthate adsorbed on pyrrhotite is substantially reduced as evidenced by infrared and UV/Vis spectroscopy. However, DETA does not adsorb on pyrrhotite as evidenced by infrared and X-ray photoelectron spectroscopy. DETA shifts the potential of the onset of xanthate adsorption on pyrrhotite by approximately 200 mV toward anodic direction, which is thought to be due to the increased solubility of surface oxidized species on pyrrhotite in the presence of DETA. A window of selectivity for the separation of pentlandite and pyrrhotite is provided by the results obtained in this study.

Introduction

Recently, diethylenetriamine (DETA) has been used as a depressant for pyrrhotite in the mining industry. DETA makes it possible to remove pyrrhotite more efficiently, while increasing the recovery of copper, nickel, and platinum. Plant experience shows that DETA is most effective at pH 9-9.5, works best under highly oxidizing conditions, and is sensitive to water chemistry.

Although the effectiveness of DETA as a pyrrhotite depressant has been verified in plant practice, its mechanism is not well understood. everal different mechanisms may be speculated based on the general chemistry of DETA and the operating experience at the mill:

1. DETA could adsorb on pyrrhotite selectively to passivate the mineral, thereby preventing xanthate adsorption.

2. Iron hydroxy-DETA complexes may adsorb on pyrrhotite selectively, rendering the surface hydrophilic.