pronounced micellar catalysis may be the consequence, in part, of an energy loss in transferring the initial state of the substrate to a more polar environment in the transition state. It also should be noted that **3** interacts more strongly than **2** with the protons adjacent to the sulfonate head group (*i.e.*, $\mathrm{C}H_2\mathrm{SO}_3$).

Our general conclusion is that considerable care is required in interpreting solubilization sites in micellar systems, since not only is the structure of micelles incompletely understood but also the reactants, transition states, and products may have different environments in the micellar phase.

Additivity in the Carbon-13 Chemical Shifts of 1,2-Disubstituted Ethanes[1]

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^{13}C chemical shifts were obtained on 54 compounds of the type XCH_2CH_2Y, with X and Y varying over the groups H, CH_3, $CH{=}CH_2$, $C{\equiv}CH$, $C{\equiv}N$, C_6H_5, $COCH_3$, OH, OCH_3, Cl, Br, I, and NO_2. The observed range of shifts was 80 ppm. The data were analyzed in terms of an additivity model, with a characteristic α- and β-substituted effect assigned to each group X and Y according to a linear regression analysis. The standard deviation of this analysis was 2.5 ppm, and the groups showing generally poorest additivity behavior were I and H.

Introduction

The use of the ^{13}C nmr (cmr) chemical shift parameter for studying substituent effects emerged early in the history of cmr research. Much of the cmr work of the 1960's was concerned with exploring and cataloging the gross patterns of substituent effects on ^{13}C shieldings, and many of these gross patterns are now fairly well characterized at an empirical level.

One aspect of substituent effects to receive early attention is the extent to which they are additive. A general type of defining relationship for additivity effects in ^{13}C chemical shifts can be summarized in eq 1.

$$^{i}\delta_{P}^{A,B,\ldots} = {}^{i}\delta_{P}^{A} + {}^{i}\delta_{P}^{B} + \ldots \qquad (1)$$

In this equation, $^{i}\delta_{P}^{A,B,\ldots}$ represents the chemical shifts of the *i*th specific carbon of a "polysubstituted" species related to a parent compound P by substitution of the groups A, B, . . . at precisely defined positions on P, measured with respect to the *i*th carbon of P as the chemical shift reference. The symbol $^{i}\delta_{P}^{A}$ represents the chemical shift of the *i*th carbon of a species related to P by the introduction of a specific substituent A at a specific position. An alternative and equivalent representation of the additivity relationship is embodied in eq 2, where $^{i}\delta_{P,R}$ represents the chemical shift of the *i*th

$$^{i}\delta_{R}^{A,B,\ldots} = {}^{i}\delta_{P}^{A} + {}^{i}\delta_{P}^{B} + \ldots + {}^{i}\delta_{P,R} \qquad (2)$$

specific position in P with respect to some chemical shift reference line R.

Previous studies of additivity relationships in ^{13}C chemical shifts,[3-12] based upon relationships like those of eq 1 or 2, or upon specialized variations of them, have been concerned largely with exploring the kinds of systems for which the relationships are applicable within certain arbitrary limits, and to search for specific cases in which the failures of additivity relationships are most dramatic. Such cases of large deviation have been

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Table I: ^{13}C Chemical Shifts and Additivity Relationships for X–C^{x}H$_2$–C^{y}H$_2$–Y Compounds[a]

X	Y	δ^x	δ^y	δ^x_{calcd}[b]	δ^y_{calcd}[b]	Method[c]	Source[d]	δ^i[e]	δ^j
OH	OH	−36.47	−36.47	−37.89	−37.89	1	Ea		
Br	Br	−3.23	−3.23	−6.20	−6.20	1	Ea		
Cl	Cl	−16.93	−16.93	−19.03	−19.03	1	Ea		
$C^iH{=}C^jH_2$	$CH{=}CH_2$	−6.31	−6.31	−6.66	−6.66	1; C	Al		
OC^iH_3	OCH_3	−45.02	−45.02	−44.84	−44.84	1; A, B	Al	−31.14	
H	H	+20.25	+20.25	+19.19	+19.19	2	M		
C^iH_3	CH_3	+1.84	+1.84	+2.48	+2.48	2; B, C, E[g]	M	+13.57	
C^iN	CN	+12.58	+12.58	+12.96	+12.96	2; C	Ea	−91.57	
C_6H_5	C_6H_5	−10.72	−10.72	−9.53	−9.53	2; C	Ea		
I	I	−1.67	−1.67	+9.55	+9.55	2	Al		
$C^iOC^jH_3$	$COCH_3$	−9.83	−9.83	−10.08	−10.08	2; C, B	Ea	−179.61	
I	C_6H_5	+20.99	−13.20	+17.01	−16.99	1; C	Ea		
I	C^iH_3	+18.26	0.00	+15.43	−3.40	1; A, B	Ea	+11.63	
I	OH	+13.50	−40.02	+14.68	−43.02	1; C, F	Ba		
I	H	+28.27	+6.19	+23.59	+5.15	1; C, E[f]	Ea		
Br	OC^iH_3	−3.18	−45.47	−4.17	−47.87	1; C	Fr	−31.16	
Br	C_6H_5	−5.76	−12.29	−4.81	−10.92	1; A	Ba		
Br	$CH{=}CH_2$	−4.45	−10.10	−2.21	−10.65	1; A	Ba		
Br	Cl	−3.81	−16.41	−6.32	−18.91	1; C	Ba		
Br	CN	+0.76	+4.88	+0.04	+6.72	1; A	Ba		
Br	OH	−7.69	−35.73	−7.14	−36.95	1; C	Ba		
Br	C^iH_3	−8.06	+0.64	−6.39	+2.67	1; A, B	Al	+14.29	
Br	H	+0.11	+7.86	+1.77	+11.22	1; C	Ea		
Cl	CN	−12.22	+5.21	−12.67	+6.60	1; C, F	Ea		
Cl	H	−13.03	+8.35	−10.94	+11.10	2; C, E[f]	M		
Cl	C_6H_5	−17.07	−12.08	−17.52	−11.04	1; A	Ea		
Cl	COC^iH_3	−18.80	−11.76	−16.15	−12.96	1; C	Fr	−2.51	
Cl	C^iH_3	−20.04	+0.83	−19.10	+2.55	1; A, B	Ba	+15.07	
Cl	OH	−19.16	−35.87	−19.85	−37.07	1; C	Ea		
CN	C_6H_5	+8.26	−4.23	+8.11	−4.68	1; C	Ea		
CN	OC^iH_3	+8.61	−40.27	+8.75	−40.63	1; A	CS	−31.28	
CN	C^iH_3	+8.40	+7.72	+6.53	+8.91	1; A, B	Ea	+14.19	
CN	H	+16.49	+16.72	+14.69	+17.46	1; B	Ea		
C^iN	OH	+5.72	−30.52	+5.78	−30.71	2; C	Al	−92.89	
OH	H	−30.15	+9.30	−28.98	+10.28	1; A, B	Al		
OH	C^iH_3	−36.65	+1.25	−37.14	+1.73	1; A, B	Al	+17.10	
OH	$CH{=}CH_2$	−34.57	−10.23	−32.96	−11.59	1; A	Ba		
OH	OC^iH_3	−34.15	−47.26	−34.92	−47.81	1; C	CS	−31.24	
OH	C_6H_5	−36.16	−12.24	−35.56	−11.86	2; C	Ea		
OH	$C{\equiv}CH$	−43.39	+4.52	−37.37	+5.70	1; C, F	Al		
OC^iH_3	H	−40.67	+12.37	−38.90	+13.25	1; C	P	−30.40	
OC^iH_3	C^jH_3	−47.37	+4.17	−47.06	+4.70	1; C	P	−30.66	+17.05
COC^iH_3	H	−9.17	+19.60	−4.87	+13.98	1; B, C	Ea	−1.50	
COC^iH_3	C^jH_3	−18.10	+9.76	−13.03	+5.82	1; A, B, C	Ea	−1.96	+13.69
COC^iH_3	$CH{=}CH_2$	−0.91	−15.41	−8.85	−7.89	1; A	Al	−2.22	
C_6H_5	H	−1.91	+11.64	−2.95	+12.61	2; A, C	Ea		
C_6H_5	C^iH_3	−11.12	+2.50	−11.11	+4.06	1; A, B	CS	+13.49	
C_6H_5	$CH{=}CH_2$	−8.59[i]	−8.44[i]	−6.93	−9.26	1; C	Al		
NO_2	C^iH_3	−50.19	+6.04	−51.00	+6.41	1; B, D	Ea	+16.83	
NO_2	H	−43.65	+15.33	−42.84	+14.96	1; D	Al		
$C^i{\equiv}C^jH$	C^hH_3	+6.69	+4.96	+6.44	+2.25	1; A, B	KK	−56.51	−41.01
$C^iH{=}C^jH_2$	H	0.00	+14.28	−2.68	+15.21	2; B, C	Ph	−128.06	−100.89
$CH{=}CH_2$	C^iH_3	−8.98	+4.83	−10.84	+6.66	1; C	KK	+14.00	
$C^i{\equiv}C^jH$	H	+15.09	+13.57	+14.60	+10.80	2; C	Fa	−58.55	−40.92
CH_3	H	+10.55	+10.83	+10.64	+11.03	2; C, E[g]	M		

[a] Chemical shifts in parts per million with respect to C_6H_{12}. Positive numbers refer to higher shielding. [b] Values calculated according to eq 3. [c] The numbers 1 and 2 refer to the frequency sweep and Fourier transform modes, respectively. The designations A, B, C, D, and E refer to the methods of peak assignment employed, as indicated in the text. The designation F refers to use of internal dioxane as the reference rather than C_6H_{12}, for reasons of solubility, using the relationship $\delta^s_{C_6H_{12}} = \delta^s_{C_4H_8O_2} - 40.10$ ppm in order to convert the shift of species s with respect to dioxane to the shift of species s with respect to cyclohexane. [d] The source of the compound, according to the key: Ea, Eastman; Al, Aldrich; KK, K and K; Ba, J. T. Baker; M, Matheson; Fr, Frinton; CS, Chemical Samples; Fa, Farchan; Ph, Phillips; P, prepared as indicated in the Experimental Section. [e] Chemical shift of the C^i substituent carbon, as indicated in column X or Y. [f] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961). [g] Reference 6. [h] Chemical shift of the methyl carbon is +14.14 ppm. [i] Assignments of δ^x and δ^y may be reversed.

viewed as betraying a special kind of pairwise interaction that is either absent or largely additive in the cases for which the equation holds within the specified limits. These patterns of additivity and deviations from additivity can be important in providing guidelines and tests for emerging theories of chemical shifts. From a more practical point of view, to the extent that additivity relationships are reasonably valid, they provide a valuable means of making peak assignments and in making optimum choices of experimental systems; these advantages are especially apparent if there is a reliable basis for predicting for what cases one is likely to encounter large deviations from the additivity relationship.

Most of the previously reported results on additivity relationships in ^{13}C chemical shifts were based upon data in which uncertainties of ±1 ppm are not uncommon. Such uncertainties are appreciable fractions of the magnitude of effects or relationships that may be of interest. As currently available methods of both the continuous wave and Fourier transform types are capable of providing data routinely with precision limits smaller than the above by nearly a factor of 100, a more detailed and precise appraisal seems in order. The present report is concerned with exploring additivity relationships in high-precision chemical shifts in 54 compounds of the type XCH_2CH_2Y, 1,2-disubstituted ethanes, including ethyl compounds ($X = H$).

Experimental Section

Materials. All compounds except methyl ethyl ether and methyl propyl ether were obtained from commercial suppliers and were used as obtained unless gc or pmr analysis showed purity of less than 98%. In those cases, the materials were distilled. The commercial source of each substance is indicated in Table I. The methyl ethyl ether and methyl propyl ether were prepared by standard Williamson synthesis procedures.[13]

Measurements. The cmr spectra were obtained on natural-abundance samples in one of two modes: (1) center band, frequency sweep at 25.1 MHz on a ^{19}F-locked, synthesizer-based spectrometer system using time averaging, based on modifications of a Varian HA-100 spectrometer described previously;[14] (2) pulse-Fourier-transform mode at 22.6 MHz using a Digilab pulse and FTS/NMR-3 data system interfaced to a Bruker HFX-90 spectrometer. In each mode, both coherent and incoherent proton decoupling were employed. Unless sample volatility required probe cooling, the sample temperature was typically 44 ± 1° in method 1 and typically 38° in method 2. Data precision of about ±0.02 ppm was typical in both modes. Samples were neat liquids containing 10% cyclohexane as an internal standard; this concentration was chosen because of sensitivity limits of method 1, with which the project was initiated.

Results and Discussion

Table I contains the ^{13}C chemical shifts of 54 compounds of the type XCH_2CH_2Y, with X and/or Y spanning the following range of groups: H, CH_3, $CH{=}CH_2$, $C{\equiv}CH$, $C{\equiv}N$, C_6H_5, $COCH_3$, OH, OCH_3, Cl, Br, I, NO_2. Assignments of the carbon resonances were based on the following five approaches: (A) the use of coherent proton decoupling in conjunction with previously assigned proton resonances; (B) off-resonance proton decoupling, for distinguishing between ^{13}C resonances of the two methylene groups of interest and resonances of the carbons in a substituent; (C) comparison with similar compounds with assigned ^{13}C resonances, including the *gross* application of additivity relationships, where such large shift differences are predicted that deviations of a few parts per million would not introduce uncertainties; (D) broadening due to an adjacent ^{14}N nucleus; and (E) resonances for the species have been assigned previously. The specific method(s) of assignment used for each compound is also shown in Table I. Also included in Table I are ^{13}C chemical shifts of some substituent carbons.

In analyzing the data in terms of exploring the extent of validity of additivity relationships, we start with a model that assumes that each substituent X exerts a distinct substituent effect at both the α and β positions. Thus, for a compound $X{-}C^xH_2C^yH_2{-}Y$

$$^{x}\delta = \Delta_\alpha^{\ x} + \Delta_\beta^{\ y} + \delta_{\mathrm{cx}}^{\ \mathrm{E}} \qquad (3)$$

$$^{y}\delta = \Delta_\alpha^{\ y} + \Delta_\beta^{\ x} + \delta_{\mathrm{cx}}^{\ \mathrm{E}} \qquad (4)$$

where δ^x is the chemical shift of the C^x carbon with respect to cyclohexane, $\Delta_\alpha^{\ x}$ is the substituent effect exerted by X at the α position, and $\delta_{\mathrm{cx}}^{\ \mathrm{E}}$ is the chemical shift of ethane with respect to cyclohexane. The data in Table I were subjected to a linear regression analysis[15] based upon eq 3 and 4, and the resulting computed chemical shifts are included in Table I. The substituent effects $\Delta_\alpha^{\ x}$ and $\Delta_\beta^{\ x}$ found in this way are collected in Table II. This set of substituent parameters, which accounts for chemical shifts covering a range of 80 ppm, leads to a standard deviation of 2.48 ppm. This is a measure of reliability of this additivity model, with two parameters per substituent and only one basic "structural" parameter. The value of this last parameter was given as 19.19 ppm by the linear regression. This value compares to 20.25 ppm, which was obtained by direct measurement. These results lead to the conclusion that for most X, Y combinations, the chemical shifts can be predicted within useful limits without explicit recognition of the pairwise combinations; only

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parameters that specifically recognize each separate substituent are necessary. While there is considerable precedent for such relationships in the cmr literature, these results are still noteworthy in the light of the high concentrations employed and the attendant medium effects that are expected.

Table II: Additivity Constants for Substituent Effects on ^{13}C Shielding

X	Δ_α^{X} [a]	Δ_β^{X}
I	+4.40	−14.04
CN	−4.50	−1.73
C≡CH	−4.59	−8.39
CH_3	−8.55	−8.16
Br	−17.42	−7.97
$CH{=}CH_2$	−21.87	−3.98
$COCH_3$	−24.06	−5.21
C_6H_5	−22.14	−6.58
Cl	−30.13	−8.09
OH	−48.17	−8.91
OCH_3	−58.09	−5.94
NO_2	−62.03	−4.23

$\delta_{cx}^{E} = 19.19$

[a] Values in parts per million, as defined in eq 3 and 4.

Of the 99 shifts of the 54 compounds which were characterized in the analysis, only 15 shifts (corresponding to 11 compounds) showed deviations from additivity, *i.e.*, difference between shift calculated according to eq 3 and experimental shift, greater than or equal to 3 ppm. Within the framework of the working model, such deviations could be due to any of the following effects, some of which are interrelated: (i) conformational effects, (ii) specific intermolecular or intramolecular interactions between X and Y, (iii) variation in C–C–H and/or C–C–X bond angles, and (iv) medium effects. While it is not likely that one could determine the importance of each of these contributions at the present time, two points are worth noting. First, all of the five iodine-containing compounds fall into the list of ten compounds that give large deviations. Iodine, as a substituent, is well known to introduce large and poorly characterized influences into ^{13}C chemical shifts;[16–20] the influences have been attributed from time to time to intramolecular and intermolecular neighbor anisotropy effects, intramolecular and intermolecular dispersion effects, and steric interactions. The second point is that three of the eleven compounds on this list of large deviations have X = H. This may indicate that such compounds have an uncommonly low level of X–Y interaction or related geometry perturbations, considerably lower than the average, so they appear to be the deviant compounds.

It is reasonable that to a considerable extent the factors responsible for the substantial deviations between predicted and experimental chemical shifts that occur in some cases tend to mutually compensate for each other in the linear regression analysis. In this sense, the substituent parameters given in Table II can be considered reasonable estimates of the intrinsic substituent effects that operate at the carbon attached to the substituent and at the carbon atom separated from the substituent by one CH_2 group. The substituent parameters given in Table II are not susceptible to fundamental interpretation by any theories currently available. However, they should provide meaningful guidelines for emerging theories of substituent effects on ^{13}C chemical shifts, as well as for the empirical prediction of experimental chemical shifts.

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