²H Isotope Effect on ¹³C Chemical Shifts of

Nitro-Benzo-9-Crown-3

Moghimi [*+], *Abolghasem*

Chemistry Department, University of Imam Hossein, Tehran, P.O. Box 16575-347 I.R. Iran

Rastegar, Majid and Ghandi, Mahdi

Chemistry Department, University of Tehran, Tehran, I.R. Iran

Bijanzadeh, Hamid Reza

Chemistry Department, University of Tarbiat Modarres, Tehran, I.R. Iran

ABSTRACT: *Deuterium substitution on two ortho-substituted -OCH₂- fragments in Nitro-Benzo-9-Crown-3 induces low frequency shifts, positive $^{mn}\Delta Cj$, in all ^{13}C NMR resonances which is an indication of the increased shielding in this crown ether. The magnitude of these shifts vary from $^{13}\Delta C7=716$ to $^{54}\Delta C3=15$ ppb for C7 and C3 carbons directly attached to ^2H, respectively. The influences of concentration and solvent, $CDCl_3$, CD_3COCD_3, and C_6D_6, on $^{mn}\Delta Cj$ values were investigated. The $^{mn}\Delta Cj$ values depended more on the nature of the solvent than on the concentration. The order of induced isotope shifts is: $^{13}\Delta$, $^{51}\Delta > ^{24}\Delta$, $^{42}\Delta > ^{34}\Delta$, $^{43}\Delta > ^{56}\Delta$, $^{65}\Delta > ^{45}\Delta$, $^{54}\Delta$. The isotope shifts observed are suggested to be a sum of contributions from low frequency shift due to inductive-type and negative hyperconjugation perturbations. The C-D bond, as a poorer electron acceptor than a C-H bond induces less positive charge on directly attached oxygens O1 and O2. This, in turn, causes shielding of C1 and C2 in C1O1CD₂ and C2O2CD₂ fragments. The difference in $^{34}\Delta C1$ and $^{43}\Delta C2$ values is attributed to the conformational dependence of the negative hyperconjugation. The C1 and C2, are in fact, not equally affected by the two CD₂ groups by negative hyperconjogation because of the existence of NO₂ group attached to the benzene ring.*

KEY WORDS: *NMR, ^{13}C NMR, ^2H Isotope Shift, ^2H Isotope Labeling, Crown Ethers, Nitro-Benzo-9-Crown-3*

INTRODUCTION

²H isotope labeling in crown ethers has shown enormous potential in investigation of the conforma- tional analysis[1], solution and solid phase NMR spectral analysis[1,2], and solid phase dynamic processes[3].

The synthesis of some ^2H labeled crown ethers including B9C3-d4[2a], NO2-B9C3-d4[2b], cyclohexyl-9C3-d4[1] and COOH-B24C8-d4[3c] crown ethers have been recently reported by selective incorporation of deuteriums at methylene ether carbon position. The synthesis of 18C6-d4[3a], 12C4-d4[3b], DB15C5-d4[2d] have also been reported by G. W. Buchanan *et al*. The deuterated nine-membered ring crown ethers were synthesized to simplify solution and solid phase NMR spectra while the other deuterated crown ethers synthesized to investigate the dynamic process in crown cavity by solid phase ^2H-NMR .

In this paper the first report on the ^2H/^1H isotope effect on ^{13}C-NMR chemical shifts in crown ethers is presented and the mechanisms that can rationalize the resultant $^i\Delta C_j$ values for NO2-B9C3 crown ether are discussed. The term "Isotope Shifts", $^i\Delta C_j$, i being the number of bonds intervening between observed nuclei and ^2H, is used for ^2H/^1H isotope effects, throughout this paper. Such effects on the magnetic shielding of nuclei have been known for a long time. In 1957, Tiers reported the low frequency shift for ^{19}F signal in n-C_3F_7D in comparison to that of n-C_3F_7H, indicating positive $^2\Delta$[4]. Later report of longer-range deuterium isotope shifts for carbon was generally introduced in the literature[5]. Interestingly, it has been shown that isotope shifts can be transmitted to six or seven bonds remote from ^2H in some cases[5e,6]. However, one of the major problems has always been the rationalization of the observed $^i\Delta C_j$ values [6,7].

EXPERIMENTAL

Material

1 and 1-d4 were prepared according to the previously reported procedure[2b]. Deuterated solvents $CDCl_3$ (%98), CD_3COCD_3 (%99.8), C_6D_6 (%99.95) were purchased from Merck (Darmstadth, Germany).

NMR and Method

The isotope shifts $^{nm}\Delta C_j$ measurements were conducted at 125.76 MHz ^{13}C-NMR on a Bruker Avance 500 DRX spectrometer at a probe temperature of 300°K. The mixture of 1 and 1-d4 under two conditions: i) in

CDCl$_3$ at different concentration levels in the range of 0.133 - 0.533 M, and ii) in different solvents, CDCl$_3$, CD$_3$COCD$_3$, C$_6$D$_6$ at 0.533M concentration were used. In order to determine the signs of the $^{nm}\Delta C_j$ values, at least one nonequimolar mixture of labeled and unlabeled crown ethers was tested in each solvent. In a typical experiment, 6.5 µs ^{13}C pulse, 2s pulse delay, 65 Kb of memory for spectral window of 26,000 Hz, an acquisition time of 0.83 s, and a digital resolution of 0.6 Hz/point were selected. Depending on the concentration, 10,000 to 20,000 NS was choosen.

RESULTS AND DISCUSSION

The structures and numbering schemes of NO$_2$-B9C3, 1, and NO$_2$-B9C3-d4, 1-d4, are presented in Fig.1. Since the ^{13}C chemical shift is depended on the solvent and concentration, measurements were made as the mixtures of labeled and unlabeled crown ethers in a range of concentrations as well as in different solvents at equal concentration to evaluate the effect of these two factors on $^i\Delta C_j$ values. The results of isotope shift measurements in 0.133 – 0.533 M CDCl$_3$ solution and in three different solvents CDCl$_3$, CD$_3$CODC$_3$, and C$_6$D$_6$
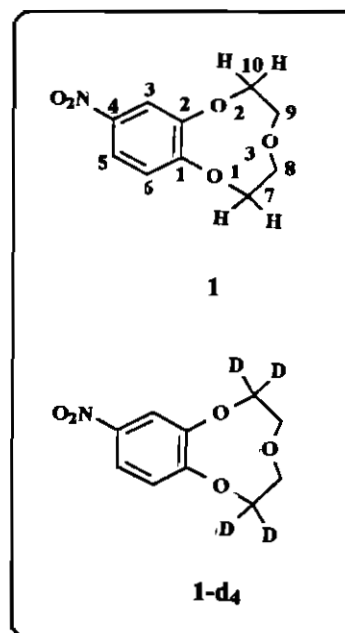

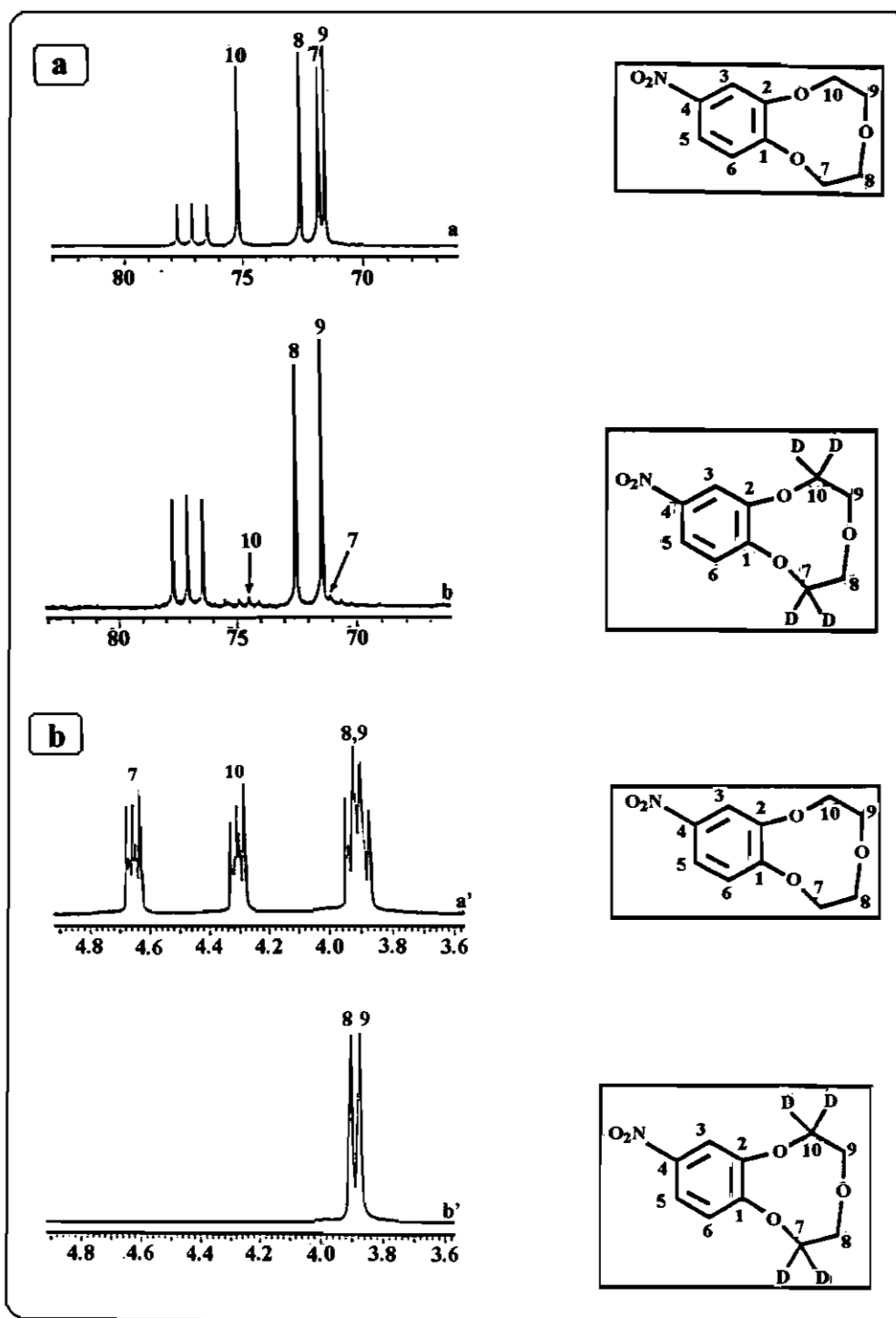*Fig. 1: The structures of NO$_2$-B9C3 , 1 , and NO$_2$ – B9C3-d4 , 1-d4*

Fig. 2: The aliphatic region of ^1H and ^{13}C NMR spectra of 1 and 1-d4

measurements in 0.133 – 0.533 M CDCl₃ solution and in three different solvents CDCl₃ , CD₃CODC₃ , and C₆D₆

at 0.533 M concentration level by 125.67 MHz ¹³C-NMR are given in Tables 1-4 .

Since ΔCj values in 1-d4 are depended on the position of both d2 couples, the normally used symbol $^{i}\Delta Cj$ has been replaced in this article by $^{mn}\Delta Cj$ which indicates the distances m and n from two d2 couples. Based on the definition given for ΔCj, the positive and negative signs indicate lower and higher frequency shifts respectively.

The first step in investigating the isotope shifts is the correct NMR spectral analysis and chemical shift assignments, particularly in complicated cases. In the present case, the relatively more complicated part of the assignment is the methylene region which can be analyzed by

two-dimensional ^{1}H-^{1}H COSY, ^{1}H-^{13}C HETCOR, and long range ^{1}H-^{13}C HETCOR NMR spectra as reported before[2b].

Since 1 and 1-d4 have no symmetry elements, they show ten ^{13}C signals in solution. The aliphatic region of ^{1}H and ^{13}C-NMR spectra of these two crown ethers have been compared in Fig. 2. As it is clear, the CD$_2$ carbon signals have been shifted to lower frequencies, the two ^{1}H multiplet peaks at 4.65 and 4.30 ppm corresponding to protons attached to C7 and C10 have been eliminated, and the ^{1}H multiplet at 3.9 ppm has changed to two

Table 1: $\delta\ ^{13}C$ *(ppm)* * *for the mixture of 1 and 1-d4 in* $CDCl_3$ *at different concentrations*

Concent.	0.533 M		0.266 M		0.133 M	
Compound Ci	1	1-d4	1	1-d4	1	1-d4
C1	157.180	157.138	157.127	157.084	157.097	157.053
C2	150.494	150.441	150.435	150.380	150.396	150.341
C3	119.827	119.812	119.885	119.869	119.940	119.925
C4	142.440	142.412	142.492	142.464	142.485	142.458
C5	121.918	121.883	121.918	121.883	121.908	121.873
C6	119.972	119.952	120.051	120.032	120.114	120.098
C7	71.838	71.122	71.862	71.145	71.826	71.109
C8	71.546	71.411	71.559	71.423	71.560	71.424
C9	72.578	72.464	72.597	72.483	72.622	72.507
C10	75.184	74.462	75.214	74.504	75.247	74523

* *Digital resolutions are* $\pm$ *0.6 Hz/point*

Table 2: $\delta\ ^{13}C$ *(ppm)* * *for the mixture of 1 and 1-d4 in different solvents (0.533 M solutions)*

Solvent.	CDCl$_3$		CD$_3$COCD$_3$		C$_6$D$_6$	
Compound Ci	1	1-d4	1	1-d4	1	1-d4
C1	157.180	157.138	158.767	158.729	158.364	158.326
C2	150.494	150.441	152.249	152.201	151.873	151.823
C3	119.827	119.812	120.867	120.850	121.243	121.228
C4	142.440	142.412	143.831	143.809	144.099	144.075
C5	121.918	121.883	123.289	123.253	123.022	122.985
C6	119.972	119.952	121.018	120.992	121.243	121.228
C7	71.838	71.043	73.169	72.401	72.857	71.963
C8	71.546	71.411	72.658	72.513	72.392	72.255
C9	72.578	72.464	73.668	73.554	73.612	73.497
C10	75.184	74.462	76.502	75.784	76.246	75.523

* *Digital resolutions are* $\pm$ *0.6 Hz/point*

Table 3: $^2H/^1H$ Isotope shifts for NO_2-B9C3 in CDCl₃ at different concentrations

Concent. Δδ (ppb)	0.533 M	0.266 M	0.133 M
$^{34}\Delta C1$	42	43	44
$^{43}\Delta C2$	53	55	55
$^{54}\Delta C3$	15	16	15
$^{65}\Delta C4$	28	28	27
$^{56}\Delta C5$	35	35	35
$^{45}\Delta C6$	20	19	16
$^{15}\Delta C7$	716	717	717
$^{24}\Delta C8$	135	136	136
$^{42}\Delta C9$	114	114	115
$^{51}\Delta C10$	722	710	724

a) Digital resolutions are ± 0.6 Hz/point

b) ΔCi = δCi (NO₂-B9C3) - δCi (NO₂- B9C3-d4)

Table 4 : $^2H/^1H$ Isotope shifts for NO_2-B9C3 in different solvents (0.533M solutions)

Solvent Δδ (ppb)	CDCl₃	CD₃CODC₃	C₆D₆
$^{34}\Delta C1$	42	38	38
$^{43}\Delta C2$	53	48	50
$^{54}\Delta C3$	15	17	15
$^{65}\Delta C4$	28	22	24
$^{56}\Delta C5$	35	36	37
$^{45}\Delta C6$	20	26	15
$^{15}\Delta C7$	716	768	892
$^{24}\Delta C8$	135	138	137
$^{42}\Delta C9$	114	115	115
$^{51}\Delta C10$	722	717	723

singlets because of the removed vicinal $^3J_{HH}$ couplings.

A typical ^{13}C-NMR spectrum of the mixture of 1 and 1-d4 is shown in Fig.3, where three regions are separately shown for clarity. A close look at the $^{mn}\Delta Ci$ values in different solvents and in CDCl₃ at different level of concentration, Tables 3 and 4, as well as the typical ^{13}C-NMR spectrum shown in Fig.3, reveals that an upfield shift (i.e. positive $^{mn}\Delta Ci$) has occurred for all C_i's. Inspection of the isotope shift values reveals that they are, in general, more de pendent on the nature of the solvent than on concentration. A logical way to demonstrate the solvent dependence of isotope shifts [5b] is the average $^{mn}\Delta Cj$ values and their standard deviations. From the data presented in Table 3 and 4, it is clear that the standard deviation for ΔC7 values at different concentrations in CDCl₃ is much less than that in different solvents. The largest $^{mn}\Delta Cj$ observed corresponds to carbons, C7 and C10, directly attached to deuteriums. C7 and C10 Shift to lower frequencies by more than 700 ppb because of the inductive effect[9] of ^2H owing to the shorter C-D distance caused by the zero-point vibration energy[10]. The second $^{mn}\Delta Cj$ in value, ~ 140 ppb, corresponds to the C8 and C9, which are two bonds away

from ^2H's. The increased electron density on Cα is partially induced onto Cβ, in saturated systems, causing a positive $^2\Delta$.

Generally speaking, the order of shielding effects is: $^{15}\Delta$, $^{51}\Delta > ^{24}\Delta$, $^{42}\Delta > ^{34}\Delta$, $^{43}\Delta > ^{56}\Delta$, $^{65}\Delta > ^{45}\Delta$, $^{54}\Delta$. This means C3 and C6 have shifted to lower frequencies than other carbons. It is interesting to note that the ΔC₅ and ΔC₂ are larger than ΔC₄ and ΔC₁ respectively in all the cases. This could be due to the influence of nitro substitution group on the average orientation of the para oxygen's lone pairs.

In rationalizing the positive ΔC₁ and ΔC₂, it seems that the negative hyperconjugation[11] is the main factor compared with inductive effect, Fig. 4. The later factor could not be a major contribution because it can not explain the difference between ΔC₁ and ΔC₂ as well as ΔC₄ and ΔC₅. According to negative hyperconjugation, (-) Hyp., a C-D bond is a poorer electron acceptor than a C-H bond [12,13]. Therefore, the oxygen lone pairs inject less electron density into the backbone of an anti C-D bond relative to C-H bond. So, the relatively less positive charge on oxygen O_1 and O_2 attached to CD_2 is induced to the adjacent carbons C1 and C2
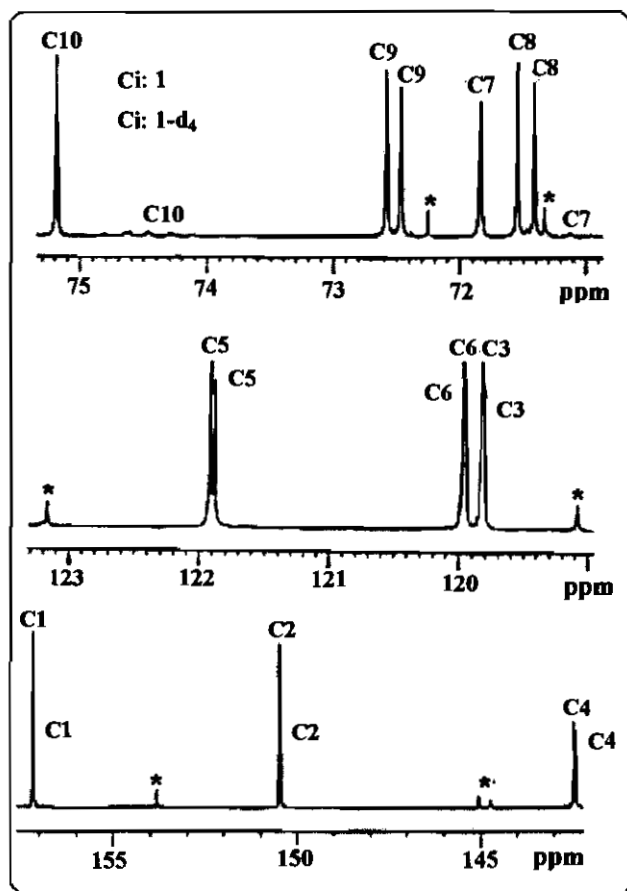
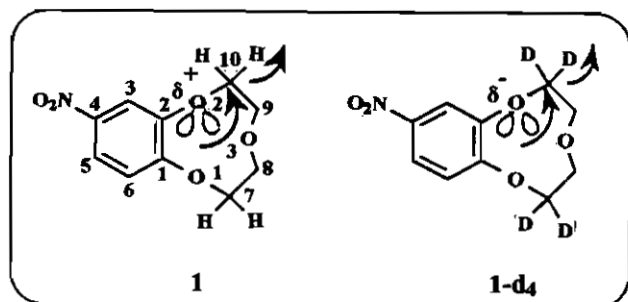Fig. 3: A typical ^{13}C NMR spectrum of a mixture of 1 and 1-d4

Fig. 4: The negative hyperconjugation in 1 and 1-d4

causing more shielding. For this reason the C-D bond in 5,5-dimethyl-1,3-dioxane-2-d1 prefersthe equatorial position by about 50 cal/mol while this preerence is just 6.3 cal/mol in cyclohexane-d1[9]. In fact, the conformer with axial oxygen is more stabilized by (-) Hyp. due to a

greater interaction between anti oxygen lone pair and axial H over that with axial ^2H. Anet has named this effect as the "reverse anomeric effect" [9].

In order to find out why ΔC_2 and ΔC_5 are greater than ΔC_1 and ΔC_4 respectively, the availability of oxygen lone pairs in (-)Hyp. and the conformational dependence of (-)Hyp. have to be considered. According to the X-ray crystal structure of NO_2-B9C3 [2b], the two torsional angles C7O1C1C6 and C10O2C2C3, being 179° and 73.9°, are quite different in the solid phase [2b]. The introduction of 4-NO_2 group, in fact, induces a flattening effect in the C10O1C1C6 unit. This means that C1 and C2 are not equally affected by the two CD_2 groups by (-)Hyp. mechanism. Considering the fact that one of the major conformations in solution is close to that reported in the solid phase, because of -NO_2 group, one would expect to see the angular dependency of ΔC_2 and ΔC_1 shown in Fig.5. Based on the different (-) Hyp. power levels shown in Fig.5, one expects to have less disturbed, in chemical shift, para carbon to O1 once C10 is deuterated.
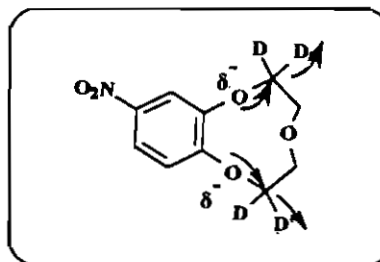

Fig. 5: The conformational dependence of (-) Hyp. for two -CD_2O part of 1-d4

The arguements on the difference between ΔC_3 and ΔC_6 are not logical because of the fact that the differential shifts of only 1 ppb in 0.133 M CDCl₃ solution is too small to be considered.

CONCLUSIONS

^2H isotope labeling at C7 and C10 methylene positions of NO_2-B9C3 crown ether results in the lower frequency shifts, positive $^{mn}\Delta Cj$, for all ^{13}C signals in ^{13}C NMR spectra. The maximum shift was observed for the two deuterium directly bonded carbons, C7 and C10, and the minimum shift for the C3. The magnitude of the

measured isotope shift is dependent more on the nature of solvent than on the concentration of the crown ether. The isotope shifts observed for C7, C8, C9 and C10 could be explained by the ^2H inductive effect. The positive $^{mn}\Delta C1$ and $^{mn}\Delta C2$ contribute to both inductive and negative hyperconjugation effects and their difference is due to the conformational dependence of negative hyperconjugation.

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