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Chemical Shifts of Ethylenic Carbons in Polyunsaturated Fatty Acids and Related Compounds

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The ^{13}C NMR of ethylenic carbon atoms in the methylene-interrupted *cis* double bonds as found in polyunsaturated fatty acids (PUFAs), their precursors and analogs was studied. The chemical shifts of unsaturated carbon atoms are strongly dependent on a combination of electric field effects from the head group, steric hindrance and the presence of other double bonds. A full set of shift parameters were determined based on a reference value given by a long aliphatic alkene (*cis*-6-dodecene at 129.99 ppm) and various functionalities (double bond, ester, aldehyde, acetal, hydroxyl methyl, etc.) with one, two and three double bonds. Application of shift parameters to polyfunctionalized polyenes, high PUFAs and new analogs of arachidonic acids shows that the method is a convenient way to predict the chemical shift of all ethylenic carbon atoms. © **1997 John Wiley & Sons, Ltd.**

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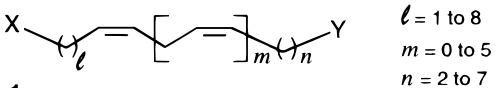
INTRODUCTION

Polyunsaturated fatty acids (PUFAs),[1] their synthetic precursors, and some pheromones exhibit a common main structural feature which usually consists of several methylene-interrupted *cis* double bonds (**1**) (Scheme 1). The PUFAs are defined by the number of carbon atoms, C18–C22, the number of double bonds, 1–6, and the position of the first double bond with respect to the ω position: $n-9$, $n-6$ and $n-3$. Thus, arachidonic acid (AA), all-*cis*-5,8,11,14-eicosatetraenoic acid, is C20:4, $n-6$; linoleic acid (LA) is C18:2, $n-6$; α-linolenic acid (α-LNA) is C18:3, n $-$ 3; eicosapentaenoic acid (EPA) is C20:5, $n-3$; and docosahexaenoic acid (DHA) is C22:6, $n-3$. In most studies, the ^{13}C NMR chemical shifts for ethylenic carbons are either not described or quoted without assignment. This is the case with β,γ-ethylenic aldehydes and their corresponding acetals,[1,2] ethylenic alcohols having 1–3 double bonds[3] and various bifunctionalized dienes.[3,4] Moreover, different assignments are sometimes reported for shifts taken from the same ethylenic skeleton [X = COOMe,[5] CH_3;[6,7] $n=1$; Y = $CH(OR)_2$, $l=4$; $m=0$]. Until recently, the ^{13}C NMR of high PUFAs (EPA, DHA) did not include complete assignments of olefinic carbon atoms.[8] However, papers have been devoted to the study of ^{13}C NMR of unsaturated compounds bearing the *cis*-skipped polyene system in the PUFAs.



1

l = 1 to 8
m = 0 to 5
n = 2 to 7

X, Y = CH_3, COOMe, $CH(OR)_2$, CHO, CH_2OH, CH_2BR, ...

Scheme 1. General compounds **1**.

Batchelor *et al.*[9] introduced 'linear field effects' to show that the shifts of unsaturated carbons are strongly dependent on both steric and electric field effects arising from the head group (the function on C1) and from various substituents (including other unsaturated groups). To help determine the chemical shift of each ethylenic carbon atom within fatty acids, they defined a few substituent shift parameters, based on functionalities such as methylcarboxylate, ω-3-methyl and groups with unsaturation.

Gunstone[10] described many PUFAs and proposed specific assignments for several mono- and dienoic acids and for α- and β-linolenic acids. The chemical shifts of ethylenic carbon atoms for high PUFAs were based on shift parameters from the electric field model by Gunstone[11] and by Aursand and Grasdalen.[12] Subsequently, Bianchi and co-workers[13] discussed and ruled out the electric field effect and proposed a σ-inductive model to explain the shift of ethylenic carbon atoms. Since the electric polarization acts through bonds instead of space, the inductive model contains no geometrical term. They introduced equations with a few parameters and introducted an attenuation factor (1.78

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ppm per methylene between the polar function and the ethylenic carbon), which is the same for all reported groups (carboxylic ester and acid, hydroxyl, double bond).

During the course of our work towards the total syntheses of PUFAs (α-LNA, AA, EPA and DHA), we have prepared several ethylenic compounds of the general structure **1**.[6,14–17] The data reported here permit the chemical assignment for any given olefinic carbon atom in mono-functionalized ($Y = CH_3$) mono-, di- and tri-(*cis* skipped) ethylenic compounds **1**. These analyses are based on the other groups present in the molecule [$X = CH_3$, COOMe, $CH(OR)_2$, CHO, CH_2OH, etc.] This analysis leads to a new set of shift parameters for assigning ethylenic carbon atoms of PUFAs, bifunctionalized mono- and diethylenic compounds [X, $Y = COOMe$, $CH(OR)_2$, CHO, CH_2OH, etc.] and of new synthetic arachidonic acid analogs and precursors obtained by heterocyclization.[18]

EXPERIMENTAL

The ^{13}C NMR spectra of all the products described here were recorded on a Bruker AC 200 spectrometer at 50.32 MHz in $CDCl_3$ solutions (*ca.* 0.15 M), and chemical shifts are given in ppm relative to the solvent (77.10 ppm). The spectra were recorded at room temperature and the instrumental conditions are as followed: spectral width 11 904 Hz, data size 16K, pulse 90° (3 μs), acquisition time 0.68 s and delay time 2 s. The ^{13}C reference value of an ethylenic carbon atom within a long chain is 129.99 ppm as given by **3** (the literature[19] gives 129.89 ppm for **3**).

RESULTS AND DISCUSSION

Methods based on lanthanide shift reagents and two-dimensional NMR experiments

In the initial studies of chemical shifts for ethylenic carbon atoms we used the upfield shift reagent $Pr(fod)_3$ at several concentrations. For carbons located near the polar head group this lanthanide reagent induces an upfield shift that decreases monotonically along the carbon chain. Several measurements on the dienic and trienic acetals **1** [*l*. $n = 1$, $m = 1$ and 2, X = CH(OR), $Y = CH_3$], AA (*l*, $m = 3$, $n = 4$, X = MeOOC, $Y = CH_3$), EPA ($l = 3$, $m = 4$, $n = 1$, X = MeOOC, $Y = CH_3$) and DHA ($l = 2$, $m = 5$, $n = 1$, X = MeOOC, $Y = C_3$) with different lanthanide concentrations afforded a first assignment for the ethylenic carbon atoms.[20] However, these results were not in agreement with literature data.[5–7] The only one with the same assignment was the ethylenic carbon atom nearest to the head group which underwent the strongest upfield variation.

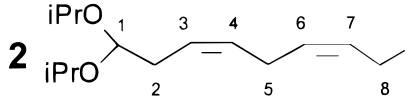
Therefore, it was necessary to complement the lanthanide experiments by other unambiguous NMR techniques. Taking the dienic acetal **2a** ($Y = CH_3$) as a model, we established the chemical shifts of olefinic protons ($\delta_{H3} = 5.41$, $\delta_{H4} = 5.42$, $\delta_{H6} = 5.28$ and $\delta_{H7} = 5.35$ ppm) and the *Z*, *Z*-configuration of the double bonds ($J_{3,4} = 10.3$ and $J_{6,7} = 10.6$ Hz) by selective irradiation of selected protons H_3, H_5 and H_8.[16] Then, heteronuclear two-dimensional experiments showing cross peaks allowed unambiguous assignments for each ethylenic carbon atom, which differed from those obtained in the lanthanide experiments. Table 1 summarizes the results for olefinic carbon chemical shifts in compounds **2**, and includes literature data[5,6] and those from the lanthanide shift reagent[20] and from the two-dimensional NMR experiments.[16]

These new results show that lanthanide experiments can be ruled out because the effect of a polar head group increases with increasing concentration of the praseodyme, and leads to a new polarization of the olefinic system which can be very different. On the other hand, 2D NMR experiments are unreliable because in many cases the ethylenic protons appear as an unresolved broad signal near 5.3 ppm and can not be selectively irradiated. Consequently, it is difficult and sometimes impossible to obtain useful information from ^1H NMR, including two-dimensional NMR.

Methods based on shifts parameters

The discussion is still open to assess if the polarization of ethylenic carbon atoms comes from action through space or bonds. Any model used to assign and predict the chemical shifts of ethylenic carbon atoms in PUFAs and related compounds must include all parameters. The shift of an unsaturated carbon atom is strongly dependent on a combination of electric field and steric

Table 1. Assignments of ethylene carbon atoms of 2, depending on the methodology



2

	δ (ppm) for **2a**, Y = CH_3			
	131.99	130.24	127.07	124.60
Corresponding literature assignments, Y = $(CH_2)_4CH_3$,[5] $(CH_2)_4COOMe$[6]	C3	C7	C6	C4
Praseodyme experiments, Y = CH_3[20]	C7	C6	C4	C3
NMR irradiation and 2D, Y = CH_3[16]	C7	C4	C6	C3

effects. Non-equivalence of the ^{13}C chemical shifts of unsaturated carbons in functionalized alkenes results from the electric field generated by the head group. The shifts can be interpreted in terms of changes in electron density. The direct effect of such a polarization (on isolated double bonds) is to induce opposite shifts on the two olefinic resonances, the olefinic carbon nearest from the head group being shifted upfield and the other one downfield.

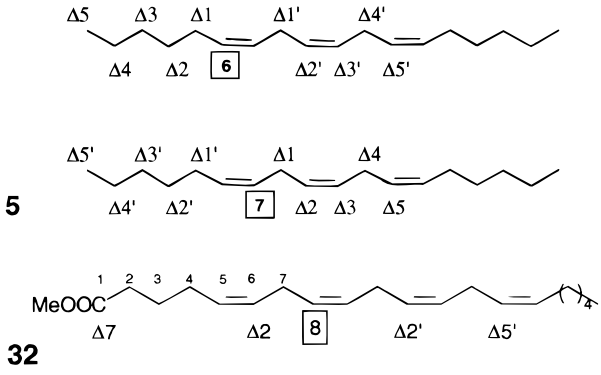
In polyunsaturated compounds such as **1** with $m > 0$, the assignment of signals for a given double bond is more complex because the shifts arise from the dipolar head group *and* from the other double bonds.[9] The chemical shift of unsaturated carbon atoms will depend on substituent shift parameters: the presence of a functional group such as carboxylic methyl ester, acetal, aldehyde, hydroxymethyl, bromomethyl, methyl (for the $n - 3$ family) group, and unsaturated groups.

The parameters introduced here permit the prediction of chemical shifts in PUFAs, bifunctionalized compounds **1** (X, Y $\neq CH_3$) and new AA analogs. Finally, the calculated shifts are compared with other experimental data.

Shift parameters from other double bonds in all methylene-interrupted *cis* polyenic hydrocarbons. Along the linear carbon chain of PUFAs and their synthetic intermediates, the shifts are derived from a reference value given by the ethylene carbon atoms of *cis*-6-dodecene (**3**), which is a long aliphatic alkene bearing no other functionality. The shift parameters arising from other methylene-interrupted *cis* double bonds in the carbon chain are taken relative to the standard value. For this purpose, we synthesized several unsaturated hydrocarbons having one to five methylene-interrupted *cis* double bonds (**3**, **4**, **5**, **6**, **7** and **8**: X, Y = CH_3, l, $n = 1$ or 4, $m = 0$–4) (details of the synthesis of the set of polyene hydrocarbons will be reported elsewhere).[21] Compound **8** ($n = 2$) will allow the evaluation of the steric effect due to a methyl group in the $n - 3$ family of PUFAs.

All compounds are numbered from X which has the C1. The chemical shift of a given ethylenic carbon atom such as C6 or C7 in the triene **5** depends on the effects of functionalities at carbons on each side of the double bond, i.e. on carbons designated Δ1, Δ2, Δ3, etc. (carbon α, β, γ, etc. on the same side as C6 or C7) and carbons designated Δ1′, Δ2′, Δ3′, etc. (carbon α', β', γ', etc. on the other side to C6 or C7), as shown in Scheme 2.

The substituent effect translates into a parameter Δ related to the function responsible for the shift (in this example another double bond) and to its location relative to the given ethylenic carbon atom (n or n'). $^{C=C}\Delta 2$ is the shift parameter from another double bond located at the β-position to the measured carbon. $^{C=C}\Delta 2'$ is the shift parameter from another double bond located at the β'-position (across the olefinic linkage of the measured carbon). For example, C8 in AA **32** ($l = 3$, $m = 3$, $n = 4$, X = COOMe, Y = CH_3) sustains the $^{C=C}\Delta 2$ effect from unsaturation C5=C6, the $^{COOMe}\Delta 7$ effect from functional group at C1 and, on the other side of the C8=C9 double bond, the $^{C=C}\Delta 2'$ and $^{C=C}\Delta 5'$ effects from last unsaturations on C11 and C14.



Scheme 2. Substituent effect on ethylenic carbon atoms C6 and C7 in **5** and on C8 in arachidonic acid **32**.

The ^{13}C NMR spectra of compounds **3**–**8** are described with assignments in Table 2. Assignments were performed as indicated in Fig. 1.

Using the chemical shift of 6-dodecene (**3**) as the reference value for an ethylenic carbon atom (129.99), the effect of a second double bond gives the $^{C=C}\Delta 2$ and $^{C=C}\Delta 2'$ shift parameters for C6 and C7 in diene **4**, as shown in Fig. 1. Then, triene **5** permits the determination of the $^{C=C}\Delta 5$ and $^{C=C}\Delta 5'$ shift parameters from a third double bond, and so on until complete specification of parameters and, therefore, assignment of carbon atoms C6 to C12 in pentaene **7**.

The same shift parameters are found from one compound to another. Thus, the $^{C=C}\Delta 2$ and $^{C=C}\Delta 2'$ parameters appear four times whereas $^{C=C}\Delta 5$, $^{C=C}\Delta 5'$ and $^{C=C}\Delta 8$, $^{C=C}\Delta 8'$ are recognized three times and twice, respectively, according to Fig. 1. Combining the data in Fig. 1 and Table 2, we calculated average values for each $^{C=C}\Delta n$ parameter in this series (Table 3).

The magnitude of the parameters is directly related to the distance between the double bond considered and the other ethylenic carbon atoms, which make the $^{C=C}\Delta 11$ and $^{C=C}\Delta 11'$ parameters negligible. All the shift parameters are cumulative and the chemical shift of a

Table 2. ^{13}C NMR of ethylenic carbon atoms of polyenic hydrocarbons: l, $n = 4$, X = Y = CH_3

Compound	X, Y	l, n	m	C6	C7	C9	C10	C12
3	CH_3	4	0	129.99				
4	—	—	1	130.21	128.00			
5	—	—	2	130.49	127.74	128.35		
6	—	—	3	130.55	127.65	128.57	128.05	
7	—	—	4	130.55	127.62	128.63	127.96	128.26
8	—	1	2	132.04	127.18	128.35		

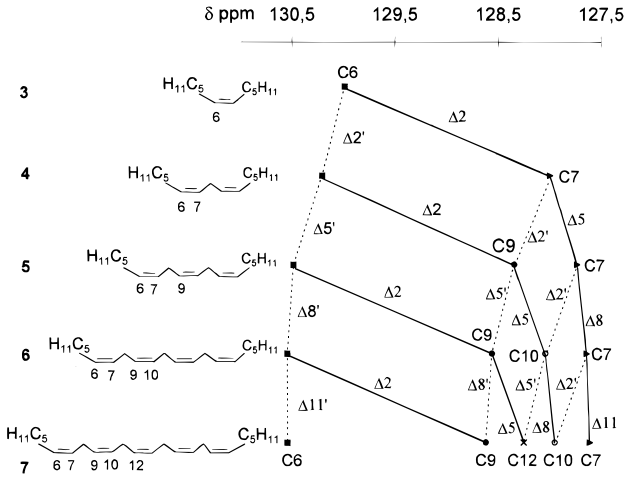


Figure 1. Chemical shifts of ethylenic carbon atoms of compounds **3–8** with the corresponding **Δ*n*** and **Δ*n*′** shift parameters (from Table 2).

given ethylenic carbon atom will depend on its position within the polyenic system. For instance, C10 in **6** is calculated as $129.99 + {}^{C=C}\Delta 2 + {}^{C=C}\Delta 5 + {}^{C=C}\Delta 2' =$ 128.08 ppm (*vs.* 128.05 measured) and C9 in **7** as $129.99 + {}^{C=C}\Delta 2 + {}^{C=C}\Delta 2' + {}^{C=C}\Delta 5' + {}^{C=C}\Delta 8' = 128.67$ (*vs.* 128.63 measured).

In all compounds the two carbons atoms of the end olefinic group (C6 and C7) have the highest (C6) and the lowest (C7) chemical shift of the sequence. This is due to the cumulative polarization of all downfield parameters ${}^{C=C}\Delta n'$ on C6 and of all the upfield parameters ${}^{C=C}\Delta n$ on C7. The current set of parameters was calculated relative to the olefinic double bond function and for PUFAs of the $n-6$ family. For compounds of family of $n-3$ there should be a steric effect due to the ω-methyl near the last double bond. We evaluated this effect on **8** of the $n-3$ family ($n=1$) by comparing its NMR spectrum with that of **5** ($n=4$) as shown in Fig. 2.

The methyl effect decreases rapidly along the unsaturated chain: ${}^{Me}\Delta 5 = 0$ and ${}^{Me}\Delta 5'$ should be negligible. The ${}^{Me}\Delta 2$ and ${}^{Me}\Delta 2'$ parameters are opposite in direction to the effect of the polarization by a double bond ($+1.55$ and -0.56 *vs.* -1.92 and $+0.30$), and their intensities are lower and higher, respectively.

Table 3. Set of Δ*n* parameters for double bonds

Parameter	${}^{C=C}\Delta 2$	${}^{C=C}\Delta 5$	${}^{C=C}\Delta 8$	${}^{C=C}\Delta 2'$	${}^{C=C}\Delta 5'$	${}^{C=C}\Delta 8'$
Shift (ppm)	−1.92	−0.29	−0.09	+0.30	+0.23	+0.06

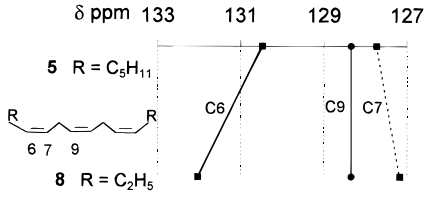


Figure 2. Modification of the chemical shift of an ethylenic carbon atom due to the methyl group in the $n-3$ family.

Shift parameters from functional groups in monofunctionalized methylene-interrupted *cis* polyenic compounds. We synthesized 26 monofunctionalized compounds bearing one to three *cis*-skipped double bonds, having long ($n-6$ family) or short ($n-3$ family) aliphatic chains, illustrated by the general formula **1**. The electric field effects for various monofunctionalized polyenic compounds were based on this set. The intermediates in the synthesis of PUFAs have been described in previous papers. We prepared some of these compounds to record their ^{13}C NMR spectra under the same conditions. The partial spectra data (olefinic carbons chemical shifts) are described in Table 4.

It was easy to determine the electric field effect of the polar head group (X = acetal, aldehyde, alcohol, bromide, phosphonium) on each ethylenic carbon carbon atom when $n=1$ or 4. Direct comparison of the NMR spectra of the new functionalized compounds with the previously studied polyenes **3–7** gave the corresponding parameters in the $n-6$ family ($X = CH_3$, $l=4$). For instance, the ${}^{acetal}\Delta 2$ and ${}^{acetal}\Delta 2'$ shift parameters of the diisopropoxy group in 3-nonenal diisopropylacetal (**9**) are obtained by difference between the measured chemical shift and the previously defined standard value for an isolated double bond in **3**: ${}^{acetal}\Delta 2 = 124.28 - 129.99 = -5.71$ and ${}^{acetal}\Delta 2' = 132.11 - 129.99 = +2.12$). On the other hand, the ${}^{acetal}\Delta 5$ and ${}^{acetal}\Delta 5'$ parameters for the diisopropoxy group in acetal **2a** [*l*, *m*, $n=1$, $X = CH(OiPr)_2$, $Y = CH_3$], belonging to the $n-3$ family, were determined by comparing the experimental data and the calculated shift based on Δ2 and Δ2′ parameters of both the other double bond and methyl $n-3$, as shown in Table 5.

Calculations made for each ethylenic compound allow us to assign an average value to the Δ2–Δ8′ parameters and for X = double bond, methyl ($n-3$ family), $CH(OiPr)_2$, $CH(OMe)_2$, CHO, CH_2OH, CH_2Br, Ph_3PCH_2. The results are summarized in Table 6 and Fig. 3.

The effects of the parameters are opposite depending on which side of the double bond the polar head group is located (Δ*n* or Δ*n*′ series). The strongest effect is due to the aldehyde function and all effects decrease very rapidly along the carbon chain. The electric field effect of the triphenylphosphonium group does not give a comprehensive set of parameters Δ5, Δ5′, Δ8 and Δ8′. Another kind of interaction involving the phenyl groups and the unsaturated groups along the carbon chain may modify the polarization of ethylenic carbon atoms. This precludes presenting a suitable set of parameters for **13b**, **24** and **25**. For one given ethylenic carbon atom within a specific compound, the chemical shift will be the sum of each parameter for surrounding functional groups added to the reference value for olefin **3** (129.99). The efficiency of the method is demonstrated by the difference of less than 0.05 ppm between calculated shifts and experimental data (for instance, C6 in **14b** is $129.99 + {}^{C=C}\Delta 2 + {}^{ald}\Delta 5 = 126.56$ *vs.* 126.55 measured).

Shift parameters from the methyl carboxylate group. The last set of parameters apply to the methylcarboxylate group. This group, or the associated carboxylic acid, is often the head group of many natural polyunsaturated compounds. We evaluated these parameters from a few

Table 4. ^{13}C NMR data of ethylenic carbon atoms of monofunctionalized compounds 2 and 9–25: $l = 1$, Y = C_3

Compound	X	*m*	*n*	C3	C4	C6	C7	C9	C10	Ref.
9	$CH(OiPr)_2$	0	4	124.28	132.11					6
2a		1	1	124.60	130.24	127.07	131.99			16
2b		1	4	124.69	130.27	127.68	130.46			6
10a		2	1	124.81	129.95	127.93	128.53	127.06	132.03	17
10b		2	4	124.83	129.98	127.94	128.57	127.61	130.51	6
11	$CH(OMe)_2$	0	4	123.29	132.59					This work
12		1	1	123.62	130.62	126.76	132.04			16
13	CHO	0	4	118.11	135.47					6
14a		1	1	118.36	133.48	125.94	132.61			16
14b		1	4	118.42	133.62	126.55	131.19			6
15a		2	1	118.64	133.20	126.86	129.20	126.75	132.21	17
16b		2	4	118.69	133.29	126.88	129.29	127.33	130.71	6
17a	CH_2OH	0	1	124.47	134.58					17
17b		0	4	125.01	133.45					This work
18a		1	1	125.39	131.44	126.67	132.19			16
18b		1	4	125.40	131.61	127.44	130.72			This work
19		2	1	125.64	131.24	127.77	128.75	127.01	132.15	17
20a	CH_2Br	0	1	125.19	134.88					17
20b		0	4	125.77	133.23					This work
21a		1	1	126.14	131.34	126.60	132.39			16
21b		1	4	126.14	131.38	127.14	130.87			This work
22		2	1	126.35	131.05	127.48	128.91	126.94	132.04	17
23a	$CH_2P(Ph)_3$, Br	0	1	125.06	133.97					17
23b		0	4	125.6	132.37					This work
24		1	1	126.07	130.4	125.9	132.03			16
25		2	1	125.8	129.45	126.22	128.11	125.86	131.33	17

unsaturated esters taken from the $n-6$ family ($n = 4$) to avoid the steric effect of the ω-methyl as met in the $n-3$ family. Examples were chosen with $l = 2$, 3 or 7 to match directly the major PUFAs whose first ethylenic carbon atom is C4 (DHA), C5 (γ-LNA, AA, EPA) or C9 (α-LNA, LA). They are given in Table 7. Simple calculations based on the spectra of unsaturated hydrocarbons **3**, **5** and **8** (Table 8) provide a new set of shift parameters related to a methyl carboxylate located at Δn and $\Delta n'$ positions to a double bond. The calculated shift parameters differ slightly from those proposed by Gunstone.[10]

Table 5. $^{acetal}\Delta 5$ and $^{acetal}\Delta 5'$ shift parameters from the diisopropylacetal group in 2a. [l, m, $n = 1$, X = $CH(OiPr)_2$, Y = CH_3]

Carbon	Exp.	Calc.	New parameters
C3	124.60	$129.99 + {}^{acetal}\Delta 2 + {}^{C=C}\Delta 2' = 124.58$	
C4	130.24	$129.99 + {}^{C=C}\Delta 2 + {}^{acetal}\Delta 2' = 130.19$	
C6	127.07	$129.99 + {}^{C=C}\Delta 2 + {}^{Me}\Delta 2' = 127.51$	Exp. − Calc. = $-0.44 = {}^{acetal}\Delta 5$
C7	131.99	$129.99 + {}^{C=C}\Delta 2' + {}^{Me}\Delta 2 = 131.84$	Exp. − Calc. = $+0.15 = {}^{acetal}\Delta 5'$

Table 6. Parameters for an ethylenic carbon atom linked to various functions

Functions	Δ2	Δ5	Δ8	Δ2′	Δ5′	Δ8′
Double bond	−1.92	−0.29	−0.09	+0.30	+0.23	+0.06
Methyl ($n-3$)	+1.55			−0.56		
Diisopropylacetal	−5.67	−0.41	−0.17	+2.17	+0.22	+0.07
Dimethylacetal	−6.69	−0.70		+2.58	+0.35	
Aldehyde	−11.87	−1.51	−0.46	+5.49	+0.87	+0.13
Alcohol	−4.92	−0.72	−0.22	+3.38	+0.32	+0.08
Bromide	−4.18	−0.91	−0.28	+3.30	+0.57	+0.04
Ph_3P^+	−4.42	Ind.	Ind.	+2.22	Ind.	Ind.

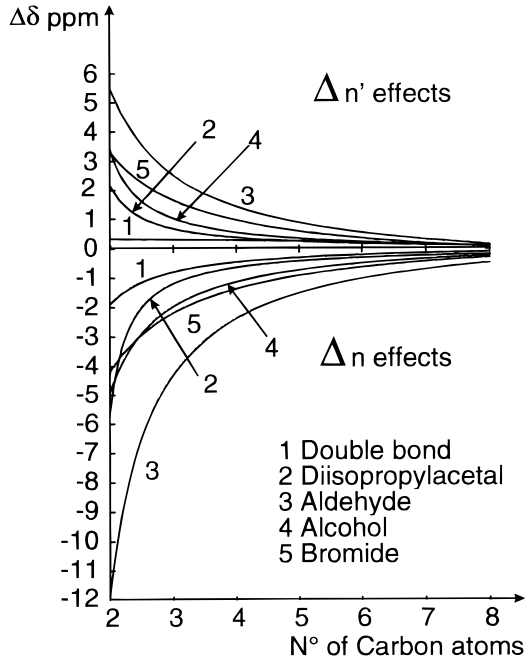


Figure 3. Δ effects for various functional groups as calculated curves from experimental data.

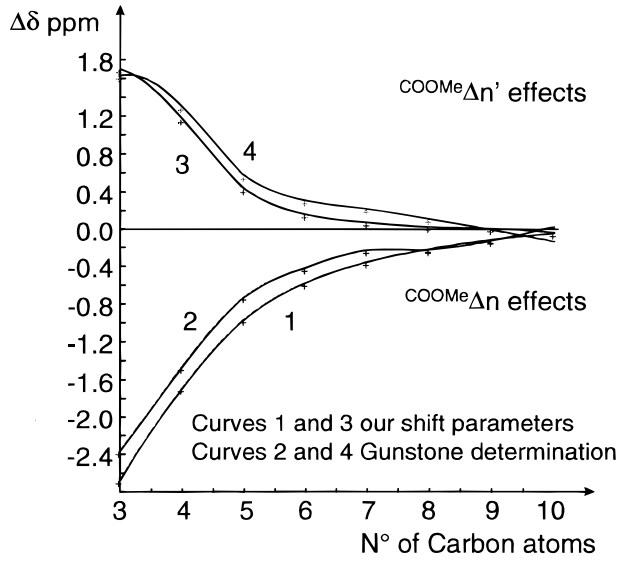


Figure 4. Parameters from methyl carboxylate in compounds **26–30**.

The value of the shift parameters decreases monotonically along the carbon chain from C4 ($^{COOMe}\Delta 3$ position) to C13 ($^{COOMe}\Delta 11'$ position), as shown in Fig. 4, which matches very well the plots obtained by Knothe and Bagby.[21] The polar head group induces no effect on the $^{COOMe}\Delta 11$ to $^{COOMe}\Delta 20$ positions, as indicated by the spectrum of α-linolenic acid methyl ester (**31**). Indeed, the shifts of C12 and C13 are identical in **31** and in unsaturated hydrocarbons **5** and **8** (128.34 *vs.* 128.35). Altogether, the various parameters presented in Tables 6 and 8 should permit accurate assignments or chemical shifts for unsaturated carbon atoms in many compounds such as PUFAs, bifunctionalized olefins and new analogs of arachidonic acid.

Application to the chemical shift of ethylenic carbon atoms in PUFAs.

We synthesized several PUFAs, from LA (two double bonds) to DHA (six double bonds), through different pathways based on the *cis*-Wittig olefination.[6,16–19] We applied the current new set of shift parameters to α-LNA, AA, EPA and DHA and then compared them

Table 7. δ (ppm) of ethylenic carbon atoms in *cis* unsaturated esters: $n = 4$, M = COOMe, Y = CH_3

Compound	*l*	*m*	C4	C5	C6	C7	C8	C9	C10	C12
26	2	0	127.30	131.71						
27	2	1	127.62	129.8		127.50	130.63			
28	3	0		128.30	131.17					
29	4	0			129.03	130.43				
30	7	0						129.78	130.02	
31	7	2						130.34	127.81	128.34

Table 8. Parameters of ethylenic carbon atoms induced by the methyl carboxylate group

	Position							
	$^{COOMe}\Delta 3$	$^{COOMe}\Delta 4$	$^{COOMe}\Delta 5$	$^{COOMe}\Delta 6$	$^{COOMe}\Delta 7$	$^{COOMe}\Delta 8$	$^{COOMe}\Delta 9$	$^{COOMe}\Delta 10$
Shift parameter	−2.68	−1.69	−0.96	−0.57	−0.35	−0.21	−0.11	−0.04
Gunstone[8]	−2.37	−1.46	−0.72	−0.41	−0.22	−0.22	−0.12	—
	Position							
	$^{COOMe}\Delta 3'$	$^{COOMe}\Delta 4'$	$^{COOMe}\Delta 5'$	$^{COOMe}\Delta 6'$	$^{COOMe}\Delta 7'$	$^{COOMe}\Delta 8'$	$^{COOMe}\Delta 9'$	$^{COOMe}\Delta 10'$
Shift parameter	1.71	1.18	0.44	0.17	0.08	0.03	0.01	—
Gunstone[8]	1.64	1.31	0.58	0.32	0.23	0.12	—	—

Table 9. Calculated and experimental chemical shifts of ethylenic carbon atoms in α-LNA, AA, EPA and DHA methyl ester: X = COOME, Y = CH_3

	α-LNA (**31**)[14] ($l=7, m=2, n=4$)			AA (**32**)[6] ($l=3, m=3, n=4$)			EPA (**33**)[12] ($l=3, m=4, n=1$)			DHA (**34**)[15] ($l=2, m=5, n=1$)		
Carbon	Calc.	Exp.	Diff.	Calc.	Exp.	Diff.	Calc.	Exp.	Diff.	Calc.	Exp.	Diff.
C4										127.90	127.93	−0.03
C5				128.89	128.96	−0.07	128.89	129.00	−0.11	129.40	129.38	0.02
C6				128.87	128.96	−0.09	128.87	128.90	−0.03			
C7										128.09	128.14	−0.05
C8				128.25	128.27	−0.02	128.31	128.31	0.00	128.16	128.14	0.02
C9	130.31	130.34	−0.03	128.11	128.22	−0.11	128.07	128.16	−0.09			
C10	127.81	127.81	0.00							128.37	128.32	0.05
C11				128.04	127.93	0.11	128.27	128.16	0.09	128.23	128.18	0.05
C12	128.37	128.34	0.03	128.60	128.64	−0.04	128.31	128.28	0.03			
C13	128.37	128.34	0.03							128.22	128.18	0.04
C14				127.69	127.62	0.07	127.99	127.93	0.06	128.37	128.32	0.05
C15	127.22	127.19	0.03	130.58	130.54	0.04	128.66	128.62	0.04			
C16	132.07	132.04	0.03							127.99	127.93	0.06
C17							127.13	127.07	0.05	128.66	128.63	0.03
C18							132.13	132.09	0.04			
C19										127.13	127.06	0.07
C20										132.13	132.09	0.04

with the corresponding experimental data. The results are summarized in Table 9. Note that the calculated and experimental shifts match very well. The difference between the calculated and experimental values, typically less than 0.1 ppm, indicates the accuracy of the method. For instance, the chemical shift of ethylenic carbon atoms C9 and C10 in α-LNA are calculated as follows:

$$\delta C9 = 129.99 + {}^{COOMe}\Delta 8 + {}^{C=C}\Delta 2' + {}^{C=C}\Delta 5'$$
$$= 130.31 \text{ ppm } (vs.\ 130.34)$$
$$\delta C10 = 129.99 + {}^{COOMe}\Delta 8' + {}^{C=C}\Delta 2 + {}^{C=C}\Delta 5$$
$$= 127.81 \text{ ppm } (vs.\ 127.81)$$

Calculation of C8 in DHA is

$$\delta C8 = 129.99 + {}^{COOMe}\Delta 6' + {}^{C=C}\Delta 2' + {}^{C=C}\Delta 2 + {}^{C=C}\Delta 5 + {}^{C=C}\Delta 8$$
$$= 128.16 \text{ ppm } (vs.\ 128.14).$$

Application to the chemical shift of ethylenic carbon atoms of bifunctionalized olefinic and skipped polyenic compounds

During the course of previous studies on the total syntheses of PUFAs, we prepared new compounds of general interest as synthetic building blocks for organic chemistry. They feature one or two *cis* double bonds ($l = 1$, $m = 0$ or 1 and $n = 1, 2, 3$) associated with two functionalities [X, Y = COOMe, $CH(OiPr)_2$, $CH(OMe)_2$, CHO, CH_2OH, CH_2Br, CH_2PPh_3]. We applied the preceding set of parameters to calculate the chemical shift of ethylenic carbon atoms C3 and C4 in these intermediates (Table 10). for **35**–**44**, having one double bond ($m = 0$) and two different functional groups very close to the unsaturation l, $n = 1$, the calculated shifts are sometimes different from the experimental data. This may be due to the steric and electronic interactions between the two functionalities and the double bond. This is particularly noticeable when a bulky (CH_2PPh_3) or a very polar (CHO) group is

Table 10. Chemical shifts of ethylenic carbons in monoethylenic bifunctionalized compounds: $l = 1$, $m = 0$, $n = 1$

			C3			C4			
Compound	X	Y	Calc.	Exp.	Diff.	Calc.	Exp.	Diff.	Ref.
35	$CH(OiPr)_2$	$CH(OiPr)_2$	126.51	126.59	−0.08	—	—	—	16
36	$CH(OiPr)_2$	CHO	129.81	129.75	0.06	120.29	120.66	−0.37	16
37	$CH(OiPr)_2$	CH_2OH	127.70	128.11	−0.41	127.24	127.39	−0.15	14
38	$CH(OiPr)_2$	CH_2Br	127.62	127.50	0.12	127.98	128.12	−0.14	14
39	$CH(OiPr)_2$	CH_2PPh_3	126.54	127.03	−0.49	127.74	128.25	−0.51	14
40	$CH(OiPr)_2$	COOMe		128.02			123.17		16
41	$CH(OMe)_2$	COOMe		127.07			123.33		16
42	$CH(OMe)_2$	CHO	128.79	128.47	0.32	120.70	120.76	−0.06	16
43	CHO	CHO	120.61	123.43	−2.82				16
44	CH_2OH	COOMe		129.89			123.84		16

involved. Nevertheless, we can assume that the olefinic carbon nearest to the most electronegative group is shifted upfield. This can be deduced from the data in Table 6, where the Δ2 and Δ5 parameters perfectly match the order of electronegativity: CHO > COOMe > $CH(OMe)_2$ > $CH(OiPr)_2$ > Ch_2OH, CH_2Br, CH_2PPh_3 > C=C.

The calculated shifts of bifunctionalized compounds **45–53**, having one or two double bonds and a methylcarboxylate group, are very close to the experimental data. In these skeletons, the aliphatic chain with two and three methylenes acts as a spacer and pushes away the two functionalities. Consequently, the assignment of all ethylenic carbon atoms is very accurate (Table 11). These last results illustrate very well the usefulness of our method for evaluating the chemical shift of any ethylenic carbon atom involved in *cis* (and skipped) double bonds.

Application to the chemical shift of ethylenic carbon atoms in precursors and analogs of arachidonic acid

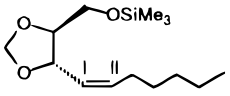
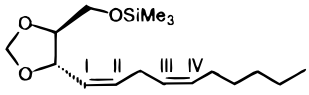
The heterocyclic AA (methyl ester) analog **61** and its precursors **54–60** are potential inhibitors of the cyclooxygenase pathway and may act as new biologically active compounds. In these structures, the ethylenic carbon atoms are directly bonded to a 1,3-dioxolane ring. Analyses of the NMR spectra show that the heterocycle induces both electric and steric field effects that are very different from those of other functionalities. During the course of the synthetic work we prepared **54** and **55** having one and two double bonds, respectively, on the same appendage of the heterocycle. We chose these two compounds as models to calculate the shift effects from a dioxolane because the silyloxymethyl group could mimic the expected steric effect arising from the other unsaturated chains. These products provide a new set of shift parameters from the 1,3-dioxolane ring at positions Δ1, Δ1′, Δ4 and Δ4′ to an unsaturated carbon atom. The $^{diox}\Delta 1$ and $^{diox}\Delta 1'$, then $^{diox}\Delta 4$ and $^{diox}\Delta 4'$ are calculated from the standard value given by olefin **3** and the experimental shifts measured in **54**, then in **55** (Table 12).

For the first time, the Δ1′ parameter appears greater than the corresponding Δ1. A very strong steric effect should be at the origin of such a result. The correct assignment of ethylenic carbon atoms has been confirmed by NMR experimentations on diene **55**: irradiations to determinate the chemical shifts of ethylenic protons, then a two-dimensional experiment to assign the ethylenic carbon atom shifts. Compounds **57–61** feature two *cis* double bonds directly bonded to the 1,3-dioxolane ring. These unsaturations are separated by two carbon atoms that give a *cis,cis*-1,5-diene moiety instead of a 1,4-diene structure. In order to calculate the chemical shifts of such unsaturated carbon atoms, we evaluated the parameters from one double bond at posi-

Table 11. Calculated and experimental chemical shifts of ethylenic carbon atoms in various bifunctionalized unsaturated compounds: $l = 1$, Y = COOMe

Compound	X	*m*	*n*		C3	C4	C6	C7	Ref
45	$CH(OiPr)_2$	0	3	Calc.	125.50	130.47			17
				Exp.	125.5	130.6			
				Diff.	−0.05	−0.20			
46	CHO	0	3	Calc.	119.30	133.79			17
				Exp	119.37	133.94			
				Diff.	−0.07	−0.15			
47	CH_2OH	0	3	Calc.	126.25	131.68			17
				Exp.	126.58	131.71			
				Diff.	−0.33	−0.03			
48	CH_2Br	0	3	Calc.	126.99	131.60			17
				Exp.	127.06	131.68			
				Diff.	−0.07	−0.08			
49	CH_2PPh_3	0	3	Calc.	126.75	130.52			17
				Exp.	126.76	130.99			
				Diff.	−0.01	−0.47			
50	$CH(OiPr)_2$	1	3	Calc.	124.70	129.89	128.84	128.82	14
				Exp.	124.83	129.90	128.89	128.89	
				Diff.	−0.13	−0.02	−0.05	0.07	
51	CHO	1	3	Calc.	118.50	133.20	127.74	129.47	14
				Exp.	118.55	133.07	127.73	129.51	
				Diff.	−0.05	0.14	0.01	−0.04	
52	$CH(OiPr)_2$	1	2	Calc.	124.79	129.67	129.37	127.83	17
				Exp.	124.66	129.64	129.26	127.73	
				Diff.	0.13	0.03	0.11	0.10	
53	CHO	1	2	Calc.	118.59	132.99	128.27	128.48	17
				Exp.	118.73	132.96	128.27	128.50	
				Diff.	−0.14	0.03	0.00	−0.02	

Table 12. Determination of parameters $^{diox}\Delta 1$, $^{diox}\Delta 1'$, $^{diox}\Delta 4$, $^{diox}\Delta 4'$ for compounds 54 and 55

Compound	Structure		I	II	III	IV
54		Calc.	129.99	129.99		
		Exp.	126.12	136.07		
		Diff.	$^{diox}\Delta 1 = -3.87$	$^{diox}\Delta 1' = 6.08$		
55		Calc.	126.43	134.12	128.07	130.29
		Exp.	126.41	134.15	126.77	131.31
		Diff.	0.02	−0.03	$^{diox}\Delta 4 = -1.3$	$^{diox}\Delta 4' = 1.02$

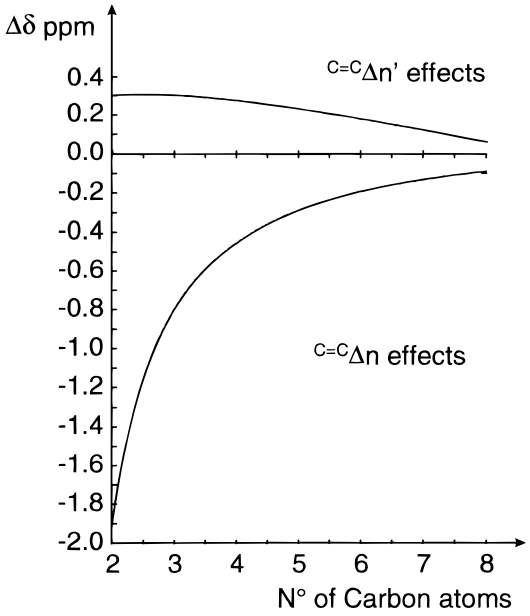


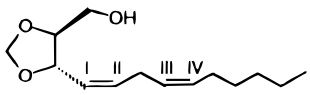
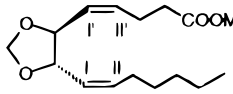
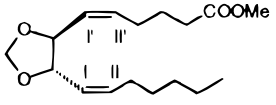
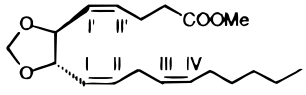
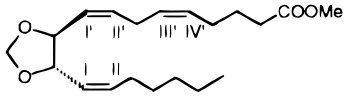
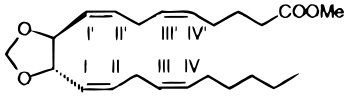
Figure 5. Parameters of ethylenic carbon atoms induced by *cis* double bonds (enlargement of Fig. 3).

tions Δ3, Δ3′, Δ6 and Δ6′ to an unsaturated carbon atom. The values presented in Table 3 lead to a graph that affords the required new parameters (Fig. 5). The chemical shifts of **56–61** were calculated with the new parameters. Comparison with the experimental data gives reasonable agreement (Table 13). Some differences are larger than found in previous applications, particularly on CII (0.16–0.62 ppm). This may be due to an inaccurate $^{diox}\Delta 1'$ value calculated from a silyl ether. A silyl group may induce a proximity effect larger on CII than on CI. This effect vanishes in other compounds **56–61** even though the same parameter value is applied. Nevertheless, this has no effect on assigning the correct chemical shift to the olefinic carbon atoms. It is noteworthy that the method works very well for both ester and aliphatic chains on the dioxolane ring.

CONCLUSION

We have shown with many examples that the ^{13}C chemical shifts of ethylenic carbon atoms depend on

Table 13. Calculated and experimental chemical shifts of ethylenic carbon atoms in precursors and AA analogs

Compound	Structure		I	II	III	IV	I′	II′	III′	IV′
56		Calc.	126.43	134.15	126.77	131.31				
		Exp.	126.47	134.77	126.47	131.45				
		Diff.	−0.04	−0.62	0.30	−0.14				
57		Calc.	124.95	136.44			127.01	133.68		
		Exp.	124.83	136.96			126.96	133.53		
		Diff.	0.12	−0.52			0.06	0.15		
58		Calc.	125.09	136.39			126.48	134.67		
		Exp.	125.08	136.80			126.47	134.05		
		Diff.	0.01	−0.41			0.01	0.62		
59		Calc.	125.25	134.52	126.54	131.49	126.82	133.86		
		Exp.	125.25	134.84	126.77	131.24	126.65	133.94		
		Diff.	0.00	−0.32	−0.23	0.25	0.17	−0.08		
		Calc.	125.11	136.54			125.68	134.09	127.76	129.80
		Exp.	124.92	136.76			125.53	134.18	127.95	129.56
		Diff.	0.19	−0.22			0.15	−0.09	−0.19	−0.24
61		Calc.	125.41	134.62	126.58	131.49	125.44	134.27	127.67	129.86
		Exp.	125.24	134.72	126.65	131.16	125.48	134.33	127.95	129.63
		Diff.	−0.17	−0.10	−0.07	0.33	−0.04	−0.06	−0.28	0.23

steric and electric field effects from functionalities around the double bond. Several sets of shift parameters for various functions such as ester, acetals, aldehyde and alcohol have been evaluated. This study includes the mutual effects of one or more double bonds separated by long distances. Moreover, we found that all the effects are simply cumulative regardless of the number of functionalities or unsaturated groups. The method is applicable to a wide variety of molecules and provides a convenient way to calculate the chemical shifts of all their ethylenic carbon atoms. Extension of such sets of parameters to all types of carbon chains or skeletons mixed with other databases should greatly help chemists to predict chemical shifts and to identify compounds by ^{13}C NMR spectroscopy.

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