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INTRINSIC NMR ISOTOPE SHIFTS OF CYCLOOCTANONE AT LOW TEMPERATURE

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저온에서의 싸이클로옥타논에 대한 고유동위원소 효과

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Abstract : Several isotopomers of cyclooctanone were prepared by selective deuterium substitution. Intrinsic isotope effects on ^{13}C NMR chemical shifts of these isotopomers were investigated systematically at low temperature. These istope effects were discussed in relation to the preferred boat-chair conformation of cyclooctanone.

Deuterium isotope effects on NMR chemical shifts have been known for a long time.[1] Especially in a conformationally mobile molecule, isotope perturbation could affect NMR signals through a combination of isotope effects on equilibria and intrinsic effects.[2] The distinction between intrinsic and nonintrinsic effects is quite difficult at ambient tenperature due to involvement of both equilibrium and intrinsic isotope effects. However if equilibria between possible conformers of cyclooctanone are slowed down enough on the NMR time scale by lowering temperature, it should be possible to measure intrinsic isotope shifts from the separated signals at low temperature.

^{13}C NMR has been successfully utilized in the study of molecular conformation in solution when one deals with stable conformers or molecules where rapid interconversion occurs at ambient temperature. The study of dynamic processes in general requires analysis of spectra at several temperature. Anet et al. did ^{1}H NMR study of cyclooctanone at low temperature to freeze out a stable conformation, but were not able initially to deduce which conformation was stable because of the complexity of alkyl region in the ^{1}H NMR spectrum.[3] They also reported the ^{1}H and ^{13}C NMR spectra of the C_9-C_{16} cycloalkanones with changing temperature from $-80℃$ to $-170℃$, but they did not report a variable temperature ^{13}C NMR study of cyclooctanone. For the analysis of the intrinsic isotope effect with relation to cylooctanone conformation, ^{13}C NMR spectra are obtained in the present work at low temperatures (up to $-150℃$) in order to find the chemical shifts at the temperature at which the dynamic process can be "frozen-out" on the NMR time scale and cyclooctanone can be observed as a stable conformation. Both the ring inversion 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, slowing down just the ring inversion process has no apparent effects on the ^{13}C spectra because exchange of environments

within the pairs of methylene carbons can still occur by the pseudorotational process.

Several isotopomers of cyclooctanone were prepared by selective deuterium substitution (*Fig.* 1) : complete deuterium labeling at C-2 and C-8 positions gave cyclooctanone-2, 2, 8, 8-D_4 : complete labeling at C-2 and C-7 positions afforded the 2, 2, 7, 7-D_4 isotopomer : di-deuteration at C-3 gave the 3, 3-D_2 isotopomer : mono-deuteration provided cyclooctanone-2-D, 4-D and 5-D isotopomers : and partial deuteration on the C-2 and C-8 positions, with a chiral and difunctional case catalyst. gave the trans-2, 8-D_2 isotopomer. These isotopomer were investigated systematically in relation with cyclooctanone conformation and intrinsic isotope effects on ^{13}C NMR chemical shifts at low temperature. The determination of the intrinsic effects could help in the analysis of the more complex effects at higher temperature. For quantitative analysis of intrinsic isotope effects, the ^{13}C NMR spectrum has been obtained for a mixture of the labeled and unlabeled compounds because the signal separations are very small.

요약 : 선택적으로 중수소를 치환시킨 싸이클로옥타논의 여러 동위원소 이성질체들을 합성하였다. 고유동위원소 효과에 의해 영향을 받는 ^{13}C NMR 화학적 이동값들을 각 이성질체에 대해 저온에서 계통적으로 관찰하였다. 특히 싸이클로옥타논이 선호하는 안정한 형태 이성질체인 클 boat-chair 형과 연관시켜 이 효과들을 논의하였다.

Key words : Isotopomer, Intrinsic isotope effect, ^{13}C NMR chemical shifts, boat-chair conformation.

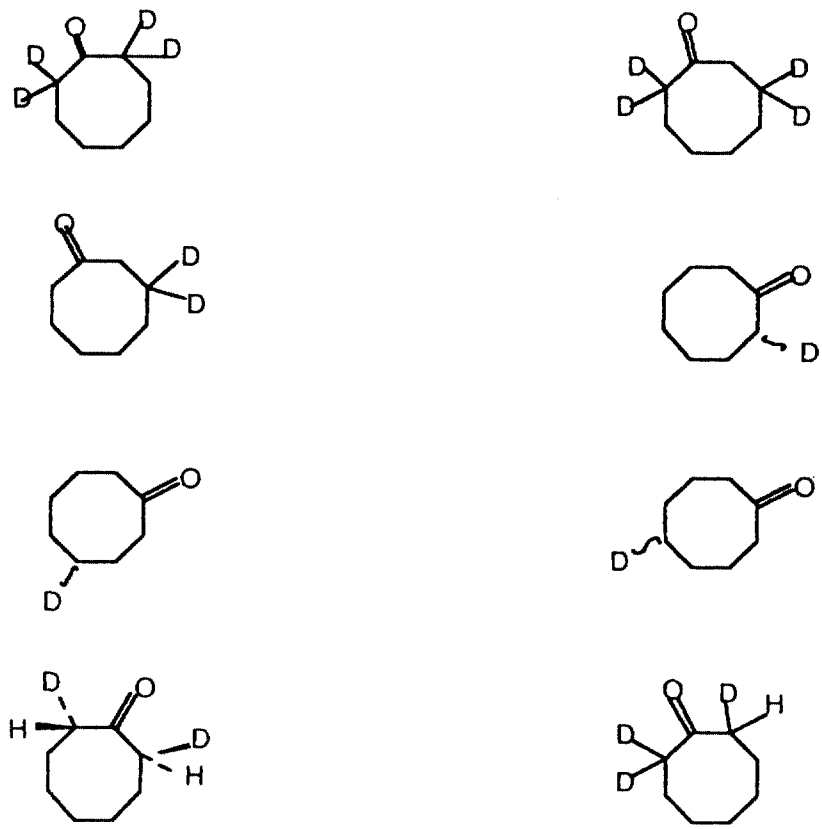

Fig. 1. Selectively deuterated cyclooctanone.

1. EXPERIMENTAL

^{13}C NMR spectra were recorded on a 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 resoultion (ca. 0.001ppm/point). Temperature was controlled during acquisition of spectra for the purpose of determining isotope shifts ; spectra recorded while temperature varied by more than ±1℃ were discarded. All chemical shifts reported were referenced to Me_4Si (0.00ppm) either directly for ^1H NMR spectra or indirectly for ^{13}C spectra by using solvent signals for reference : $CDCl_3$(77.00ppm) as a triplet, CF_2Cl_2(126.30ppm) as a triplet, $CFCl_3$(115.670ppm) as a doublet. ^{13}C NMR spectra of unlabeled and labeled cyclooctanone samples were measured with a width of 20000 Hz and 65000 data points. ^{13}C NMR spectra of the deuterated and the mixture of deuterated and undeuterated cyclooctanones (2:1 ratio) were compared for signal assignments.

SYNTHESIS OF CYCLOOCTANONE-2,2,8,8-D_4

Cyclooctanone-2, 2, 8, 8, D_4 was prepared by the deuterium exchange method.[4]

^{13}C NMR($CDCl_3$) : 217.71(s, C-1), 40.91(p, J_{CD}=19.5HZ, C-2, C-8), 26.82(s, C-4, C-6), 25.19(s, C-3, C-7), 24.44ppm(s, C-5).

SYNTHESIS OF CYCLOOCTANONE-2-D.[5]

I-Trimethylsilyloxycyclooctene. Chlorotrimethylsilane (15.3mL, 13.1g, 0.121mol) and triethylamine (37mL, 27g, 0.27mol) were added to a solution of cyclooctanone (13.63g, 0.108mol) in THF. The work up was done with pentane, and with sat. sodium bicarbonate solution. The residue was distilled(bp 108~125℃, at 25mm) to give 15.6g of product (85%) as a clear liquid. ^{13}C NMR($CDCl_3$) : 152.69, 105.33, 41.87, 30.95, 27.75, 26.32, 26.28, 25.45, 0.32ppm(CH_3).

^1H NMR($CDCl_3$) : 4.71(t, 1H), 2.38(m, 2H), 2.15(m, 2H), 1.52(m, 8H), 0.20(s, 9H, CH_3).

Cyclooctanone-2-D. To a mixture of 1-trimethylsilyloxycyclooctene (8.3g, 0.042mol), D_2O (10.0g, 0.500mol) and 14 drope of 20% DCl solution were added to enough THF to give a homogeneous solution which was poured into a sat. NaCl solution to which a little $NaHCO_3$ had been added. The aqueous solution was extracted with ether and the combined ether extracts were washed with sat. NaCl solution, dried with $MgSO_4$, filtered, and evaported. The residue was distilled (bp 65℃, at 8.5mm) to give 3.4g of cyclooctanone-2-D(64%).

^{13}C NMR($CDCl_3$) : 216.82(s, C-1), 41.28(s, C-8), 41.05(t, C-2, J_{CD}=19.6Hz), 26.57(s C-4 or C-6), 26.44(s, C-4 or C-6), 24.97(s, C-3 or C-7), 24.86(s, C-3 or C-7), 24.06ppm(s, C-5).

^1H NMR($CDCl_3$) : 2.51(m, 3H), 1.88(m, 4H), 1.52(m, 4H), 1.36ppm(m, 2H).

SYNTHESIS OF CYCLOOCTANONE-2, 8-D_2

This procedure followed the method of Hine et al.[6], as modified by botkin.[7,8]

^{13}C NMR($CDCl_3$) : 218.07(s, C-1), 41.35(t, C-2, J_{CD}=19.5Hz), 26.89(s, C-4 or C-6), 25.32(s, C-3 or C-7), 24.48ppm(s, C-5).

^1H NMR ($CDCl_3$) : 2.38(m, 2H), 1.88(m, 4H), 1.56(m, 4H), 1.39ppm(m, 2H).

Mass Spectral Data(Electron Impact Nuclide 12-9DG 70eV 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), 43.03(100.00), 41.998(95.93), 41.231(77.30), 28.216(32.18), 27.174(34.72),

SYNTHESIS OF CYCLOOCTANONE-2,2,7,7,-D_4

Cycloheptanone-2,2,7,7-D_4. This process was same as the cyclooctanone-2,2,8,8-D_4. Distillation gave 9.24g(83%) cycloheptanone-2,2,7,7-D_4.

^{13}C NMR($CDCl_3$) : 214.2(s), 42.5(p, J_{CD}=20 Hz, C-2, C-7), 29.8(s), 23.6ppm(s). 1-(Dibromomethyl)-1-Cycloheptanol-2,2,7,7,-D_4. This preparation was

done by a modified procedure of Nicolaou et al.[10]

^{13}C NMR($CDCl_3$) : 77.31(s, C-1), 60.51(s, -CH_2Br_2), 36.12(p, J_{CD}=20 Hz, C-2, C-8), 28.71, 22.36ppm.

^1H NMR($CDCl_3$) : 5.68(s 1H), 2.51(br s, 1H), 1.80-1.40ppm(m, 8H).

Cyclooctanone-2,2,7,7-D_4.

^{13}C NMR($CDCl_3$) : 217.45(s, C-1), 41.60(s, C-8), 41.19(p, J_{CD}=19.39Hz, C-2), 26.78(s, C-4 or C-6), 25.40(s, C-3), 24.35ppm(s, C-5).

^1H NMR($CDCl_3$) : 2.42(br s, 2H), 1.21-1.83ppm (m, 8H).

SYNTHESIS OF CYCLOOCTANONE-3,3,-D_2

The cyclooctanone-2,2,7,7-D_4 was prepared and was reflaxed with H_2O during which time the mixture was monitored by ^1C NMR spectroscopy. After workup in the usual manner, 2.8g of cyclooctanone-3,3-D_2(95%) was obtained.

^{13}C NMR($CDCl_3$) : 218.08(s, C-1), 41.82(s, C-2 or C-8), 27.18(s, C-4 or C-6), 25.95(s, C-3), 25.19ppm (s, C-5).

SYNTHESIS OF CYCLOOCTANONE-5-D:[9,10,11,12]

5-hydroxy-cyclooctyl-1-tetrahydropyranyl ether, 5-tosyl-cyclooctyl-1-tetrahydropyranyl ether, 5-D-cyclooctyl-1-tetrahydropyranyl ether, cyclooctanol-5-D and cyclooctanone-5-D were prepared as the method of references.

5-hydroxy-cyclooctyl-1-terahydropyranyl ether.

^{13}C NMR($CDCl_3$) : 95.45, 74.61, 70.32, 61.29, 35.19, 31.23, 30.39, 24.80, 19.54, 18.83ppm.

^1H NMR($CDCl_3$) : 4.52(m, 1H), 3.85(m, 1H), 3.73(m, 1H), 3.45(m, 1H), 1.40~1.95ppm(m, 20H).

5-tosyl-cyclooctyl-1-tetrahydropyranyl ether.

^{13}C NMR($CDCl_3$) : 141.61(s), 131.68(s), 126.94 (s), 126.60(s), 93.63(s), 80.71(s), 71.68(s), 59.54 (s), 33.50(s), 30.92, 30.89, 28.57, 22.73, 18.63, 16.88 ppm(CH_3).

^1H NMR($CDCl_3$) : 7.20~7.92(m, 4H), 4.63(m, 1H), 3.20~3.80(m, 2H), 2.32(m, 2H), 1.03~1.80ppm(m, 23H).

5-D-Cyclooctyl-1-Tetrahydropyranyl Ether.

^{13}C NMR($CDCl_3$) : 93.62, 72.71, 59.467, 32.01, 28.76, 24.93, 23.24, 20.51, 17.14ppm.

^1H NMR($CDCl_3$) : 4.66(t, 1H), 3.45(m, 1H), 1.00~2.24ppm(m, 21H).

Cyclooctanol-5-D.

^{13}C NMR($CDCl_3$) : 71.49(s, −OH), 34.28(s), 27.01(s), 24.54(s, J_{CD}=18.6Hz), 22.40ppm(s).

Cyclooctanone-5-D.

^{13}C NMR($CDCl_3$) : 218.26(s, C-1), 41.86(s, C-2 or C-8), 27.98(s, C-4 or C-6), 25.54(s, C-3 or C-7), 24.21ppm(t, J_{CD}=19.8Hz, C-5).

SYNTHESIS OF CYCLOOCTANONE-4-D.

The preparation of cyclooctanone-4-D was done by following the same general method used for cyclooctanone-5-D.

4-tosyl-cyclooctyl-1-tetrahydropyranyl ether.

^{13}C NMR($CDCl_3$) : 143.52, 134.15, 129.27, 127.07, 96.16, 83.31, 75.06, 62.07 38.91, 37.79, 36.66, 32.65, 25.19, 22.27, 21.66, 19.41, 14.87ppm(CH_3).

^1H NMR($CDCl_3$) : 7.82(m, 2H), 7.42(m, 2H), 4.60(m, 1H), 3.72(m, 2H), 3.51(m, 2H), 2.42(m, 2H), 1.30~2.01(m, 16H), 1.21ppm(t, 3H).

4-D-cyclooctyl-1-tetrahydropyranyl ether.

^{13}C NMR($CDCl_3$) : 99.54, 71.68, 61.55, 37.23, 36.06, 32.65, 30.85, 29.53, 27.39, 25.32, 22.03, 19.54ppm.

Cyclooctanol-4-D.

^{13}C NMR($CDCl_3$) : 70.90(s, C-1), 33.53(s, C-2 or C-8), 27.39(s, C-5), 25.63(s, C-4), 25.33(t, J_{CD}=19.2Hz, C-4), 22.81ppm(s, C-3 or C-7).

Cyclooctanone-4-D. ^{13}C NMR($CDCl_3$) : 213.78(s, C-1), 41.96(s, C-2), 27.79(s, C-4), 27.42(t, J_{CD}=18.2Hz, C-4), 26.00(C-3 or C-7), 25.02ppm(s, C-5).

Results and Discussion

Attempts to sort out assignments of the methylene carbon peaks at room temperature led to use of specifically deuterated cyclooctanone prepared for this study. The intrinsic isotope effects are useful because they differ depending on bond separation.

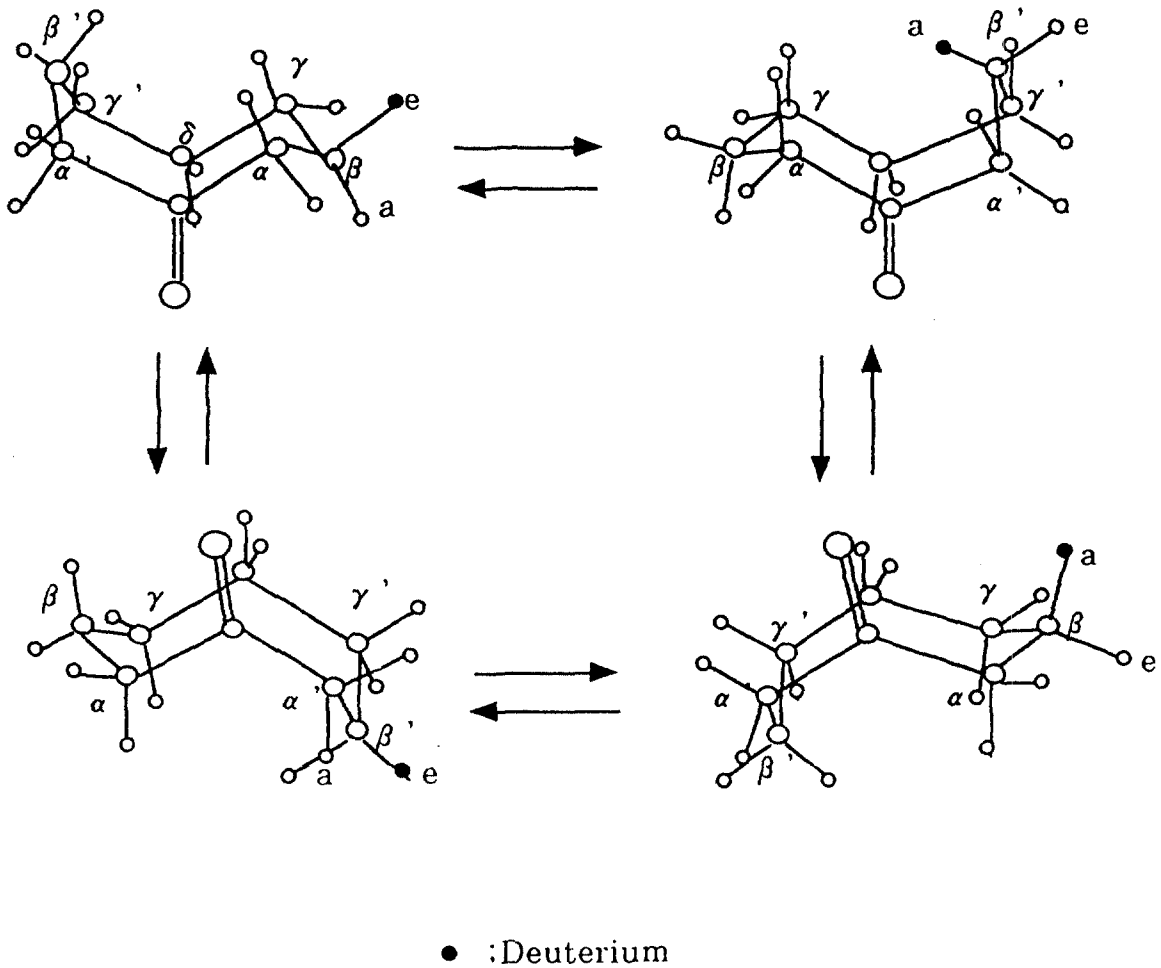

Fig. 2. Systemetic nomenclature of cyclooctanone.

To designate the position of attachment of a particular hydrogen and deuterium atom, Anet[3] was used α, α', β, etc., and the hydrogen atom environment could then be indicated by denoting axial or equatorial. This is consistent with systematic nomenclature(*Fig.* 2), i. e., cyclooctanone-2-D has a deuterium at C-2. In the case of complete α-deuteration, the assignment for the room temperature ^{13}C spectrum can be explained by the following (*Fig.* 3) : (1) Complete deuteration on the C-2 and C-8 positions gives rise to splitting of the ^{13}C signal at 41.47ppm from a singlet to a pentet and to reduced signal intensity because of the reduced NOE effect and splitting pattern. The methylene carbons adjacent to the carbonyl carbon appear in the most downfield positions among the methylene signals. (2) C-3 and C-7, C-4 and C-6 carbons are assigned according to the different intrinsic isotope shifts. The upfield shift on the signal at 26.03ppm was 0.194ppm, which is larger than that on the signal at 27.79ppm (0.094ppm). Thus, the 26.03ppm signal is assigned to C-3 and C-7 carbons and 27.29ppm to C-4 and C-6. (3) The chemical shift of the carbonyl carbon is expected to occur in the most downfield position in the ^{13}C NMR spectrum, and peak intensity as a quaternary carbon is expected

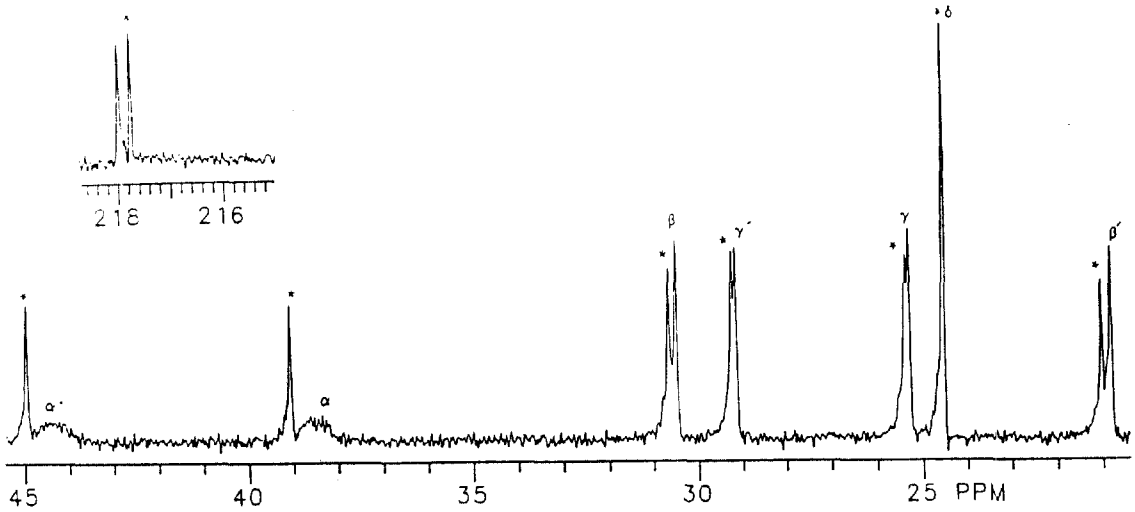

Fig. 3. ^{13}C Spectrum of the 2 : 1 mixture of cyclooctanone 2,2,8,8-D_4 and cyclooctanone at −148.5℃. (Peaks marked with on asterisk are due to the unlabled cyclooctanon.)

to be weak. (4) The peak intensity of the C-5 (δ) carbon is weaker than that of the methylene carbons because it has no equivalent methylene carbon.

The assignment of chemical shifts for methylene carbons above −90℃ is determined by replacing various protons with deuterium and observing the effect on the ^{13}C spectrum of cyclooctanone. Separate carbon signals are discerned only if the temperature is low enough, as determined by the conformational barrier and frequency separations which are dependent on the field strength of the spectrometer. The ^{13}C signals for cyclooctanone at −125℃ were broad except for the carbonyl and δ carbons : the rate of exchange was starting to slow down at this temperature but the ^{13}C signals were still broadened due to not having reached the point of slow dynamic process at this temperature. The conformational equilibria were slow enough at −148.5℃ on the NMR time scale at 75.4 MHz observation frequency, since the seven methylene carbons were well resolved at this temperature. The ^{13}C signals of the low temperature ^{13}C NMR spectrum can be readily assigned since the averaged signals at room temperature will split symmetri-

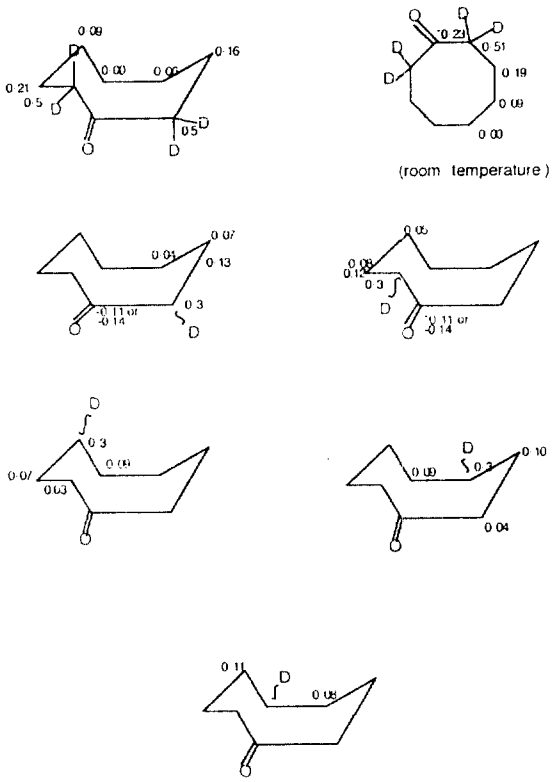

Fig. 4. ^{13}C NMR isotope shifts for cyclooctanone-2,2,8,8-D_4, and approximate isotope shifts for mono-2-D, 4-D, and 5-D isotopomers of cyclooctanone at low temperature.

cally to upfield and downfield directions from the original position. The assignment between the ^{13}C signals of methylene carbon pairs(C-2 and C-8, C-3 and C-7, and C-4 and C-6 carbon pairs) in deuterated cyclooctanone at low temperature can be done by application of the γ-gauche and deuterium effect on chemical shifts.[13, 14] Also, the methylene carbons next to the carbonyl carbon appear in the most downfield positions between 40ppm and 45ppm and can be assigned to the α and α' carbons (C-2 and C-8) for the cyclooctanone-2, 2, 8, 8-D_4 at -148.5℃. The upfield chemical shifts can be assigned to the carbon in a pair which has more γ-gauche relationships to other carbons. 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. On the other hand, the α, β, and γ carbon resonances are split into 1 : 1 doublets(actually pairs of singlets) at low temperature. The spliting of signals is consistent with the presence of a single boat-chair conformation whcih lacks C_2 or C_s symmetry (i. e., no axis, or no plane of symmetry coincident with the $C_\delta-C=O$ plane). The signals of carbonyl and C-5(δ) carbons were not split at all temperature(to -148.5℃) in agreement with the presence of a single kind of conformation(a chiral conformation and its mirror image are taken to be the same kind of conformation). The carbonyl carbons, C-1 (271.83ppm) and C-5 (25.25ppm), can be fixed.

Table 1 and *Fig* 5 summarize the chemical and deuterium isotope shifts for the cyclooctanone-2, 2, 8, 8-D_4 at low temperature. Deuterium isotope effects on ^{13}C chemical shifts were measured at 75.4 MHz. $^n\Delta$ C(D) is the difference between a chemical shift in the unlabeled and deuterium labeled compound and n indicates the number of bonds separating the observed carbon and deuterium. A positive sign indicates an upfield shift in the deuterated cyclooctanone since $\Delta\ \delta C=\delta C$(undeuterated) $-\delta C$(deuterated)in Hansen's notation.[15]

Table 1. ^{13}C NMR Chemical (δ C^a and Isotope Shifts^b) for Cyclooctanone-2, 2, 8, 8-D_4 Isotopomer at -148.5℃

Position	δ C^a	$^n\Delta$ C(D)^b
C=O	217.77	−0.23
α	38.78	0.50
β	30.15	0.16
γ	24.87	0.06
δ	24.03	0.00
α'	44.44	0.50
β'	20.51	0.21
γ'	28.74	0.09

[a]Chemical shifts for undeuterated compound, in parts per million from TMS ; CF_2Cl_2 solvent was the reference. [b]Signals for directly deuterated carbons are broad and complex.

(1) One-bond Deuterium Isotope Shift. The one-bond intrinsic isotope shift of the α carbon is expected to be similar to that of the α' carbon of cyclooctanone-2,2,8,8-D_4. The isotope shifts of α and α' carbons from the reference peaks of unlabeled cyclooctanone are not detectably different, but these are only roughly obtained: both of the one-bond isotope shifts are about +0.5ppm(the positive sign indicates an upfield shift in the deuterated cyclooctanone). The time-averaged multiplet peak was clearly identified as a pentet in a room temperature ^{13}C NMR specrtum(*Fig.* 3) since the axial and equatorial coupling constants of α and α' carbons were averaged(J=+19.5Hz) in the time-averaged spectrum. In the room temperature spectrum, the isotope shift for the averaged α and α' signals was 0.51ppm. However, in the low temperature specrtum, these multiplet peaks were more complicated and appeared to be a cluster of peaks because coupling constants between carbon and equatorial and axial deuterium are different in the "frozen-out" boat-chair conformation. The shifts are thus obtained only approximately due to complicated splitting patterns of α and α' carbons

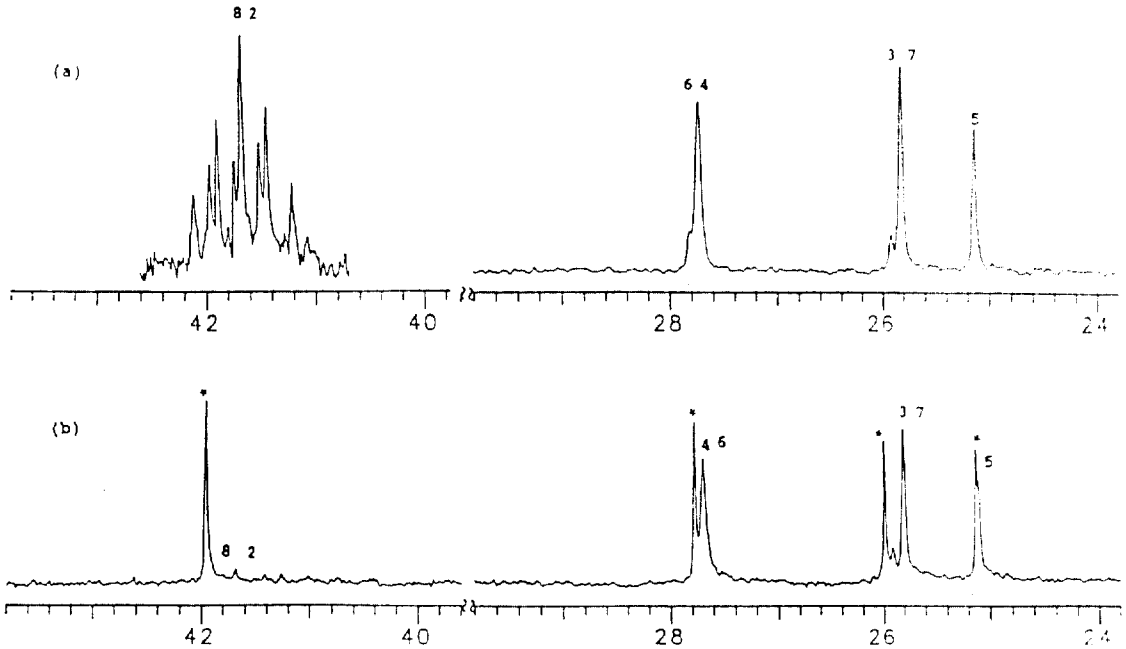

Fig. 5. (a) The ^{13}C NMR spectrum of cyclooctanone-2,2,8,8,-D_4 at 18.5℃. (b) The ^{13}C NMR spectrum of a 2 : 1 mixture of cyclooctnone-2,2,8,8-D_4 and cyclooctanone at 18.5℃.

in the ^{13}C NMR specrtum of cyclooctanone-2,2,8,8-D_4.

Isotope shifts of 2-D, 4-D, and 5-D mono-isotopomers are also listed in *Fig.* 5. A directly mono-deuterated carbon is split into a triplet with reduced signal intensity, and shifted to upfield from unlabeled carbon peak. The apparent one-bond deuterium isotope shift is about 0.3ppm for all of the mono-deuterated carbons. It is even more complicated to measure one bond isotope shifts in the ^{13}C NMR spectra of mono-deuterated isotopomers than for the tera-deuterated isotopomer. Mono-deuterated cyclooctanone-2-D and cyclooctanone-4-D each have four possible boat-chair conformations because of the four possible environments for the deuterium(*Fig.* 2). Thus, in a low temperature spectrum of cyclooctanone-2-D, it is theoretically possible to see four signals, having small chemical shift differences, for each carbon atom. These four diastereomeric boat-chair conformers could give four different chemical shifts at directly deuterated positions in the low temperature ^{13}C NMR spectrum. Since each conformer has a different chemical and magnetic environment at α carbons, α and α' resonance peaks of conformers with small chemical shift differences will appear as cluster peaks in the spectrum (for example, two triplets and two singlets are possible for the α carbon of 2-D isotopomer). Furthermore, even if all four of the signals are not separated, coupling constants to axial and equatorial deuteriums will differ slightly, and lead to two nearly overlapping triplets for the directly deuterated carbons.

Besides the above facts, signals in the low temperature ^{13}C NMR spectrum are somewhat broad because of the increased viscosity at low temperature. (In solids and viscous liquids T_1 can be very long, especially at low temperature : T_2, is very

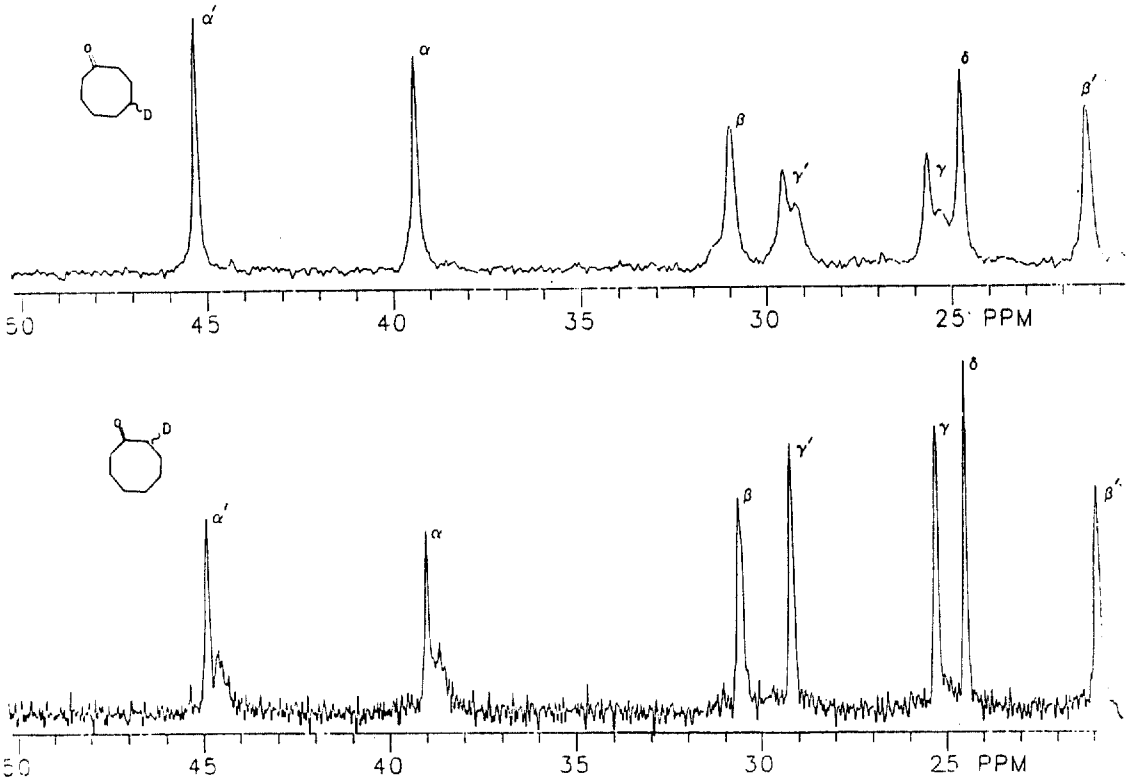

Fig. 6. Low temperature ^{13}C NMR spectra of cyclooctanone-2-D and cyclooctanone-4D. (a) No reference signals from unlabeled cyclooctanone are present. Isotope shifts were measured from spectra which did contain the reference.

short, since the magnetic coupling to neighboring spins is very large.)[16] These broad signals at low temperature raise additional difficulty to measure small isotope shifts. One-bond isotope shifts reported above are only roughly obtained because of the complexity of the observed multplet signal. For example, the ^{13}C NMR spectra of cyclooctanone-2-D and cyclooctanone-4-D are compared in *Fig.* 6. The directly deuterated carbon peaks in the spectrum of each isotopomer are easily distinguishable from the other peaks due to the reduced intensity and multiplicity. Two sets of broad carbons were assigned to deuterated α and α' carbons in the boat-chair conformation of cyclooctanone-2-D. Similarly, two sets of broad multiplet peaks around 29.13ppm and 25.20ppm can be assigned to deuterated γ and γ' carbons boat-chair conformations of cyclooctanone-4-D at low temperature. In the case of cyclooctanone-5-D, the peak affected by the one-bond isotope shift and also the other signals should be simpler since there is no equivalent methylene carbon. However, there are still two possible expected signals at each carbon because two different boat-chair conformers (with deuterium either axial or equatorial) are involved in cyclooctanone-5-D. However, the deuterated signals for the δ position in cyclooctanone-5-D were too weak and did not appear in the spectrum, so the one-bond isotope shift could not be measured.

(2) Two-bond Isotope Effects on ^{13}C shifts. β and β' carbon peaks (around 30ppm and 25ppm) in b h

cyclooctanone-2-D and 4-D isotopomers are expected to show four different signals with small chemical shift differences among them. However. these peaks are relatively broad : the four different signals appear close together since the difference of chemical shifts is small. Involvement of several conformations in the low temperature ^{13}C NMR spectra of deuterated cyclooctanones leads to broad signals arising from the several combined peaks. Also, these β and β' carbons may be affected by different long-range coupling constants($^{2}J_{CD}$) which may make more complicated signals. Therefor, resolution-enhancement was applied for spectra of each isotopomer. In the case of 2-D isotopomer, three peaks for both β and β' are shown in the resolution-enhanced spectrum of cyclooctanone-2-D(*Fig.* 7). Also, the γ and γ' carbon peaks are broad, but two peaks for both γ and γ' appear in the resolution-enhanced spectrum of cyclooctanone-2-D.

The spectrum in *Fig.* 7 illustrates the difficulty in extracting intrinsic isotope shifts from the low temperature spectra. Theoretically, with infinitely fine resolution, four signals would be seen for each type of carbon in a mono-deuterated isotopomer, but in no case are four signals seen in *Fig.* 7(Also the unlabeled cyclooctanone is present. which makes

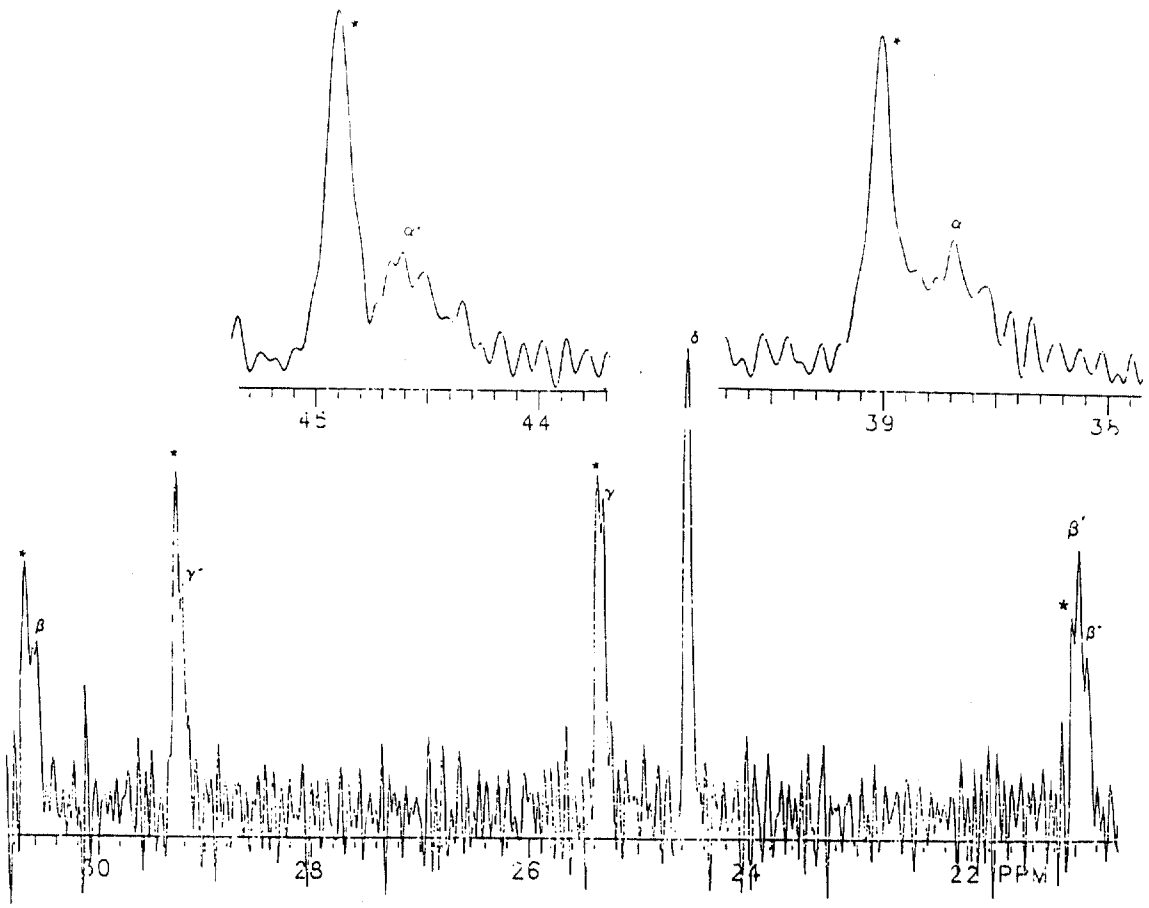

Fig. 7. The resolution-enhanced ^{13}C NMR spectrum of cyclooctanone-2-D with some unlabeled cyclooctanone. (Asterisks indicate peaks of unlabeled cyclooctanone : numbers indicate the signal assignments to particular carbon atoms, i. e., 2 indicates C-2.)

it theoretically possible to see five signals for each type of carbon). Clearly severe overlapping of signals occurs. Further, even when signals are seperated, there is no unequivocal way to assign them to particular conformers of an isotopomer. Thus, the data must be considered as estimates of the intrinsic shifts and are reported only for the purpose of showing the magnitude of isotope shifts at the various positions. Since assignments within a cluster of peaks cannot be made with certainty, it is assumed that all isotope shifts are upfield and show the usual dependence on distance from site of deuteration. Intrinsic shifts normally decrease with the number of bonds separating the observed carbon from deuterium.[17] Some carbons are not significantly affected by intrinsic isotope effects because the carbons are more than three-bonds away from deuterium. A relatively sharp peak for the δ carbons is observed in 2-D isotopomer since intrinsic shifts are seldom observed beyond three-bonds, as in 2,2,8,8-D_4 isotopomer, for example, where no intrinsic isotope shift is observed at this position.

Two-bond isotope effects were observed at β and β' in the 2,2,8,8-D_4 isotopomer, and values were 0.16ppm and 0.21ppm, respectively. This isotopomer with complete methylene deuteration provides larger isotope effects on a position two-bonds away from deuterium than partially deuterated isotopomers. In the case of partially deuterated isotopomers, for example, the observed values at β and β' position in 2-D isotopomer were 0.08 and 0.12ppm, 0.07 and 0.013ppm, respectively. Also, the values at those position in 4-D isotopomer were 0.10ppm and 0.07ppm. The 5-D isotopomer had isotopoe shifts of 0.08ppm at the γ carbon and 0.11ppm γ' carbon, each two-bonds away from deuterium. The two-bond isotope effects were of the usual magnitude, i. e., about 0.1ppm per deuterium.

The two-bond isotope effect for a carbonyl carbon next to a deuterated carbon was observed as a downfield shift(negative sign). The carbonyl carbon signal of α-deuterated compounds was assigned to a broad downfield peak and this peak was much broader than that of unlabeled cyclooctanone because of coupling to deuterium. The two -bond isotope effect of 2,2,8,8-D_4 isotopomer was -0.23ppm (*Table* 1). In the case of mono-deuterated 2-D isotopomer, the observed values are -0.11 and -0.14ppm. The carbonyl carbon of the 4-D and 5-D isotopomers are not affected by deuteration since these carbonyl carbons are far from deuterium.

A negative isotope effect on the ^{13}C chemical shift of the carbonyl cabon, using a mixture of acetone and acetone-D_6, has been reported.[18] The downfield isotope effect on the carbonyl carbon of the deuterated compound was -0.28ppm. The Breitmaier group has primarily interpreted the downfield shift in terms of hyperconjungtive influence, i. e., reduced hyperconjugative ability of C-D compared to C$-$H.[19] Wehrli and his group also observed a down filed isotope effect on carbonyl carbon in the ^{13}C NMR spectrum of cyclodecanone-2-D.[20] Kresge has reported downfield intrinsic isotope shifts in several types of carbonyl compounds, and also attributed the downfield deviation to isotopic perturbation of hyperconjugated.[21]

(3) Three-bond Isotope Effects on ^{13}C shifts. There are few reports of three-bond deuterium isotope shifts, because a typical value is one-quarter to one-third of two-bond deuterium isotope effects. The usual three-bond deuterium isotope shift is an upfield shift even though unusual downfield shifts have been observed.[22] Observed three-bond isotope effects on γ and γ' carbons in 2,2,8,8-D_4 were small, i. e., about 0.06ppm and 0.09ppm, respectively, and were upfield shifts as usual. Three-bond isotope effects on γ and γ' of the mono-deuterated isotopomer were 0.04ppm and 0.05ppm, respectively, due to the presence of deuterium at α and α' carbons. These three-bond isotope effects were shown at α and α'carbons of the 4-D isotopomer with corresponding values of 0.03 and 0.04ppm, respectively.

The magnitude of these effects on the completely

deuterated isotopomer is larger than that of partially deuterated isotopomers. Deuterium isotope shifts are the largest at the carbon to which deuterium is directly attached, and rapidly attenuate with bond separations.

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