Carbon-13 Nuclear Magnetic Resonance Spectra of *p*-Aminobenzoic Acid Oligomers: Range Dependence of Additive Substituent Effects

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Received January 22, 1978; revised May 22, 1978

Analysis of ¹³C chemical shifts of *p*-aminobenzoic acid oligomers indicates that ¹³C NMR additivity rules of 1,4-phenylene derivatives are distorted by interactions among substituents. These interactions are sharply attenuated, and additivity rules become more exact, as the substituents are placed farther apart. Additivity deviation terms of amino-substituted monomeric and dimeric series are correlated with corresponding terms of analogous nitro-substituted series.

INTRODUCTION

Carbon-13 NMR chemical shifts of nonequivalent carbon atoms in any series of monosubstituted aromatic derivatives may be expressed in ppm relative to the unsubstituted parent compounds according to Eq. [1](1, 2).

$$\Delta \delta_x^{(k)} = \delta_x^{(k)} - \delta_H^{(k)}.$$
 [1]

Here subscripts x and H refer to x-substituted and parent compounds respectively, and superscript (k) is the nonequivalent carbon index. Since chemical shifts $\delta^{(k)}$ are typically reported in ppm downfield from TMS, $\Delta \delta_x^{(k)}$ values have units of ppm where positive signs indicate downfield displacements. These values are known as substituent induced chemical shift effects and will be hereafter referred to as substituent displacements.

Chemical shift measurements of several series of di- and trisubstituted benzene derivatives have shown that substituent displacements are additive within <2 ppm over a chemical shift range of 50–60 ppm (2). This additivity rule excludes series with sterically interacting substituents such as ortho-phenylene derivatives (2), and may be stated in terms of Eq. [2],

$$\delta_{xy}^{(k)} = \delta_H^{(k)} + \Delta \delta_x^{(k)} + \Delta \delta_y^{(k)}, \qquad [2]$$

where subscripts y and xy refer to y-substituted and x, y-disubstituted aryl derivatives respectively. The <2 ppm deviation from additivity is small in relation to the chemical shift spectrum of aromatic carbon nuclei, and has proven exceedingly useful in spectral assignments of phenyl derivatives. On the other hand, relative to the 0.01-0.05 ppm reproducibility currently obtainable in Fourier transform instruments, it is significant and merits further attention. Deviations from additivity in meta and para disubstituted benzenes have been discussed in terms of substituent interactions transmitted through the phenylene ring (3). In the styrene series, for instance, plots of α , β -vinyl carbon shifts as well as corresponding electron densities vs weighted field and resonance components of $\sigma \rho$ Hammett parameters are linear (3, 4). These observations suggest that field and conjugative interactions between the vinyl group and para (or meta) substituents distort additivity rules of ¹³C NMR substituent displacements in this series. Internal shift correlations of 2,2' and 3,3' protons among several series of 1,4-phenylene derivatives have also been assessed in terms of substituent-substituent interaction parameters (5).

As more complex molecules are studied by 13 C NMR spectrometry, peak assignment of nonequivalent carbons becomes progressively more challenging. In the absence of heteronuclear coupling information, isotopic substitution seems to be the method of choice in this field, but becomes less practical with increasing molecular size. It appears to us that further study of the scope of substituent additivity rules in multi-substituted aryls as a representative class of molecules might be useful at this time. We therefore wish to raise the following questions: (1) What is the intersubstituent range dependence of 13 C NMR additivity rules in these systems? (2) When aryl substituents are placed at close range, the chemical shifts of intervening carbons would be expected to reflect substituent-substituent as well as substituent-aryl interaction effects. To what extent are parameters related to each interaction extractable from 13 C NMR shifts of multi-substituted aryls?

The first question is approached by studying chemical shifts of the homologous p-aminobenzoyl series I-III as a function of x and y.



The second question is explored by correlating additivity deviations in one series of aromatic derivatives (I, II $x = NH_2$) with deviations in analogous series (I, II $x = NO_2$) of comparable size and geometry. In the expectation that answers to these questions could provide useful information related to chemical shift assignments and eventually to electronic and reaction parameters of aromatic molecules, we report a study of substituent displacement in *p*-aminobenzoic acid oligomers.

ASSIGNMENTS

Chemical shifts of aromatic carbon nuclei of p-aminobenzoic acid monomers (I), dimers (II) and trimers (III) are listed in Tables 1, 2, and 3, respectively. All oligomers were assigned according to the following comparative criteria:

| ompoun | d | | | | | |
|--------|-----------------|--------------------|--------|--------|--------|--------|
| # | x | у | C1 | C2 | C3 | C4 |
| 1 | NH ₂ | CO₂H | 153.07 | 112.55 | 131.15 | 116.96 |
| 2 | NH_2 | CO ₂ Me | 153.37 | 112.60 | 130.97 | 115.79 |
| 3 | NH_2 | CO ₂ Et | 153.32 | 112.56 | 130.92 | 116.07 |
| 4 | NH_2 | CH ₃ | 145.96 | 114.02 | 129.15 | 123.93 |
| 5 | NH_2 | Br | 147.96 | 115.72 | 131.21 | 105.97 |
| 6 | NH_2 | OH | 140.56 | 115.21 | 115.50 | 148.19 |
| 7 | NH_2 | NO ₂ | 155.61 | 112.36 | 126.29 | 135.69 |
| 8 | NH_2 | NH ₂ | 138.72 | 115.26 | 115.26 | 138.72 |
| 9 | NH_2 | Н | 148.51 | 113.83 | 128.71 | 115.60 |
| 10 | NO ₂ | CO ₂ H | 150.01 | 123.62 | 130.62 | 136.67 |
| 11 | NO_2 | CO ₂ Me | 150.13 | 123.73 | 130.51 | 134.95 |
| 12 | NO_2 | CO ₂ Et | 150.10 | 123.70 | 130.45 | 135.21 |
| 13 | NO ₂ | CH3 | 146.21 | 123.17 | 130.04 | 145.55 |
| 14 | NO_2 | Br | 146.73 | 125.21 | 132.72 | 129.21 |
| 15 | NO_2 | OH | 139.59 | 126.08 | 115.72 | 163.86 |
| 16 | NO_2 | NO ₂ | 150.76 | 124.93 | 124.93 | 150.76 |
| 17 | NO_2 | н | 147.69 | 123.17 | 129.73 | 135.14 |
| 18 | н | CO ₂ H | 132.78 | 128,50 | 129.22 | 130.78 |
| 19 | н | CO ₂ Me | 133.20 | 128.67 | 129.02 | 129.57 |
| 20 | Н | CO ₂ Et | 133.08 | 128.59 | 128.97 | 129.85 |
| 21 | Н | CH_3 | 125.19 | 128.08 | 128.79 | 137.25 |
| 22 | Н | Br | 127.28 | 130.51 | 131.19 | 121.64 |
| 23 | Н | OH | 118.75 | 129.29 | 115.18 | 157.27 |
| 24 | Н | н | 128.21 | 128.21 | 128.21 | 128.21 |

TABLE 1 Chemical Shifts^a of Monomers (I)

^{*a*} ppm downfield from TMS.

(1) Symmetry Factors. Integrated intensities of equivalent carbon pairs are higher than those of identically substituted single carbons.

(2) Relaxation Rates. Protonated carbons relax faster than nonprotonated carbons. Hence, integrated intensities of the former are expected to be higher than those of the latter (6).

(3) Substituent Displacements. Assignments of monomers are consistent with published substituent displacements (2).

(4) Homologous Fit. Chemical shifts of structurally similar carbons in any homologous series of identically disubstituted monomer, dimer and trimer are matched for best fit. Assignments of C2 carbons in homologs 2, 26, and 44 provide one example of this approach.

(5) Analogous Fit. Dipeptide derivatives listed in Table 2 are grouped in three sets of six analogous compounds with fixed substituents at the amino terminals and variable substituents at the carboxy terminals (CO_2H , CO_2Me , CO_2Et , CH_3 , Br and H). Six additional sets of three dimers with fixed carboxy terminals and variable amino terminals (NH_2 , NO_2 and H) may be also generated. Trimers listed in Table 3 are grouped likewise. These sets correspond to variable perturbations at the two

| Compo | und | | | | | | | | | | |
|-------|-----------------|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| # | x | у | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 |
| 25 | NH ₂ | CO₂H | 152.39 | 112.56 | 129.54 | 120.66 | 165.58 | 143.97 | 119.11 | 130.09 | 124.66 |
| 26 | NH_2 | CO ₂ Me | 152.44 | 112.57 | 129.58 | 120.63 | 165.62 | 144.35 | 119.19 | 129.95 | 123.48 |
| 27 | NH_2 | CO ₂ Et | 152.43 | 112.54 | 129.55 | 120.58 | 165.58 | 144.29 | 119.14 | 129.88 | 123.72 |
| 28 | NH_2 | CH_3 | 151.94 | 112.54 | 129.21 | 121.28 | 165.11 | 137.19 | 120.16 | 128.78 | 131.72 |
| 29 | NH_2 | Br | 152.19 | 112.54 | 129.35 | 120.78 | 165.31 | 129.13 | 121.91 | 131.16 | 114.38 |
| 30 | NH_2 | Н | 152.06 | 112.54 | 129.29 | 121.16 | 165.27 | 139.73 | 120.11 | 128.38 | 122.83 |
| 31 | NO ₂ | CO ₂ H | 149.28 | 123.49 | 129.30 | 140.21 | 164.24 | 142.74 | 119.70 | 130.24 | 126.05 |
| 32 | NO_2 | CO ₂ Me | 149.25 | 123.44 | 129.27 | 140.08 | 164.23 | 143.06 | 119.71 | 130.06 | 124.78 |
| 33 | NO_2 | CO ₂ Et | 149.23 | 123.43 | 129.26 | 140.09 | 164.18 | 142.99 | 119.69 | 129.99 | 125.06 |
| 34 | NO_2 | CH ₃ | 149.04 | 123.41 | 129.04 | 140.64 | 163.56 | 136.15 | 120.48 | 129.04 | 133.17 |
| 35 | NO_2 | Br | 149.12 | 123.39 | 129.12 | 140.19 | 163.83 | 138.01 | 122.27 | 131.40 | 115.82 |
| 36 | NO_2 | н | 149.07 | 123.43 | 129.13 | 140.57 | 163.79 | 138.66 | 120.47 | 128.61 | 124.09 |
| 37 | H | CO_2H | 131.77 | 127.76 | 128.39 | 134.66 | 165.95 | 143.29 | 119.50 | 130.21 | 125.53 |
| 38 | Н | CO ₂ Me | 131.79 | 127.71 | 128.34 | 134.56 | 165.97 | 143.64 | 119.56 | 130.04 | 124.31 |
| 39 | Н | CO_2Et | 131.77 | 127.73 | 128.35 | 134.56 | 165.91 | 143.58 | 119.51 | 129.97 | 124.56 |
| 40 | Н | CH ₃ | 131.34 | 127.52 | 128.26 | 135.03 | 165.30 | 136.60 | 120.39 | 128.91 | 132.55 |
| 41 | Н | Br | 131.55 | 127.57 | 128.30 | 134.66 | 165.53 | 138.49 | 122.18 | 131.30 | 115.24 |
| 42 | Н | Н | 131.43 | 127.58 | 128.29 | 134.99 | 165.51 | 139.14 | 120.34 | 128.50 | 123.57 |

TABLE 2 Chemical Shifts^a of Dimers (II)

^{*a*} ppm downfield from TMS.

terminals which are significantly attenuated with increasing range separating any aromatic carbon nucleus and the site of perturbation. The constraint of analogous fit requires that chemical shifts of analogous carbons are displaced in consistent proportion to the magnitude of the perturbation and the distance from the origin of the perturbation. The C3, C8 and C13 assignments for analogs 43-47 and 48-52 listed in Table 3 provide an illustration of this method. The shifts of the amino series converge with those of the nitro series along the sequence $C3 \rightarrow C8 \rightarrow C13$, reflecting a range dependent attenuation of strong perturbations originating from the amino terminals. On the other hand, the shifts of all analogs with invariant amino terminals converge more rapidly in the opposite direction, $C13 \rightarrow C8 \rightarrow C3$, in response to the weaker perturbations (i.e. $CO_2H \rightarrow CO_2Me$) originating from the carboxy terminals.

SUBSTITUENT DISPLACEMENTS

The substituent displacement of group x, $\Delta \delta_x^{(k)}$, is ordinarily computed from the x-substituted aryl derivative and the parent compound as shown by Eq. [1]. Comparable displacements $\Delta \delta_{x_y}^{(k)}$ may be determined from x, y-disubstituted and y-substituted derivatives as indicated by the following equation.

$$\Delta \delta_{x_y}^{(k)} = \delta_{xy}^{(k)} - \delta_y^{(k)}.$$
 [3]

A series of m(x-Ar-y, Ar-y) paired derivatives where x is invariant generates m

| Compo | pun | | | | | | | | | | | | | | | |
|-------|-----------------|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| * | x | y | ប | 3 | C | C4 | C3 | C6 | CJ | 8 | 60 | C10 | C11 | C12 | C13 | C14 |
| 43 | $\rm NH_2$ | CO ₂ H | 152.41 | 112.61 | 129.56 | 120.68 | 165.55 | 143.19 | 119.11 | 128.54 | 128.39 | 165.35 | 143.48 | 119.44 | 130.22 | 125.29 |
| 44 | $\rm NH_2$ | CO ₂ Me | 152.38 | 112.57 | 129.53 | 120.68 | 165.52 | 143.20 | 119.08 | 128.51 | 128.30 | 165.37 | 143.83 | 119.47 | 130.01 | 124.06 |
| 45 | $\rm NH_2$ | CO ₂ Et | 152.38 | 112.59 | 129.53 | 120.70 | 165.53 | 143.21 | 119.08 | 128.52 | 128.32 | 165.37 | 143.79 | 119.45 | 129.97 | 124.36 |
| 46 | $\rm NH_2$ | CH_3 | 152.30 | 112.58 | 129.47 | 120.76 | 165.48 | 142.74 | 119.05 | 128.21 | 128.87 | 164.76 | 136.73 | 120.33 | 128.87 | 132.34 |
| 47 | $\rm NH_2$ | Н | 152.35 | 112.58 | 129.51 | 120.73 | 165.51 | 142.87 | 119.08 | 128.31 | 128.79 | 164.98 | 139.29 | 120.31 | 128.49 | 123.39 |
| 48 | | CO_2H | 149.25 | 123.48 | 129.24 | 140.17 | 164.15 | 141.85 | 119.60 | 128.61 | 129.71 | 165.13 | 143.28 | 119.38 | 130.10 | 125.38 |
| 49 | NO_2 | CO ₂ Me | 149.25 | 123.51 | 129.29 | 140.20 | 164.19 | 141.92 | 119.60 | 128.66 | 129.65 | 165.20 | 143.70 | 119.50 | 130.02 | 124.15 |
| 50 | NO2 | CO_2Et | 149.25 | 123.50 | 129.27 | 140.17 | 164.19 | 141.92 | 119.60 | 128.66 | 129.66 | 165.17 | 143.63 | 119.47 | 129.96 | 124.44 |
| 51 | NO ₂ | CH3 | 149.24 | 123.50 | 129.25 | 140.25 | 164.14 | 141.52 | 119.59 | 128.39 | 130.20 | 164.57 | 136.65 | 120.34 | 128.89 | 132.44 |
| 52 | NO_2 | Н | 149.26 | 123.50 | 129.26 | 140.24 | 164.12 | 141.59 | 119.59 | 128.48 | 130.10 | 164.76 | 139.17 | 120.28 | 128.48 | 123.50 |
| 53 | Н | CO_2Et | 131.69 | 127.66 | 128.30 | 134.56 | 165.78 | 142.42 | 119.41 | 128.54 | 129.07 | 165.19 | 143.64 | 119.41 | 129.90 | 124.41 |
| 54 | Н | Н | 131.73 | 127.69 | 128.38 | 134.60 | 165.79 | 142.12 | 119.38 | 128.38 | 129.57 | 164.82 | 139.23 | 120.28 | 128.48 | 123.43 |
| a ppr | i downfi | eld from] | TMS | | | | | | | | | | | | | |

TABLE 3 CHEMICAL SHIFTS^a of TRIMERS (III)

SUBSTITUENT EFFECTS IN BENZOIC OLIGOMERS

values of $\Delta \delta_{x_y}^{(k)}$ for each nonequivalent carbon and these may be averaged to yield a mean substituent displacement $\overline{\Delta \delta}_{x_y}^{(k)}$ as given below.

$$\overline{\Delta\delta}_{x_y}^{(k)} = \sum_{y} \left(\delta_{xy}^{(k)} - \delta_{y}^{(k)} \right) / m.$$
[4]

The scatter in $\Delta \delta_{x_y}^{(k)}$ values for all nonequivalent carbons may be defined by the population standard deviation (PSD) from the mean substituent displacement

$$(\text{PSD})_x = \left[\sum_{k,y} (\overline{\Delta\delta}_{xy}^{(k)} - \Delta\delta_{xy}^{(k)})^2 / n\right]^{1/2}$$
[5]

where n is the product of m and the number of nonequivalent carbons.

Since amino and carboxy terminals of p-aminobenzoyl dimers (II) and trimers (III) are not symmetrically equivalent, we reserve the x notation for substituents located in amino terminals and restrict the y notation to groups bonded to carboxy terminals. Corresponding displacement and PSD equations for y substituents were similarly derived and are given below.

$$\Delta \delta_{y_x}^{(k)} = \delta_{xy}^{(k)} - \delta_x^{(k)}$$
[6]

$$\overline{\Delta\delta}_{y_x}^{(k)} = \sum_{x} \left(\delta_{xy}^{(k)} - \delta_x^{(k)} \right) / m$$
[7]

$$(\mathbf{PSD})_{y} = \left[\sum_{k,x} (\overline{\Delta\delta}_{y_{x}}^{(k)} - \Delta\delta_{y_{x}}^{(k)})^{2} / n\right]^{1/2}.$$
[8]

Mean substituent displacements of groups located in amino terminals $\overline{\Delta\delta}_{x_y}^{(k)}$, and carboxy terminals $\overline{\Delta\delta}_{y_x}^{(k)}$, are listed in Tables 4, 5 and 6. These effects are transmitted through the peptide linkage in both directions with comparable efficiencies (7). The

 TABLE 4

 Mean Substituent Displacements^a of x and y in Monomers (I)

| x | у | C1 | C2 | C3 | C4 | PSD ^b | n ^c |
|-----------------|--------------------|------|-------|-------|-------|------------------|----------------|
| NH ₂ | _ | 20.9 | -15.1 | 1.3 | -12.7 | 1.3 | 36 |
| NO_2 | | 18.6 | -4.5 | 1.1 | 6.2 | 1.3 | 36 |
| — | CO ₂ H | 3.8 | -0.5 | 1.5 | 1.7 | 0.9 | 12 |
| | CO ₂ Me | 4.1 | -0.2 | 1.3 | 0.4 | 0.9 | 12 |
| _ | CO ₂ Et | 4.1 | -0.4 | 1.2 | 0.7 | 0.9 | 12 |
| | CH3 | -2.3 | 0.0 | 0.4 | 9.3 | 0.6 | 12 |
| _ | Br | -0.8 | 2.1 | 2.8 | -7.4 | 0.8 | 12 |
| | OH | -8.5 | 1.8 | -13.4 | 30.1 | 1.0 | 12 |
| | | | | | | | |

^a ppm relative to benzene. Negative signs indicate upfield positions.

^b Population standard deviation in ppm.

 $^{^{}c}n = 4$ nonequivalent carbons per monomer multiplied by the number of monomers measured.

| т | ٨ | D | T | E | 5 | |
|----|---|---|---|----|---|--|
| 1. | А | n | L | E. | | |

| | ·· · | ···· | | | <u></u> | | | | ····· | | | |
|-----------------|--------------------|-------|--------|-------|---------|-------|-------|-------|-------|-------|------------------|----|
| <i>x</i> | У | C1 | C2 | C3 | C4 | Ç5 | C6 | C7 | C8 | C9 | PSD ^o | n° |
| NH ₂ | | 20.63 | -15.10 | 1.10 | -13.89 | -0.28 | 0.65 | -0.31 | -0.11 | -0.83 | 0.07 | 54 |
| NO_2 | _ | 17.56 | -4.21 | 0.87 | 5.55 | -1.72 | -0.52 | 0.14 | 0.07 | 0.54 | 0.05 | 54 |
| _ | CO_2H | 0.29 | 0.09 | 0.17 | -0.40 | 0.40 | 4.16 | -0.87 | 1.68 | 1.91 | 0.07 | 27 |
| | CO ₂ Me | 0.31 | 0.06 | 0.16 | -0.48 | 0.42 | 4.51 | -0.82 | 1.52 | 0.69 | 0.07 | 27 |
| | CO ₂ Et | 0.29 | 0.05 | 0.15 | -0.50 | 0.37 | 4.44 | -0.86 | 1.45 | 0.95 | 0.07 | 27 |
| | CH ₃ | -0.08 | -0.03 | -0.07 | 0.08 | -0.20 | -2.53 | 0.04 | 0.41 | 8.98 | 0.04 | 27 |
| | Br | 0.10 | -0.02 | 0.02 | -0.36 | 0.03 | -0.63 | 1.81 | 2.79 | -8.35 | 0.03 | 27 |

MEAN SUBSTITUENT DISPLACEMENTS^a OF x and y in Dimers (II)

^a ppm relative to corresponding carbons in x = H = y substituted dimer. Negative signs indicate upfield positions.

^b Population standard deviation in ppm.

^c n = 9 nonequivalent carbons per dimer x number of dimers measured.

amino substituent is the strongest perturber of all groups listed in Table 6. Its effects are transmitted through thirteen contiguous bonds, including two peptide linkages $(\overline{\Delta\delta}_{\rm NH_2}^{(11)} = 0.11 \pm 0.03 \text{ ppm})$. The farthest perturbation of the nitro group reaches C9 and is transmitted through ten contiguous bonds $(\overline{\Delta\delta}_{\rm NO_2}^{(9)} = 0.56 \pm 0.03 \text{ ppm})$. Variations in $\Delta\delta^{(k)}$ values among homologous carbons in all oligomers are comparable to the PSD of mean substituent displacements. For instance, $\Delta\delta_{\rm NO_2}^{(3)} = 1.1 \pm 1.3, 0.87 \pm 0.05$ and 0.93 ± 0.03 ppm in monomers, dimers and trimers, respectively.

PSD values gauge deviations from additivity in a finite population of n nonequivalent carbons in each *m*-series of disubstituted aryls. Our data indicate that scatter in *k*th carbon deviations from mean substituent displacements is randomly distributed throughout the population. Thus there are no structural or proximal trends in their distribution. Overall PSD values for all series of trimers, dimers and monomers are 0.03, 0.06 and 1.1 ppm, respectively. Since these deviations apply to chemical shifts measured with a reproducibility of 0.03 ppm, it appears that (1) substituent displacements of trimers are exactly additive, (2) deviations from additivity in dimers are slightly above the experimental scatter, and (3) PSD values in monomers are about 40 times larger than the reproducibility of chemical shift measurement in this work. These observations indicate that ¹³C NMR additivity rules in 1,4-phenylenes are distorted by range dependent interactions between substituents reported herein. These interactions are sharply attenuated with increasing intersubstituent ranges.

Reversal of C7, C12 peak assignments listed in Table 3 for compounds 43, 44, and 45 leads to corresponding increases in PSD values of mean substituent displacements of groups CO₂H, CO₂Me and CO₂Et (Table 6) from 0.02–0.03 ppm to 0.07–0.08 ppm. Similar effects were noted in C8, C13 assignment reversal for trimer 51. It seems that the striking sensitivity of the PSD in mean substituent displacements to assignments of structurally similar carbon provides a useful criterion for consistent ¹³C NMR shift assignments in any series of closely related aromatic derivatives.

| | 4 | 5 | 5 | Ľ | 5 | ž | 2 | 5 | 2 | 5 | 010 | 5 | 55 | 55 | 15 | quad | 5 |
|------------|--------------------|----------|------------|----------|--------|-------------|----------|----------|----------|------------|---------|-----------|-------|------|-------|------|----|
| * | • | 5 | 3 | 3 | 5 | 3 | 2 | 5 | ŝ | 5 | CT0 | | 717 | CI) | C14 | ner | r |
| $\rm NH_2$ | ļ | 20.66 | -15.09 | 1.18 | -13.86 | -0.27 | 0.77 | -0.31 | -0.05 | -0.76 | 0.17 | 0.11 | 0.03 | 0.04 | -0.05 | 0.03 | 28 |
| NO2 | ļ | 17.55 | -4.17 | 0.93 | 5.62 | -1.63 | -0.51 | 0.20 | 0.11 | 0.56 | -0.04 | -0.04 | 0.03 | 0.03 | 0.05 | 0.03 | 28 |
| I | CO_2H | 0.02 | 0.01 | 0.02 | -0.06 | 0.03 | 0.29 | 0.02 | 0.18 | -0.40 | 0.37 | 4.15 | -0.89 | 1.68 | 1.89 | 0.03 | 28 |
| | CO ₂ Me | 0.01 | 0.00 | 0.02 | -0.05 | 0.04 | 0.33 | 0.01 | 0.19 | -0.47 | 0.41 | 4.54 | -0.81 | 1.53 | 0.66 | 0.02 | 28 |
| I | CO_2Et | -0.01 | -0.01 | -0.02 | -0.05 | 0.03 | 0.32 | 0.01 | 0.18 | -0.47 | 0.39 | 4.46 | -0.85 | 1.46 | 0.96 | 0.03 | 42 |
| ļ | CH3 | -0.03 | 0.00 | -0.03 | 0.02 | 0.00 | -0.10 | -0.02 | -0.09 | 0.09 | -0.20 | -2.54 | 0.02 | 0.40 | 8.95 | 0.02 | 28 |
| a | | | | | : | | | | | | | | | | | | |
| | Elative to c | Orrespon | Cling Carb | Ons in X | | in betitut. | ed trime | r Negati | VP signs | i ateripui | n plagu | Sertions. | | | | | |

MEAN SUBSTITUENT DISPLACEMENTS^a of x and y in Trimers (III) **TABLE 6**

y substituted utimet. Negative signs indicate upheld positions. by the relative contresponding callories in x - n - y substituted triffier. In b Population standard deviation in ppm. $^{c}n = 14$ nonequivalent carbons per trimer x number of trimers measured.

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Application of the minimum PSD test to assignments based on constraints described in the previous section requires the assumption that all members of any analogous series have exclusive populations of cis or trans peptide bond diastereomers. Since no satellite peaks were ever detected under our experimental conditions, this seems to be the case here. In addition, the cis-diasteromers appear unlikely in this system (8). It is also noteworthy that chemical shift assignments of amino acid 1 and peptides 25 and 43 are consistent with undissociated (NH₂-Ar-CO₂H) rather than zwitterionic (NH₃⁺-Ar-CO₂⁻) structures in DMSO-d₆ solutions.

SUBSTITUENT INTERACTIONS

Following the assumptions originally invoked by Leffler and Grunwald (9), we introduce factored interaction terms $I^{(k)}$ in Eqs. [9] and [11] to account for additivity distortions in the dimeric and monomeric series of 1,4-phenylene derivatives.

$$\delta_{xy}^{(k)} = \delta_H^{(k)} + \Delta \delta_x^{(k)} + \Delta \delta_y^{(k)} + I_x^{(k)} \cdot I_y^{(k)}$$
[9]

$$\delta_x^{(k)} = \delta_H^{(k)} + \Delta \delta_x^{(k)}$$
[10]

$$\delta_{x'y}^{(k)} = \delta_{H}^{(k)} + \Delta \delta_{x'}^{(k)} + \Delta \delta_{y}^{(k)} + I_{x'}^{(k)} \cdot I_{y}^{(k)}$$
[11]

$$\delta_{x'}^{(k)} = \delta_{H}^{(k)} + \Delta \delta_{x'}^{(k)}$$
[12]

These equations pertain to two series of analogs each with invariant amino terminals $(x = \text{NH}_2 \text{ and } x' = \text{NO}_2)$ undergoing y variation at the carboxy terminals. $\delta^{(k)}$ terms are chemical shifts of kth carbons on the TMS scale, and $\Delta\delta^{(k)}$ terms are conventional substituent displacements as defined by Eq. [1]. Appropriate combination of Eqs. [9] through [12], namely ([9]–[10])/([11]–[12]) leads to a substituent interaction equation

$$(\Delta \delta_{y_x}^{(k)} - \Delta \delta_y^{(k)}) = (I_x^{(k)} / I_{x'}^{(k)}) (\Delta \delta_{y_{x'}}^{(k)} - \Delta \delta_y^{(k)})$$
[13]

where $\Delta \delta_{y_x}$ and $\Delta \delta_{y_{x'}}$ are substituent displacement terms derived from x (or x'), y-disubstituted series as defined by Eq. [6]. The substituent interaction equation [13] correlates deviations from additivity in the NH₂-Ar-y series, $(\Delta \delta_{y_x'}^{(k)} - \Delta \delta_y^{(k)})$ ordinate, with corresponding deviations in the NO₂-Ar-y series, $(\Delta \delta_{y_{x'}}^{(k)} - \Delta \delta_y^{(k)})$ abscissa, for each nonequivalent carbon.

If the assumptions (9) implicit in Eqs. [9] and [11] are valid, plots of double difference or additivity deviation terms for each of the nine dimeric and four monomeric carbon atoms should be linear, intercept the origin, and feature slopes equal to $I_x^{(k)}/I_{x'}^{(k)}$. Best lines for all carbons were selected by Wald's (10) method of averages rather than by least-squares regression analysis, because error estimates of data points are equal along both axes. Plots for each of the four nonequivalent carbons in the monomer series are displayed in Fig. 1. Corresponding line parameters are listed in Table 7. Normal distances of best lines from the origin are 0.3, 0.0 and 0.2 ppm for C1, C2 and C3, respectively. The average scatter in these plots is 0.09–0.13 ppm. Since the maximum probable error of each deviation term is 0.03 ppm·4, or 0.12 ppm, it is apparent that the C1, C2 and C3 plots are approximately consistent with Eq. [13] for groups $y = CO_2H$, CO_2Me , CO_2Et , CH_3 , Br and



TABLE 7 INTERACTION PARAMETERS^a of Monomers (I)

| Carbon # | Slope I _{NH2} /I _{NO2} | Intercept $y(x=0)$ | Average deviation ^b | D_{N}^{c} |
|-------------|---|--------------------|--------------------------------|-------------|
| | | (ppm) | (ppm) | (ppm) |
| 1 | 0.1 | 0.3 | 0.13 | 0.3 |
| 2 | -10.4 | -0.4 | 0.09 | 0.0 |
| 3 | 8.3 | 1.4 | 0.10 | 0.2 |
| 4 | -0.8 | -2.3 | 0.09 | 1.9 |

^a For the linear plot corresponding to Eq. [13]. Slope and intercept computed by Wald's method of averages.¹⁰ ^b Average normal distance from experimental points to best line. ^c Normal distance from best line to origin.

NO₂. This is not the case for the C4 graph. The best line is far from the origin (1.9 ppm), and omits the methyl group coordinates. Clearly, the assumptions inherent in Eqs. [9] and [11] are not valid at the C4 site. Nor are they valid at any of the carbons for substituents $y = NH_2$ and OH (corresponding data points are not shown in Fig. 1). Additivity deviation coordinates of these strong electron donating groups are off the best lines by wide margins.

Within a much smaller scale, similar trends are observed in the dimer series (Fig. 2, Table 8). The average deviation of data points is 0.01-0.02 ppm for groups $y = CO_2H$, CO_2Me , CO_2Et , CH_3 and Br. Normal distances of best lines from the origin range from 0.00 to 0.04 ppm for C1 through C8 sites. However, the C9 plot is displaced from the origin by 0.10 ppm, and the best line does not include the methyl group coordinates. The average scatter of data points in Fig. 2 (dimers) is about eight times smaller than corresponding deviations in Fig. 1 (monomers). It appears that Eq. [13] is followed more closely as the interacting groups are placed farther apart.



| Carbon # | Slope $I_{\rm NH_2}/I_{\rm NO_2}$ | Intercept $y(x=0)$ | Average deviation ^b | d_{N}^{c} |
|-------------|-----------------------------------|--------------------|--------------------------------|-------------|
| | | ppm | ppm | ppm |
| 1 | -0.15 | -0.01 | 0.012 | 0.01 |
| 2 | 1.27 | 0.03 | 0.013 | 0.02 |
| 3 | 1.68 | 0.07 | 0.010 | 0.03 |
| 4 | 2.72 | 0.01 | 0.018 | 0.00 |
| 5 | 20.7 | 0.03 | 0.014 | 0.00 |
| 6 | -0.79 | 0.04 | 0.005 | 0.03 |
| 7 | -1.46 | 0.08 | 0.011 | 0.04 |
| 8 | -0.38 | -0.01 | 0.009 | 0.01 |
| 9 | -0.46 | 0.11 | 0.009 | 0.10 |

| | TABLE 8 | | | |
|-------------|---------------------------------------|----|--------|----------------|
| INTERACTION | PARAMETERS ^{<i>a</i>} | OF | DIMERS | (\mathbf{H}) |

^{*a*} For the linear plot corresponding to Eq. [13]. Slope and intercept computed by Wald's method of averages. (10).

^b Average normal distance from experimental points to best line.

^c Normal distance from best line to origin.

The validity of Eq. [13] rests on two assumptions. First, only one interaction mechanism is operable among groups x and y in x-Ar-y derivatives:

$$(\Delta \delta_{\mathbf{y}_{\mathbf{x}}}^{(k)} - \Delta \delta_{\mathbf{y}}^{(k)}) = I_{\mathbf{x},\mathbf{y}}^{(k)}.$$
[14]

Second, interaction terms may be factored to the scalar product

$$I_{x,y}^{(k)} = I_x^{(k)} \cdot I_y^{(k)}$$
[15]

as long as the independent terms $I_x^{(k)}$ and $I_y^{(k)}$ are not variable vector quantities and perturbations associated with y variation are small (9). The introduction of two interaction mechanisms under the general categories of field (F) and resonance (R) effects (11, 12) modifies Eq. [14] to

$$(\Delta \delta_{y_x}^{(k)} - \Delta \delta_y^{(k)}) = I_{x,y}^{(k)\text{FF}} + I_{x,y}^{(k)\text{FR}} + I_{x,y}^{(k)\text{RR}}$$
[16]

and if all interaction terms in Eq. [16] are factored to scalar products, it may be shown that Eq. [13] would be converted to the following expression.

$$(\Delta \delta_{y_x}^{(k)} - \Delta \delta_y^{(k)}) = [(I_x^{(k),F} + I_x^{(k),R}) / (I_{x'}^{(k),F} + I_{x'}^{(k),R})](\Delta \delta_{y_{x'}}^{(k)} - \Delta \delta_y^{(k)}).$$
[17]

The "two mechanism" interaction equation, [17], is identical to [13], except that the numerator and denominator of the slope are sums of field and resonance parameters characteristic of groups x and x'. It follows that Eq. [17] is also not applicable to groups $y = NH_2$ and OH at all carbon sites of monomeric x-Ar-y derivatives. This suggests that scalar factoring of substituent substituent interaction terms is not valid for these groups. Aromatic resonance perturbations induced by pendant amino and hydroxyl groups are known to be substantially larger than those of halo, carboxyl, alkyl and nitro substituents. On the other hand, variations in field perturbations ascribed to all of these substituents are significantly smaller (11a). Since ¹³C NMR

substituent effects in anyl derivatives are sensitive to resonance interactions, it is not surprising that this correlation, as well as other Hammett $\sigma\rho$ reaction and spectral correlations (12), is not applicable to strong electron donors without linear combination of at least two substituent dependent $(\Delta \delta_{y_x}^{(k)} - \Delta \delta_y^{(k)})$ terms.

The C4 and C9 sites in the monomeric and dimeric series, respectively, are not correlated well by Eqs. [13] or [17]. These positions are closest to the y substituents, and field interaction perturbations are expected to be particularly prominent there (12b). The methyl group coordinates are dispersed from the others, presumably because its weighted field parameter, f·F, is substantially smaller than comparable parameters of groups CO₂R, Br and NO₂ (11a).

DISCUSSION

The representation of any molecular property Φ as an additive function of submolecular fragments follows the general limiting law that "for the disproportionation reaction RNR+SNS \rightleftharpoons 2RNS, $\Delta \Phi \rightarrow 0$ as the separation between R and S becomes large compared to their dimension" (12). This principle may be referred to as a first order additivity rule and its application to Gibbs free energy contents of reactants and products leads to the Hammett equation as a prime example (9).

That ¹³C NMR chemical shifts of aromatic compounds follow first order additivity rules has been demonstrated by linear correlations of substituent displacements with electronic parameters such as charge density (14), polarizability (5, 16) and electronegativity (17). Similar correlations with Hammett reaction parameters have also been reported (18, 19). The approximate additivity of substituent displacements in multisubstituted benzene derivatives (2) is consistent with the above correlations.

In this work we have shown that ¹³C NMR additivity rules in *p*-aminobenzoic acid oligomers, a representative class of 1,4-phenylene derivatives, are distorted by interactions among a variety of pendant groups. These interactions are sharply attenuated, and additivity rules become more exact, as these substituents are placed farther apart. Inspection of mean substituent displacements at nonequivalent carbons of the trimer series (Table 6) reveals that perturbations extending from the amino group range farther than those of nitro, carboxyl and methyl substituents (thirteen vs ten contiguous bonds). This pattern is consistent with the resonance components rather than field components of substituent effects attributed to these groups in the Swain and Lupton tabulation (11a). The mean displacements generated by the amino substituents follow a pattern of alternating signs at C1 through C5, which is typical of predominant conjugative interactions at these sites. Starting from C6, however, the sign alternation is replaced with a $(+---)\Delta\delta$ sequence terminating at C9. An opposite pattern of signs $(-+++)\Delta\delta$ may be noted for displacements of the nitro substituent at C6 through C9. Comparable effects are generated from the y terminals by CO_2R and CH_3 groups at C9-C6 positions. These patterns appear to result from π -polarization (12b) rather than resonance effects and so we conclude that π -orbitals of the central phenylene unit are polarized by the changed dipole of a perturbed peptide bond. The peptide dipole perturbation is apparently generated by conjugative interactions with the x or y substituent. The greater range of displacements caused by the amino substituent seems to result from

a stronger peptide perturbation reflective of the larger resonance component of the amino substituent effect. The reversed signs of π -polarization with electron withdrawing groups (NO₂, CO₂R) compared with those of electron donors (NH₂, CH₃) may reflect the direction of the peptide dipole perturbation. The resonance perturbation of an electron acceptor places a more positive pole near the central phenylene unit and a $(-+++)\overline{\Delta\delta}$ polarization ensues. Conversely, an electron donor leads to a less positive pole near the phenylene moiety and a $(+---)\overline{\Delta\delta}$ polarization is observed. The linkage of resonance to π -polarization noted here appears similar to the mesomeric field effect (M_F) which has been included in the FMMF treatment of substituent effects by Dewar *et al.* (11b).

The linear correlation of additivity deviation terms in amino and nitrosubstituted series of phenylene analogs indicates that substituent-substituent interaction parameters are extractable from ¹³C chemical shifts. Extension of these correlations to other x_i substituents is expected to yield a relative scale of interaction parameters I_{x_i}/I_{x_0} at each of the nonequivalent carbon sites. The significance of these scales may be explored by interpretation of the $I_{\rm NH_2}/I_{\rm NO_2}$ values listed in Tables 7 and 8 for the monomer and dimer series respectively. In the dimer series we note that the slopes are negative at C6, C7 and C8 positions. Since negative $I_{\rm NH_2}/I_{\rm NO_2}$ values imply a mesomeric "push or pull" mechanism for interactions of NH₂ and NO₂ groups with y substituents, the combined conjugative π -polarization effects suggested above for substituent displacements seem consistent with the observed slopes at C6–C8. That is, the peptide bond may be conjugatively polarized by the x substituents in opposite directions and these perturbations presumably interact with the y substituents by π -polarization leading to positive or negative $I_{\rm NH_2}I_y$ or $I_{\rm NO_2}I_y$ terms in Eqs. [9] and [11] respectively.

The observation of positive $I_{\rm NH_2}/I_{\rm NO_2}$ values at C2, C3 and C4 sites of the dimer analogs may be explained as follows. The y substituent polarizes the peptide bond by resonance interaction and this induces either (1) diminished electron release by NH₂ and increased electron withdrawal by NO₂ if y acts as a Lewis base or conversely, (2) increased electron release by NH₂ and diminished electron withdrawal by NO₂ if y acts as a Lewis acid. In either case the resultant interactions of the amino and nitro groups with the y terminals have the same polar sense and $I_{\rm NH_2}/I_{\rm NO_2}$ terms would be expected to be positive. The interactions between the perturbed peptide bond and the x substituents presumably occur by π -polarization at the C2–C4 positions.

In the monomer series (Table 7) we note a large negative slope at the C2 carbon of the phenylene ring. Since this site is ortho with respect to the x substituents, a direct conjugative perturbation of C2 appears to be the most likely mechanism for the I_x terms. This perturbation may interact with the y terminals by direct conjugation and/or by polarization of intervening π bonds. Because the amino and nitro groups act as donors and acceptors, respectively, and the former has a higher resonance parameter, a large negative value for the $I_{\rm NH_2}^{(2)}/I_{\rm NO_2}^{(2)}$ term is consistent with this mechanism. Reversal of the slope value to a large positive number at C3 suggests an interaction mechanism where the y substituent perturbs the C3 site by direct resonance. This perturbation reduces or increases electron release or withdrawal by the amino and nitro groups, respectively, depending on the nature of the yinteraction. If y is an acceptor, electron release by NH₂ will be increased and electron withdrawal by NO₂ will be reduced and vice versa if y is a donor. In both cases the x-substituents act in the same polar sense and the $I_{\rm NH_2}/I_{\rm NO_2}$ term will be expected to be positive as observed. The y-perturbation (I_y) is presumably transmitted from C3 by conjugation and/or π -polarization, and the $I_{\rm NH_2}$, $I_{\rm NO_2}$ terms may also include both conjugation and polarization components.

Our treatment of substituent displacements and interactions employs unsubstituted oligomers as reference compounds and deals with a number of substituents which differ not only in polarity but also in size and number of constituent atoms. The larger scatter and displacement from the origin noted for correlations at carbons proximate to the y terminals (C4, C9 in Figs 1 and 2 respectively) may be due in part to noncancellation of perturbations similar to the α , β , γ effects in alkanes. Reynolds *et al.* (21) have shown that such effects may be separated from electronic perturbations in aromatic systems by use of a nonpolar but isoelectronic substituent for the reference compound, i.e., CH₃(CH₂)_nC₆H₅ vs NH₃⁺(CH₂)_nC₆H₅. A similar approach is possible for intersubstituent correlations employing Eq. [13] by reducing structural variations among y substituents. Alternatively, such effects might be investigated by means of Eq. [13] with homologous x_n substituents of type CH₃(CH₂)_n.

The separate contributions of field and resonance parameters listed in Eq. [17] may be estimated by correlating additivity deviation terms in non-aromatic bicyclic systems and by studying aromatic substituents with little or no resonance activity such as R_3N^+ (11a). Application of these constraints to more extensive data sets is expected to yield a series of $I_{x_i}^F/I_{x_0}^F$ and $I_{x_i}^R/I_{x_0}^R$ interaction scales relative to a standard x_0 substituent.

Since ¹³C NMR resonances are more readily measured than reaction parameters, this approach may significantly increase the scope of intersubstituent correlations.

EXPERIMENTAL PROCEDURES

Solutions. Trimers, dimers and commercial samples of monomers (0.3 m. mole) were dissolved in DMSO- d_6 (99.5% D, 1.0 ml) at room temperature, yielding 2.1 mole% solutions. Less soluble nitro substituted trimers were suspended in DMSO- d_6 (1.5 ml, room temperature), and centrifuged before analysis.

¹³C NMR measurements. Pulsed Fourier transform ¹³C NMR measurements of most oligomers were recorded on a Varian CFT-20 spectrometer operating at 20.00 MHz. Parameters were set in the following ranges: Pulse tip angles $26^{\circ}-64^{\circ}$, cycle times 1.5-3.0 sec., 2 K-15 K transients, spectral width 4 kHz, 8192 datapoints. Chemical shift measurements of compounds 1, 25 and 43 were carried out on the Brukerian DFS-60 spectrometer, operating at 15.09 MHz^{20} and were subsequently duplicated on the CFT-20 spectrometer. Spectra of oligomers 35, 38, 40, 41, 53 and 8, 16 were recorded on the Bruker WP-80 (20.123 MHz) and HX-270 (67.89 MHz) spectrometers, respectively. All carbon spectra were proton decoupled and were obtained at an ambient temperature of $30 \pm 2^{\circ}$ in 10 mm tubes.

Chemical shifts are reported in ppm downfield from TMS using the central line of the DMSO- d_6 septet as an internal reference at 39.50 ppm. The position of this line

relative to the deuterium lock signal of the solvent was reproduced with a standard deviation of 0.03 ppm in 36 samples measured on the CFT-20 spectrometer.

Concentration effects. Chemical shifts of three 2.8 mole% and four 2.1 mole% DMSO- d_6 solutions of trimer 43 were recorded. Carbon resonances of more concentrated solutions were consistently downfield by an average value of 0.04 ppm. At the rate of 0.06 ppm/mole%, fluctuations in shifts due to small changes in concentration from one sample to another are expected to be negligible in comparison to the standard deviation of all shifts from the corresponding means in the 2.1 and 2.8 mole% solutions (0.03 ppm). The magnitude of these effects is likely to decrease at concentrations below 2.1 mole%.

Temperature effects. Chemical shifts of trimer 43 (2.1 mole% in DMSO- d_6) were measured at ambient probe temperature, 30°, and at 71°. Ambient temperature shifts were consistently downfield by an average value of 0.18 ppm. This average temperature coefficient of 0.005 ppm/deg indicates that temperature related scatter in carbon shift measurements reported herein is smaller than the overall experimental reproducibility of 0.03 ppm.

| Compound | l Sub | stituent | Melting | Literature | | Solvent of recrystal- lization |
|----------|-----------------|--------------------|----------|---------------|-----------|--------------------------------------|
| # | x | у | point | melting point | Reference | (this work) |
| 25 | NH ₂ | CO ₂ H | 277-280° | 276° | 22 | water |
| 26 | NH_2 | CO ₂ Me | 222–225° | 221-224° | 22 | anisole |
| 27 | NH_2 | CO ₂ Et | 170–173° | 176° | 22 | EtOAc |
| 28 | NH_2 | CH ₃ | 165-166° | 167-168° | 23 | Et ₂ O/hexane |
| 29 | NH_2 | Br | 201-203° | _ | | EtOH |
| 30 | NH_2 | Н | 137–138° | 137–138° | 24 | water |
| 31 | NO ₂ | CO ₂ H | 335° | 327° | 22 | purified as the pyri- dinium salt |
| 32 | NO ₂ | CO ₂ Me | 234–236° | 237–238° | 22 | EtOH |
| 33 | NO ₂ | CO_2Et | 211-213° | 216° | 22 | i-AmOH |
| 34 | NO ₂ | CH_3 | 195–197° | 197° | 25 | EtOH |
| 35 | NO ₂ | Br | 244-246° | 245° | 26 | EtOH |
| 36 | NO_2 | Н | 213-214° | 216° | 26 | EtOH |
| 37 | н | CO ₂ H | 286-287° | 278° | 27 | EtOH |
| 38 | Н | CO ₂ Me | 167-169° | 170-171° | 28 | 95% EtOH |
| 39 | н | CO ₂ Et | 148-150° | 148° | 29 | 95% EtOH |
| 40 | Н | CH ₃ | 156-158° | 158° | 29 | 95% EtOH |
| 41 | Н | Br | 202-203° | 202° | 30 | 95% EtOH |
| 42 | Н | н | 161–163° | 163° | 31 | 95% EtOH |

 TABLE 9

 Analytical Parameters of Dimers^a

^a All samples had satisfactory ¹³C, ¹H NMR and IR spectra.

Synthesis

Dimers, x = H series: Compounds 38-42 were prepared by the reaction of equimolar amounts of benzoyl chloride and the appropriate aniline derivative. In a typical preparation, the reactants (0.05 mol of each one) were added to pyridine (25 ml), and the solution was heated at 90° for 2 hrs. The reaction mixture was poured into water and the crude product was collected on a Büchner funnel and washed with water, dilute HCl and water again. The carboxylic acid (37) was obtained by saponification of the corresponding ester (39) using methanolic KOH at 60° (6 hr). The carboxylate salt, which began to precipitate after about 3 hr was collected on a Büchner funnel and washed with methanol and ether. The salt was dissolved in water and the solution was acidified with HCl to precipitate the acid.

Dimers, $x = NO_2$ series: Compounds 32-36 were prepared by a procedure similar to the one described above for compounds 38-42, using p-nitrobenzoyl chloride in place of benzoyl chloride. The carboxylic acid (31) was prepared according to the procedure described in Ref. (22), Table 9.

Dimers, $x = NH_2$ series: The carboxylic acid 25 was obtained by reduction with zinc and ammonium chloride and compounds 32-36 were obtained by reduction with phenylhydrazine according to procedures described in Ref. (22), Table 9. All the reductions proceeded smoothly and in good yield except for the reduction of 36(x = H), which formed a molecular complex with the generated amine (30). In this case, the amine was isolated by extraction of an ether solution of the complex with dilute HCl and treatment of the resulting ammonium salt with potassium carbonate.

| Compound | Sub | stituent | Melting | Literature | |
|----------|-----------------|--------------------------------|----------|-------------------|-----------|
| # | x | у | point | melting point | Reference |
| 43 | NH ₂ | CO ₂ H ^c | 335° | >310° | 22 |
| 44 | NH_2 | CO_2Me | 293-295° | discolors at 276° | 22 |
| 45 | NH_2 | CO ₂ Et | 278-279° | 266° | 22 |
| 46 | NH_2 | CHS | 279-280° | | |
| 47 | NH_2 | Н | 264-265° | | _ |
| 48 | NO_2 | CO ₂ H | >350° | >320° | 22 |
| 49 | NO_2 | CO ₂ Me | >350° | 330° | 22 |
| 50 | NO_2 | CO ₂ Et | 325-327° | 323° | 22 |
| 51 | NO_2 | CH_3 | 315-317° | _ | |
| 52 | NO_2 | H | 325-327° | 298° | 23^d |
| 53 | н | CO ₂ Et | 281–283° | — | _ |
| 54 | н | H | 299-300° | 323-324° | 23^d |

 TABLE 10

 ANALYTICAL PARAMETERS OF TRIMERS^{a,b}

^a All trimers had satisfactory ¹³C, ¹H NMR and ir spectra.

^b All trimers were recrystallized from DMF/CH₃CN except for 49, which has recrystallized from DMF alone.

^c Satisfactory elemental analysis was obtained.

^d The reference cited seems to have interchanged the m.p.'s for compounds 52 and 54. (A higher m.p. for the nitro compound, relative to the unsubstituted compound, is consistent with the other m.p.'s in these tables.)

Trimers, x = H and $x = NO_2$: The preparation of compounds 48-54 paralleled the synthesis of the corresponding dimers except that more solvent was used to cope with the lower solubility of the dimers relative to the monomers.

Trimers, $x = NH_2$: Compounds 43–47 were derived from the corresponding nitro compounds 48–52 by catalytic hydrogenation using 10% Pd/C in dimethylformamide (R.T., 50 psi, 20 hr, 60 mg catalyst/g of nitro compound). The catalyst was separated by filtration, generally after the addition of ether, and the product was precipitated by addition of water to the filtrate.

Analytical parameters of dimers and trimers are summarized in Tables 9 and 10, respectively.

ACKNOWLEDGMENTS

We thank Professor John D. Roberts for sponsoring one of us (D.A.L.) as a research fellow at the Division of Chemistry and Chemical Engineering, California Institute of Technology, June 1974 through December 1974. We thank Professor Elkan R. Blout for providing access to the CFT-20 spectrometer at the Department of Biological Chemistry, Harvard Medical School. Helpful discussions with Professors Robert I. Gelb and Lowell M. Schwartz are acknowledged. This work was supported by a research grant from the National Institute of General Medical Sciences of the National Institutes of Health, U.S. Public Health Service (GM-19645). We thank Dr. Christian I. Tanzer (Bruker Instruments, Inc., Billerica, MA) and Professor Eric T. Fossel (Department of Biophysics, Harvard Medical School) for their assistance on the WP-80 and HX-270 spectrometers, respectively.

REFERENCES

- 1. P. C. LAUTERBUR, J. Am. Chem. Soc. 83, 1846 (1961).
- J. B. STOTHERS, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972, pp. 196-205.
- 3. K. S. DHAMI AND J. B. STOTHERS, Can. J. Chem. 43, 510 (1965).
- 4. G. K. HAMER, I. R. PEAT, AND W. F. REYNOLDS, Can. J. Chem. 51, 897 (1973).
- 5. (a) D. W. BEISTEL, H. E. CHEN, AND P. J. FRYATT, J. Am. Chem. Soc. **95**, 5455 (1973); (b) D. W. BEISTEL, G. CHAPPELL, AND W. D. EDWARDS, J. Am. Chem. Soc. **99**, 1309 (1977).
- G. C. LEVY AND G. L. NELSON, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York (1972), Chap. 2.
- 7. R. G. PEWS, Chem. Comm. 458 (1971).
- 8. W. E. STEWART AND T. D. SIDDALL, III, Chem. Rev. 70, 517 (1970).
- 9. J. E. LEFFLER AND E. GRUNWALD, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N.Y., 1963, Chap. 6.
- 10. A. WALD, Annals of Math. Stat. 11, 284 (1940).
- (a) C. G. SWAIN AND E. C. LUPTON, JR., J. Am. Chem. Soc. 90, 4328 (1968); (b) M. J. S. DEWAR, R. GOLDEN, AND J. M. HARRIS, J. Am. Chem. Soc. 93, 4187 (1971).
- (a) E. M. SCHULMAN, K. A. CHRISTENSEN, D. M. GRANT, AND C. WALLING, J. Org. Chem. 39, 2686 (1974);
 (b) W. F. REYNOLDS AND G. K. HAMER, J. Am. Chem. Soc. 98, 7296 (1976).
- 13. S. W. BENSON AND J. H. BUSS, J. Chem. Phys. 29, 546 (1958).
- 14. G. L. NELSON, G. C. LEVY, AND J. D. CARGIOLI, J. Am. Chem. Soc. 94, 3069 (1972).
- 15. (a) W. B. SMITH AND D. DEAVENPORT, J. Magn. Reson. 7, 364 (1972); (b) W. B. SMITH AND T. W. PROULX, Org. Magn. Resonance 8, 205 (1976).
- 16. D. J. SARDELLA, J. Am. Chem. Soc. 98, 2100 (1976).
- 17. A. R. TARPLEY AND J. M. GOLDSTEIN, J. Phys. Chem. 76, 515 (1972).
- 18. (a) H. SPIESECKE AND W. G. SCHNEIDER, J. Phys. Chem. 35, 731 (1961); (b) P. C. LAUTERBUR, Tetrahedron Lett. 274 (1961).

- 19. (a) G. J. MARTIN, M. L. MARTIN, AND S. ODIOT, Org. Magn. Resonance 7, 2 (1975); (b) G. E. MACIEL, in "Topics in Carbon-13 NMR Spectroscopy," Vol. 1 (G. C. LEVY, Ed.), John Wiley and Sons, New York, N.Y., pp. 53-75.
- 20. B. L. HAWKINS AND J. D. ROBERTS, Proc. Nat. Acad. Sci. (U.S.), 70, 1027 (1973).
- 21. W. F. REYNOLDS, I. R. PEAT, M. H. FREEDMAN, AND J. R. LYERLA, JR., Can. J. Chem. 51, 1857 (1973).
- 22. H. BREDERECK AND H. V. SCHUH, Chem. Ber. 81, 221 (1948).
- 23. G. LOCKEMANN AND H. KÜGLER, Chem. Ber. 80, 479 (1947).
- 24. G. LOCKEMANN, T. LOBENSTEIN, AND W. NEUMANN, Chem. Ber., 75B, 1911 (1942).
- 25. L. GATTERMANN AND O. NEUBERG, Chem. Ber. 25, 1082 (1892).
- 26. P. GRAMMATICAKIS, Bull. Soc. Chim. Fr. 1956 (1960).
- 27. A. LUDWIG AND S. TACHE, Bull. Chim. Soc. Romane Chim. 39, 87 (1937).
- 28. A. WILLIAMS AND K. T. DOUGLAS, J. Chem. Soc. Perkin II, 2112 (1972).
- 29. K. TAKATORI, J. Pharm. Soc. Japan 73, 810 (1954).
- 30. W. AUTENRIETH, Chem. Ber. 38, 2534 (1905).
- 31. V. H.-HÜBNER, Ann. 208, 278 (1881).
- 32. E. J.-H. CHU, J. Am. Chem. Soc. 67, 1862 (1945).