

Notes

Determination of Substituent Effects by Multivariate Analysis in the ^{13}C NMR Chemical Shifts of 3-Substituted 4-Aminoethoxyphenylacetic Acid Derivatives

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As in all aspects of high-resolution NMR, the importance of correct ^{13}C chemical shift assignment in organic compounds can never be overstated to predict the nature of molecular structures and of substituents. Previously, we reported that the application of empirical relationship approach based on substituent effects to assign ^{13}C chemical shift was the lack of flexibility and restriction on the doubly substituted aromatic compounds.¹ To cope with these difficulties the new developments of theoretical treatment are continuously being made by various MO methods, single substituent parameters (SSP), and dual substituent parameters (DSP).² However, those analyses have the correlation within the scope of specific structural cases.

Recently a new interpretation of spectroscopic properties based on multivariate analysis was introduced.^{3,4} Principal component analysis or the closely related factor analysis is widely used as multivariate analysis. Its major advantage over other regression analyses is based on the fact that no prior knowledge of the relevance of any substituent constant is required.⁵

We now report here the comparison study of two theoretical calculations, factor and DSP analysis, and experimental assignment. The compounds analyzed are 3-substituted 4-(2-aminoethoxy)phenylacetic acid derivatives, **1**, **2**, **3**, **4**, **5**, and **6** which show analgesic effect and belong to capsaicinoids.⁶

Experimental

The preparation of the compounds has been already published.⁶ The derivatives were prepared from appropriately substituted 4-hydroxyphenylacetamides by bromoethylation, azide substitution, and reduction of the azide with palladium catalyst except for nitro derivative where triphenylphosphine-water was used. OH derivative was prepared from 3-benzyloxy-4-hydroxyphenylacetamides.

All spectra were recorded at ambient temperature on a Bruker AM-300 NMR spectrometer except for compounds **4** and **6** which were obtained on a Bruker AMX-500 NMR spectrometer. ^1H and ^{13}C chemical shifts were referenced relative to TMS, but were measured against the central DMSO peaks at 2.49 and 39.5 ppm, respectively. All 2D spectra were recorded by using pulse programs supplied by Bruker. Chemical shift analysis was done on personal computer by STATGRAPHICS program.⁷

Results and Discussion

Spectral assignment. We assigned the ^1H and ^{13}C peaks of aromatic region on the basis of 2D-COSY, HETCOR, and COLOC spectra.⁸ The protons 2, 5, and 6 in the compounds **2**, **3**, **5**, and **6** were clearly separated from those of 3,4-dimethylphenyl moiety and therefore were easily assigned on the basis of substituent effect and coupling patterns. However, the protons 2, 5, and 6 in the compounds **1** and **4** were overlapped with those of 3,4-dimethylphenyl group. Consequently, 2D-NMR techniques were required for the assignment of overlapped peaks.

The aromatic region of COSY spectrum of the compound **4** is shown in Figure 1. Partial HETCOR spectrum of the compound **4** is shown in Figure 2. From Figures 1 and 2, all the protons and methine carbons are assigned.

Finally, we applied COLOC pulse sequence for the assignment of quaternary carbons. We used the values of three-bond coupling constants which are known to be in the range of 5 to 12 Hz. Representative COLOC spectrum of the compound **4** is recorded with $J=9$ Hz and shown in

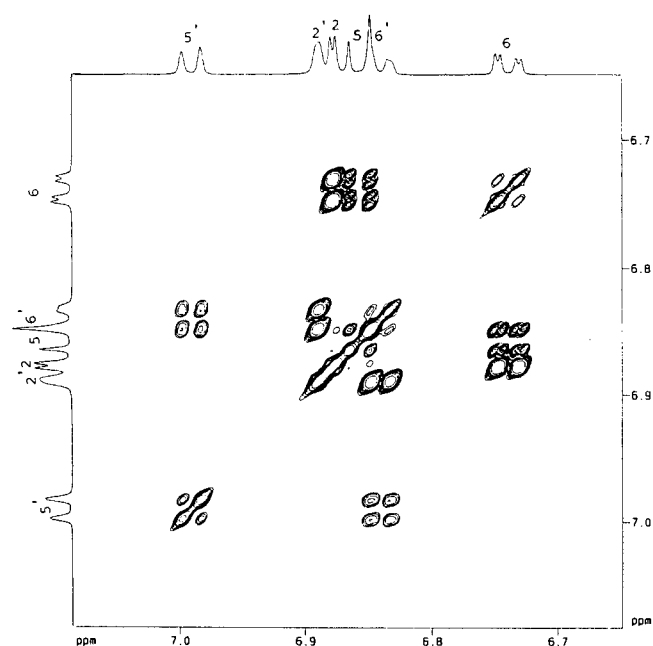


Figure 1. Partial 2D COSY spectrum of compound **4**.

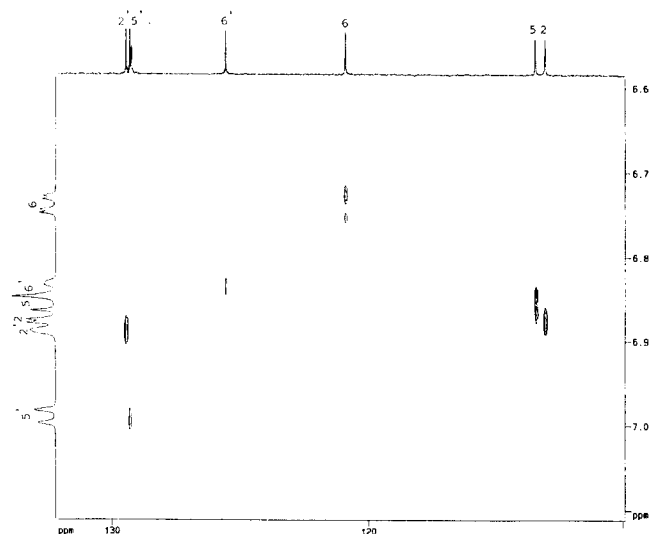


Figure 2. Partial 2D C-H correlation spectrum of compound 4.

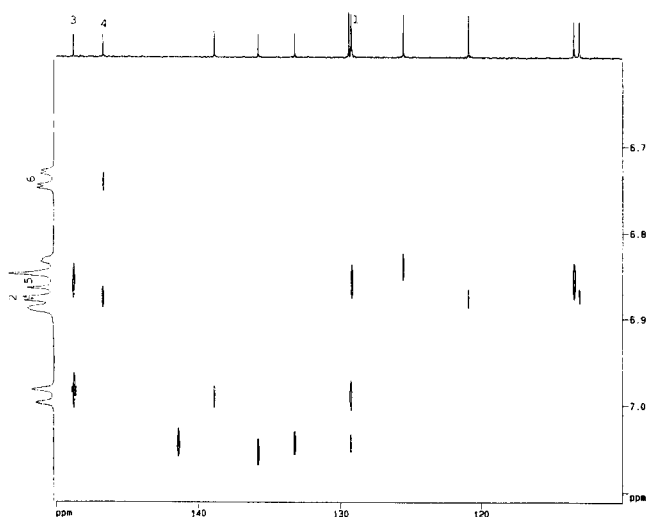


Figure 3. COLOC spectrum of compound 4 acquired with $J = 9$ Hz.

Figure 3. All the carbons were completely assigned on the basis of the methods mentioned above and the results of six carbon chemical shifts of phenyl rings are listed in Table 1.

Theoretical Analysis of Chemical Shifts. The relationship between ^{13}C chemical shift and substituent parameters suggested by Taft⁹ can be expressed as follow:

$$\delta = \delta_0 + a\sigma_F + b\sigma_R^0 \quad (1)$$

where δ_0 , a , and b are calculated chemical shifts and coefficients determined from the DSP analysis, respectively; σ_F and σ_R^0 are the substituent constants given by Taft. The results of DSP analysis of the ^{13}C chemical shift of phenyl ring carbon by using Eq. (1) are summarized in Table 2.

The values of the correlation coefficient (r) in Table 2 show that there are good correlations at *ortho* and *para* carbons, but considerable deviations are observed at *ipso* and *meta* carbons in respect to the substituent. These trends are especially significant in compound 2 and 3. Moreover, in the cases of OH substituent (3), calculated chemical shifts of carbons 3 and 4 are inverted.

In order to describe the variability in a multivariate data

Table 1. ^{13}C Chemical Shifts (ppm) of Phenyl Ring Carbons

Compounds	Carbon Number					
	1	2	3	4	5	6
1	128.51	129.89	114.22	157.29	114.22	129.89
2	128.91	114.55	137.75	144.35	111.65	116.40
3	130.59	117.00	148.27	145.53	116.17	119.20
4	129.25	113.07	148.82	146.72	113.46	120.93
5	129.65	116.48	151.45	145.04	114.91	125.05
6	129.16	125.21	139.00	150.20	115.27	135.19

Table 2. Results of Dual Substituent Parameters Analysis^a

Carbon	δ_0	a	b	r^b	SD^c
1	129.37	0.02	-0.45	0.1700	0.65
2	126.67	-7.09	22.61	0.9677	1.19
3	117.86	41.27	-38.08	0.7267	4.28
4	151.59	-4.68	11.58	0.9356	0.82
5	113.62	2.73	1.29	0.5011	1.53
6	122.99	14.30	17.33	0.9973	0.54

^a σ_F , σ_R^0 values taken from ref. 2. ^b Correlation coefficient of DSP analysis. ^c Residual standard deviation.

set, factor analysis which is an alternative to regression analysis is widely used. The ^{13}C substituent induced chemical shifts (SCS) of individual substituent were obtained by the subtraction of the chemical shift of compound 1 from the target molecules. The correlation matrix and standardized data matrix were used for the assessment. Each data point, $d_{r,c}$, in an autoscaled data matrix could be represented by equation (2)⁵:

$$d_{r,c} = d_c + a_{1,c}f_{r,1} + a_{2,c}f_{r,2} + \dots + \epsilon \quad (2)$$

where d_c is a variable mean, a is a factor loading, f is a factor score, and ϵ is the residue unexplained by the factor model. The theoretical data calculated from two factor analysis gave the result with a residual standard deviation of 1.50 ppm. Whereas 0.55 ppm standard deviation was observed by three factors, the use of four factors produced data with the error of zero which was lower than experimental error. These indicate that three factors are required to describe the SCS. The results of three factor analysis are listed in Table 3.

The first factor, a_1 , shows acceptable correlations with mesomeric parameters and accounts for most parts of variances at *ortho* and *para* positions. This fact suggests that the first factor may be a mesomeric factor. However, the

Table 3. Results of Factor Analysis

Carbon No.	Factor loadings ^a			Communalities ^b			SD ^c
	a_1	a_2	a_3	Factor1	Factor2	Factor3	
1	-0.175	0.959	0.210	0.010	0.870	0.115	0.05
2	0.881	0.219	-0.392	0.931	0.000	0.047	0.70
3	-0.189	0.400	0.896	0.109	0.635	0.255	0.23
4	0.942	-0.050	-0.121	0.870	0.010	0.024	0.71
5	0.493	0.836	0.242	0.275	0.718	0.007	0.02
6	0.988	0.004	0.006	0.913	0.000	0.064	1.12

^a Obtained by varimax rotation. ^b Fraction of total variance explained by that factor. ^c Residual standard deviation.

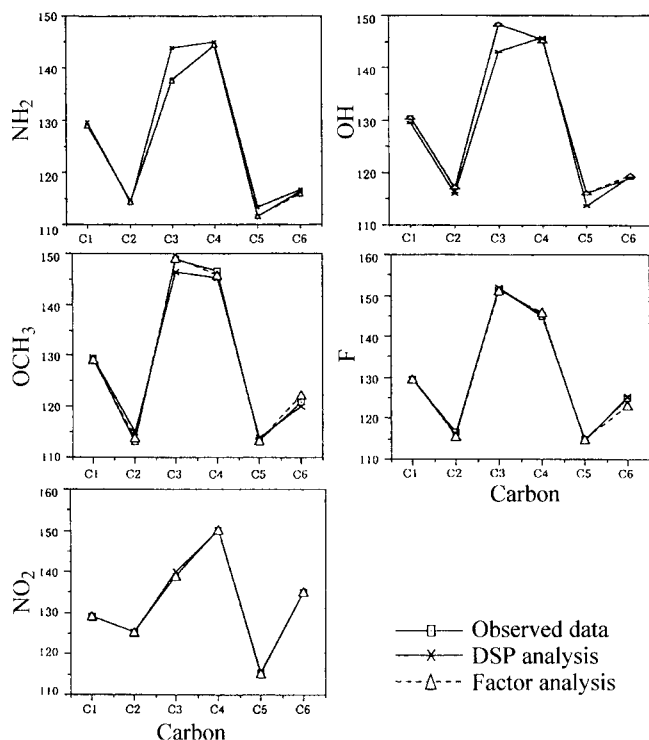


Figure 4. Plot of carbon-13 chemical shift calculated by DSP and factor analysis.

second factor, a_2 , has no correlations with commonly used empirical parameters. Considering the values of communalities, this effect is dominated at ipso and meta carbons and it may be considered as an electric field effect or a steric effect. The third factor, a_3 , has some correlations with substituent electronegativities^{10,11} and shows the pattern which diminishes with increasing distance from the position of substitution. This behavior is very similar to that of inductive effect. ¹³C chemical shifts reproduced by two

methods are plotted in Figure 4 and compared with the observed data. It can be seen clearly that DSP analysis gives a over- and/or underestimated results at carbons 3 and 5 in the cases of NH₂, OH, and OCH₃. However, the results of three factor analysis are in full accord with the observed data. This implies that extra parameter should be needed to explain the ¹³C chemical shifts of polysubstituted benzenes or that empirical parameters should be corrected in the case of polysubstituted benzenes.

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Zinc Oxide Nano-Cluster Formation in Zeolites

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The quantum size effects in semiconductor clusters have been investigated in the hope of developing a novel type of opto-electronic devices.¹⁻³ It is possible to generate well-defined clusters in zeolite pores, which would provide fine tuning of electronic properties using large variety of zeolites with different cage sizes if the zeolite pores are successfully filled with semiconductor particles. The elemental clusters, such as Se and Te clusters,³ and compound clusters, such as CdO, CdS, WO, GaP and CdSe clusters, are successfully embedded in zeolites.⁴⁻⁶ The elemental clusters are synthesized by direct absorption from the vapor phase. The compound

clusters are usually synthesized by ion-exchange in aqueous solution or deposition of MOCVD reagent, followed by subsequent treatments. For the case of ZnO, there are sparse reports on the formation and characterization of ZnO cluster in zeolite. The value of such clusters would be promising if taking advantage of the useful properties of ZnO-ZnO nano interface.^{7,8} We report ZnO cluster formation in zeolite Y and zeolite A by oxidation of Zn loaded zeolite, which was synthesized by Zn vapor deposition.⁹ Small shift of peaks and change of relative peak intensities in XRD spectra of the samples from those of zeolites prior to Zn vapor