about 5×10^{-3} M). At lower concentrations, there was enough dissolved oxygen to scavenge any semiquinone radicals which were formed.

Thin Layer Chromatography of Lignin Extracts.—Brauns native lignin samples such as aspen and Black Spruce[32] (0.1 g) were refluxed for 2 hr (with and without oxygen) in 5 ml of 1.0 M NaOH and neutralized with dilute HCl, followed by extraction with ethyl ether. The concentrated ether extracts were chromatographed on silica gel plates using benzene–ethanol (4:1) by volume) or the organic layer from a mixture of n-butyl alcohol–acetic acid–water (4:1:5 by volume) as developing solvents. The spots were visualized with 2,4-dinitrophenylhydrazine. The first solvent mixture proved best for separation of syringaldehyde from vanillin, while the latter mixture gave better separation of 2,6-dimethoxybenzoquinone from the other two components.

Commercial (alkali) lignin samples such as Meadol and kraft were extracted by boiling water followed by chloroform extraction of the aqueous solutions, or by extracting the solid lignin samples directly with chloroform. The concentrated chloroform extracts were chromatographed using the above developing solvents.

Synthesis of the Semiquinone of 2-Hydroxy-6-methoxybenzoquinone (2).—The structure of the secondary radical **2** was previously confirmed[6] by the Fremy's salt oxidation of the monomethyl ether of phloroglucinol to 2-hydroxy-6-methoxybenzoquinone, and treatment of this compound with alkali to give the corresponding semiquinone.

In the present work, this structure was further confirmed by preparation of 5-iodovanillin by the method of Pepper[33] and conversion to 5-hydroxyvanillin[34] followed by a Dakin oxidation to 2-hydroxy-6-methoxybenzohydroquinone. On treatment with alkali and air, this gives the esr spectrum of **2**.

Kinetic Studies. A. All esr rate studies were carried out under nitrogen in the apparatus described above. After the substrate and buffer were mixed, the spectrum was scanned at definite time intervals and the intensity of the central line of the spectrum was taken as a measure of radical concentration.

B.—Optical rate studies were made by dissolving definite quantities of the quinone in commercial (phosphate and borate) buffer solutions, which had been deaerated with nitrogen for 0.5 hr before mixing. Scanning of the quinone–base mixture was started as soon as the quinone had completely dissolved.

Ether Exchange.—In a typical experiment, quinone **3** (200 mg) was dissolved in 100 ml of ethanol containing 0.01 mol of NaOH. After 3 min of stirring, the red reaction mixture was poured into 200 ml of ice water, acidified, and extracted with chloroform. The pale yellow solid isolated from the chloroform solution was identified as 2,6-diethoxy-p-benzoquinone: mp 125–126° (lit.[9] 126–127°); nmr ($CDCl_3$) δ 1.40 (t, 6), 3.90 (q, 4), 5.75 (d, 2). When the latter was dissolved in CD_3OD in an nmr tube, and a small quantity of solid NaOH was added, instant exchange of ethoxyl groups with CD_3O^- was observed.

Registry No.—1, 33070-34-7; 2, 33070-35-8; 3, 530-55-2; 5 (R = Et), 33070-36-9; 5 (R = i-Pr), 33070-37-0; 7 (R = Et), 33070-38-1; 7 (R = i-Pr), 33070-39-2; 8, 15233-65-5; 9, 33122-24-6; 2-methoxy-p-benzoquinone, 33070-40-5; 2,6-dimethoxyhydroquinone dianion, 33070-41-6.

Acknowledgment.—The authors acknowledge the generous support of a National Science Foundation Institutional Grant to the Department and the Petroleum Research Fund for this work.

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Substituent Chemical Shift Correlations. Proton Magnetic Resonance Chemical Shifts for N,N,N-Trimethylphenylammonium Iodides[1a]

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N-Methyl pmr chemical shifts of 21 meta- or para-substituted N,N,N-trimethylphenylammonium (TMA) iodides were determined in deuterium oxide and acetonitrile. Infinite dilution shifts were obtained from expressions of the type (M = mol/l.) δ (D_2O), Hz = δ^0_o + (28.61 ± 6.19)M and δ (CH_3CN), Hz = δ^0_o + (166.5 ± 5.7)M − (2240 ± 2.16)M^2. The corresponding Hammett correlations were δ^0 (D_2O), Hz = 5.857σ + 217.86 (r = 0.85, N = 17) and δ^0 (CH_3CN), Hz = 5.123σ + 211.0 (r = 0.89, N = 12); one Swain–Lupton surface for our meta-substituted TMA's was given by δ^0 (CH_3CN), ppm = 0.03855 F + 0.1074 R − 3.548 (r = 0.999, N = 7, % R = 64). The proportionality of pmr substituent chemical shifts, or δ–δ relations, between pairs of families was tested. In general, the Hammett and δ–δ linear relations were often poor ($r < 0.9$), while the Swain–Lupton equation was usually good ($r > 0.95$), as judged by the correlation coefficient (r). It can be shown, however, that pmr correlations which depend solely on reactivity constants (σ, F, R) are theoretically deficient and we would discourage their use. The introduction of additional terms, *e.g.*, to correct for substituent magnetic anisotropy, appears to be essential, but the merits of such a hybrid approach are doubtful.

In investigations of the relation between the transmission of electronic effects and substituent chemical shifts (SCS = δ) our group has taken diametrically opposed positions. Initially, we assumed that the usual structure–reactivity correlations of the Hammett (eq 1) or Taft type applied to proton magnetic resonance (pmr) data.[2] Recently, we tested eq 1 on *ca.* 100 systems of the type XC_6H_4–T–H and found that SCS are often poorly represented; that is, correlation coefficients for eq 1 are low ($r < 0.9$).[3] It was also significant that the variations in ρ with the nature of the transmitting group, $-C_6H_4T-$, made little chemical sense.

$$\delta = \rho\sigma + \text{constant} \quad (1)$$

Originally, the compounds (TMA) seemed interesting, because a novel group, namely positive nitrogen, was involved in relaying substituent effects to the methyl protons.[2] Later, the anilinium family became crucial to a new approach to substituent effects, embodied in the Swain–Lupton relation;[4] F and R measure

(1) (a) Presented in part at the Third Great Lakes Regional Meeting, American Chemical Society, June 1969, and abstracted from the Ph.D. thesis of G. R. W., May 1971, Illinois Institute of Technology; (b) American Chemical Society Petroleum Research Fund (GF-760) and Division of Analytical Chemistry Summer Fellowships are gratefully acknowledged.

(2) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

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TABLE I

PROPERTIES OF THE *N,N,N*-TRIMETHYLPHENYLAMMONIUM (TMA) IODIDES[a]

Registry no.	Substituent	Mp or dp, °C[b] Found	Mp or dp, °C[b] Lit.	Iodide, % Found	Iodide, % Calcd	δ^0 (D_2O),[c] Hz	δ^0 (CH_3CN),[c] Hz	Ref[a]
98-04-4	H	226.5	228	48.47	48.23	217.98 ± 0.07	211.92 ± 0.06	*d*
	D	227–229		47.2	47.9			*e*
6140-15-4	*p*-CH_3	218–219	216–218	45.84	45.78	216.07 ± 0.01	210.19	*f*
33046-97-8	*m*-CH_3	188–188.5	177–178	45.89	45.78	216.41 ± 0.11	210.61 ± 0.1	*f*
2498-27-3	*m*-OH	185–186.5	179	45.92	45.47	215.83 ± 0.06	209.41 ± 0.09	*g*
455-08-3	*p*-F	232–233		45.69	45.14	218.41 ± 0.04	211.85 ± 0.06	
454-60-4	*m*-F	180.5–182		45.26	45.14	218.83 ± 0.05	212.34	
17311-01-2	*p*-CN	163–164	181	44.43	44.05	221.03 ± 0.04	213.62	*h*
7541-76-6	*p*-CHO	156–157		43.8	43.58	221.91 ± 0.01	214.44 ± 0.03	*i*
17310-99-5	*p*-OCH_3	261–262		43.46	43.28	216.00 ± 0.06	209.81	
2373-41-3	*m*-Cl	191–192	187, 199	42.84	42.64	218.44 ± 0.04	212.14	*j, k*
27853-26-5	*p*-$COCH_3$	179–181		41.01	41.58	220.94 ± 0.02	213.94	
1202-17-1	*p*-$N(CH_3)_2$	289.5–290	246	41.35	41.44	213.72 ± 0.11	207.30	*k*
880-00-2	*p*-COOH	238–239	238	41.4	41.32	220.67 ± 0.06	213.71	*l*
2345-55-3	*m*-COOH	203	204	41.05	41.32	221.08 ± 0.02	214.30	*h*
27389-55-5	*m*-NO_2	198–199	205	42.11	41.19	224.40 ± 0.03	216.60	*m*
33046-24-1	*m*-NO_2[n]	248		30.77	30.60	224.40 ± 0.03	216.60	
33046-25-2	*p*-Br	192	184	37.26	37.10	217.82 ± 0.10	211.01	*o*
2350-78-9	*p*-NNC_6H_5	184	184	34.54	34.56	228.88	215.76	*p*
31061-59-3	*m*-O^-					211.83 ± 0.02	208.33	*q*
33039-70-2	*p*-$N(CH_3)_2H^+$					221.32 ± 0.07	214.05	*r*
33192-03-9	*m*-CO_2^-					219.91 ± 0.03	213.18	*q*
33046-28-5	*p*-CO_2^-					219.23	*s*	*q*

[a] The citation is to a method of preparation and/or melting point. [b] These are generally decomposition ranges; see text. [c] In general, ±0.15 Hz is a good estimate of uncertainty in δ^0, the value at infinite dilution. Where a ± value is given these are standard deviations in the least squares evaluation of δ^0. [d] G. Funatsukuri, Japanese Patent 5059 (1960); also reported in *Chem. Abstr.*, **55**, 1663 (1961). [e] The salt contained 1.6 D on the ring and was prepared from *N,N*-dimethylaniline (R. J. Preto, Ph.D. dissertation, Illinois Institute of Technology, 1967). [f] K. T. Tsuboyama and M. Yanagita, *Sci. Pap. Inst. Phys. Chem. Res., Tokyo*, **53**, 337 (1959). [g] S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **80**, 3425 (1958). [h] W. Tadros and A. B. Sakla, *J. Chem. Soc.*, 1116 (1954). [i] H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949). [j] I. Heilbron, A. H. Cook, H. M. Bunbury, and D. H. Hey, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965. [k] A. Campbell Ling and F. H. Kendall, *J. Chem. Soc. B*, 440 (1967). [l] A. Zaki and W. Tadros, *J. Chem. Soc.*, 562 (1941). [m] Z. Rappoport, Ed., "Handbook of Tables for Organic Compound Identification," 3rd ed, The Chemical Rubber Co., Cleveland, Ohio, 1967. [n] This is the bromide salt. [o] V. Wolf, *Justus Liebigs Ann. Chem.*, **592**, 222 (1955). [p] R. Möhlau, *Chem. Ber.*, **17**, 1490 (1884). [q] One drop of diethylamine was added to the parent TMA in the nmr tube; an additional drop did not alter the chemical shift. [r] One drop of dilute acid (10:1 solvent–concentrated H_2SO_4, by volume) was added to the parent TMA. [s] The solubility was too low.

the field and resonance capabilities of substituent X and f and r are weighting factors appropriate to the system, the property (y) examined, the conditions, etc.

$$y = fF + rR + \text{constant} \quad (2)$$

An essential feature of the approach is that $R \equiv 0$ for $(CH_3)_3N^+$ as a substituent.[4] Our test of relation 2, both on our SCS and those of other families, disclosed some basic theoretical problems. We then went on to examine a relatively new correlative approach to SCS, which is completely independent of measures of reactivity, *e.g.*, σ, F, R, etc. This is

$$\delta_1 = s\delta_2 + \text{constant} \quad (3)$$

in which the SCS of two different families are compared directly. Meanwhile, the difficulties in using either eq 1, 2, or their analogs have been recognized by a Japanese group and it is attempting to provide rather different approaches to correlating pmr data.[5]

Experimental Section

Materials.—The *N,N,N*-trimethylphenylammonium (TMA) iodides were all known compounds, except as indicated in Table I. They were generally prepared by direct reaction of available dimethylanilines with excess methyl iodide in benzene or ether at *ca.* 25°. In a few cases, the analogous bromides were prepared. All of the salts were recrystallized to constant melting point or decomposition point (dp). Careful control in the rate of heating (2°/min) allowed good reproducibility of these characteristic temperatures. The use of sealed, evacuated capillaries offered no special advantage, judging from the behavior of the *m*- and *p*-fluoro-TMA; for, although these compounds now melted rather than decomposed, the melting points were only 3–4° lower than the decomposition points in open capillaries. All temperatures are uncorrected. They were determined with a Thomas-Hoover "Unimelt" (oil bath) or in a Mel-Temp (metal block) apparatus when temperatures over 240° were encountered. The TMA's were analyzed titrimetrically with standard silver nitrate to the eosin end point (Table I) and nmr proton counts were usually taken. Purity checks by ir and pmr spectra were also made.

Acetonitrile (Baker Analyzed Reagent) with 1% tetramethylsilane (TMS) added was stored in a nitrogen atmosphere in the dark over 4A molecular sieves. This treatment removed water, the only impurity which we could detect at the ~0.01% level. Deuterium oxide (Merck) containing 1% sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used directly. Pmr spectra of the solvents as well as ir spectra of acetonitrile showed no change over the course of the study.

Pmr Spectra.—All samples were run on a Varian A-60 spectrometer modified by an A-60A variable temperature probe insert and operating at 60.020 MHz. Chemical shifts (δ), relative to 1% internal TMS in acetonitrile and relative to 1% internal DSS in deuterium oxide, were measured by a side band (juxtaposition) technique. The audio-oscillator (HP200CD) was monitored by a frequency counter (HP5216A) operated in the period mode. Averages of several hundred periods were used to determine the side-band frequency. Oscillator and/or spectrometer drift were monitored and found negligible. The sweep width was calibrated on each use of the spectrometer, and the

(5) H. Yamada, Y. Tsuno, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **43**, 1459 (1970).

smallest sweep width setting (50 Hz) was used to allow direct reading of the chart paper to ± 0.01 Hz.

Repeated measurements were made on sealed standard samples to check probe temperature and instrument reproducibility at various times. The probe temperature was 37 ± 2°. The presence or absence of oxygen in the solutions had no observable effect on the methyl resonances of TMA. A check on the temperature dependence (20–40°) and of added water (mole fraction <0.13) in acetonitrile indicated that these factors could only introduce deviations within the error limits on δ of TMA.

Fresh solutions of TMA were prepared for each run by weighing the dry salt and diluting to volume. Aliquots were taken for further dilution. All glassware was calibrated. Generally, solutions from at least two weighed samples were used for the measurements of δ. Toward the end of this study, particularly for the deuterium oxide solutions in which the concentration dependence was slight, dilutions of aliquots were made in an nmr tube, with the help of a ruler. An error analysis showed that the concentration errors were negligible in comparison with errors in obtaining δ.

At each concentration, δ was obtained as the mean of six scans, three upfield and three downfield. Extrapolation of δ to infinite dilution (δ^0) was made from dilution plots for each compound. These plots were based on at least three points, that is, six for acetonitrile and four for deuterium oxide. The concentration range studied was low, *ca.* 2×10^{-2}–10^{-3} *M*, to minimize errors in extrapolation to δ^0. All of the dilution shift data are given in the thesis.[1b]

Computations.—Calculations were done on a Wang calculator (Model 362K) with card reader or on an IBM 1620 computer. Struble's program was used for fitting the nonlinear equations.[6]

Results and Discussion

TMA Infinite Dilution Chemical Shifts.—The infinite dilution chemical shifts, δ^0, of the various TMA's studied in acetonitrile and deuterium oxide solutions are reported in Table I. These δ^0 values were determined from dilution shift plots, that is, plots of observed chemical shift *vs.* TMA concentration. It was noted early in the study that the dilution curves of many compounds were very similar in a given solvent (Figure 1). This is also apparent analytically from fits to eq 4 in which the parameters often agree within the expressed error limits for each solvent system.[1b]

$$\delta_{obsd} = \delta^0 + c_1M + c_2M^2 + c_3M^3 \quad (4)$$

Since it was determined that TMA shifts in deuterium oxide were adequately described in terms of a linear dependence in *M*, least squares straight lines were used to determine δ^0. With reference to the similarity of dilution curves, it is interesting to note that 16 TMA, except for those of low solubility (X = *m*-O^-, *m*-CO_2^-, and NNC_6H_5), had the average slope of eq 5.

$$\delta(D_2O) = (28.61 \pm 6.19)M + \delta^0_0 \quad (5)$$

In acetonitrile, the concentration dependence was greater. Here the SCS were best fit by a shallow parabolic curve. If, for any compound, insufficient data were available to generate an independent curve, δ^0 was determined by superimposing the data on eq 6.

$$\delta^0(CH_3CN) = \delta^0_0 + (166.5 \pm 5.7)M - (2240 \pm 2.16)M^2 \quad (6)$$

A cursory check of salt effects on δ was made. In deuterium oxide solution, *p*-methyl-TMA iodide and *m*-nitro-TMA bromide have the same δ before and after being mixed. Changing the gegenion, *e.g.*, bromide for iodide, or mixing the two leaves the δ of *m*-nitro-TMA unchanged. If, however, large amounts of potassium iodide, *e.g.* 1.0 *M*, are added to *p*-methyl-TMA iodide, a change in δ can be effected, *viz.*, 216.23 to 217.74 Hz. Similar observations were recorded for the solvent acetonitrile. Specifically, a saturated solution of potassium iodide in acetonitrile raised δ in *p*-carboxy-TMA from 214.23 to 218.21 Hz and *m*-carbomethoxy-TMA from 214.68 to 219.78 Hz.

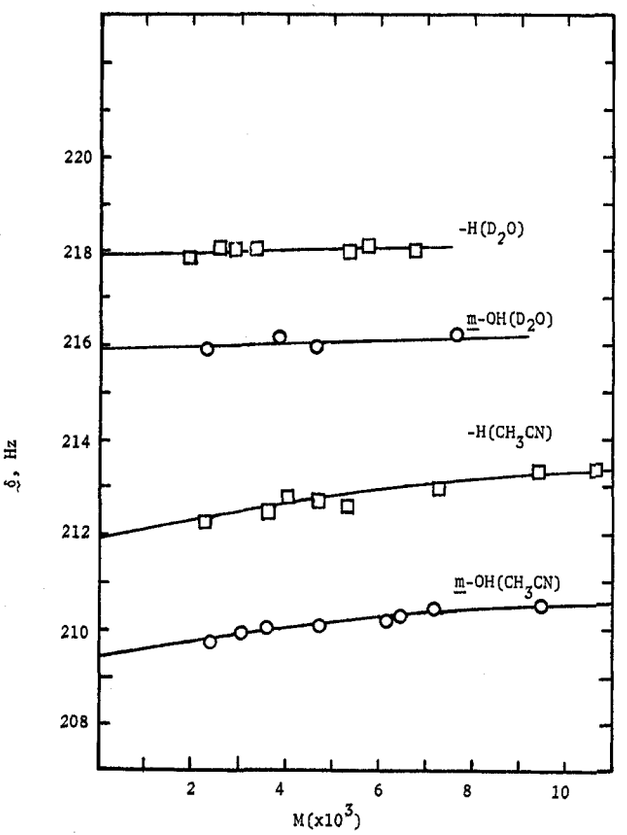

Figure 1.—Representative TMA dilution shift plots.

Other workers have obtained dilution shift curves and gegenion effects similar to ours both for TMA and pyridinium halides and ascribe these both to specific interactions as well as ion–ion association.[7] Certainly, the association of a variety of alkylammonium salts in organic solvents is known:[8] *p*-methyl-TMA iodide is *ca.* 6% associated in water and *ca.* 16% associated in propionitrile in *ca.* 10^{-3} *M* solution at 25°.[9] A salt may also change the medium in more subtle ways which may then be reflected in δ^0 of another solute.[10] In aqueous solutions, for example, δ^0 of water increases or decreases, depending on the salt added.[10] In our system, we can only guess that there are such reciprocal effects between the electrolyte and the solvent. We believe that all of these concentration dependent effects on δ are minimized as [TMA] → 0.

"Reactivity" Correlations.—Out of some 100 systems to which eq 1 has been applied,[2,3] 49 have an average correlation coefficient (*r*) of 0.88. In this respect, the

(6) G. Struble, "Non-linear least squares curve fitting program," IBM 1620 Users Group Library, Statistical Laboratory and Computing Center, University of Oregon, Eugene, Ore.

(7) (a) G. Fraenkel and J. P. Kim, *J. Amer. Chem. Soc.*, **88**, 4203 (1966); (b) W. F. Reynolds and U. R. Priller, *Can. J. Chem.*, **46**, 2787 (1968).

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(9) (a) H. J. M. Creighton and D. H. Way, *J. Franklin Inst.*, **186**, 675 (1918); (b) H. J. M. Creighton, *ibid.*, **189**, 641 (1920).

(10) (a) J. Burgess and M. C. R. Symons, *Quart. Rev., Chem. Soc.*, **22**, 276 (1968); (b) J. F. Hinton and E. S. Amis, *Chem. Rev.*, **67**, 367 (1967).

TABLE II

PMR DATA AND THE SWAIN–LUPTON EQUATION[a]

Series	Solvent	N^b	f	r	Constant, ppm	Variance × 10^3	R,[c] %	Ref
4-$XC_6H_4CH{=}CH_2$	C_6H_{12}	7	0.01651	0.1901	6.618	1.465	88	*d*
cis-4-$XC_6H_4CH{=}CHH$	C_6H_{12}	7	0.09695	0.3989	5.630	0.3453	72	*d*
trans-4-$XC_6H_4CH{=}CHH$	C_6H_{12}	7	0.1658	0.3948	5.110	0.09112	60	*d*
4-$XC_6H_4N(CH_3)_3^+$	CH_3CN	8	0.02873	0.08689	3.526	0.1353	65	*e*
	D_2O	9	0.03881	0.1112	3.634	0.1709	64	*e*
3-$XC_6H_4N(CH_3)_3^+$	CH_3CN	7	0.03855	0.1074	3.538	0.1038	64	*e*
	D_2O	8	0.06126	0.1278	3.639	0.2898	57	*e*
4-XC_6H_4OH	DMSO	20	1.059	1.653	9.259	34.57	49	*f*
	DMSO	14	0.9488	1.880	9.309	4.244	55	*f*, *g*
3-XC_6H_4OH	DMSO	7	0.9708	0.6621	9.250	4.003	30	*f*
4-$XC_6H_4CH_2Cl$	CCl_4	6	0.06337	0.1475	4.510	0.5408	59	*h*
3-$XC_6H_4CH_2Cl$	CCl_4	7	0.07331	0.1451	4.507	1.344	55	*h*
4-XC_6H_4H	CCl_4	5	0.5820	0.5321	6.908	4.575	36	*i*
3-XC_6H_4H	CCl_4	5	0.3080	0.2342	7.139	1.416	32	*i*
2-XC_6H_4H	CCl_4	5	0.8040	1.106	7.099	11.39	46	*i*

[a] Equation 2. [b] N is the number of substituents. [c] Resonance contribution, eq 9. [d] Reference 24b. [e] Our work. [f] Reference 16. [g] The six worst points have been deleted from the previous set. [h] Reference 2. [i] S. Castellano, C. Sun, and R. Kostelnik, *Tetrahedron Lett.*, 5205 (1967).

present data on TMA are no exception. Such correlations must be rated as poor, according to standards

$$\delta^0(D_2O) = 5.857\sigma + 217.86 \quad (N = 17, r = 0.85) \quad (7)$$

$$\delta^0(CH_3CN) = 5.123\sigma + 211.0 \quad (N = 12, r = 0.89) \quad (8)$$

generally accepted in the area of structure–reactivity correlations, namely, $r > 0.99$ excellent, $r > 0.95$ satisfactory, $r > 0.90$ fair.[11] Hammett pmr correlations rated from poor ("noncorrelations") to excellent continue to appear.[12] It is unfortunate that some poor correlations are tolerated or accepted, without comment on their validity or significance. A more fundamental issue, to which we shall return shortly, is that even the satisfactory correlations carry a message in the Hammett ρ which is too complex to decipher.[3,5]

At the next level of complexity are the extended structure–reactivity equations, *e.g.*, of Taft and of Yukawa and Tsuno,[13] which take a form analogous to eq 2 here. Equations of this type have occasionally been used for pmr data,[3,5,14,15] and, recently, Charton has used a similar relation to analyze pmr data of ortho-substituted families.[15c] The Yukawa–Tsuno analog of eq 2 does not really give satisfactory results for SCS of side chain protons of the benzyl fluorides[3] or the 1,1-diphenylethylenes.[15a] Because the applicability of eq 2 to pmr data had not been tested in depth and because the Swain–Lupton formalism has apparently achieved the maximum separation of field and resonance effects, we used this equation and substituent constants F and R.[4] In any system, the sensitivity to resonance effects was defined as[4]

$$\%\ R = 100(0.228\ r)/(0.365\ f + 0.228\ r) \quad (9)$$

The results of fitting a few systems to eq 2 are given in Table II. Sets of data sufficient for a test of eq 1 are often inadequate to test eq 2, since different versions of eq 2 apply to meta and para members of a given family. The fit of the data to eq 2 is, of course, better than to eq 1 and it is usually very good, as may be seen from the variances of Table II. The correlation coefficient, as calculated from coefficients of determination,[4] is 0.999 for meta-substituted TMA's in acetonitrile, 0.997 for the ortho proton of monosubstituted benzenes in CCl_4, and 0.994 for the 14 para-substituted phenols in DMSO (20 para-substituted phenols in DMSO have $r = 0.959$). The Hammett correlation for the phenols was excellent (δ *vs.* σ and σ^-, $N = 36$, $r = 0.974$)[16] and is hardly improved in the separate correlations for meta and para substituents. Our TMA data, which give poor Hammett correlations, now give excellent correlation with eq 2. In some sets, the standard deviation is less satisfactory.

Apart from the matter of fit, which might be expected to improve with the higher parameter equation, there is the question of significance. There is no obvious relation of the parameters f and r, or the $\%\ R$ to the basic aryl structure. In some families the "resonance" contribution from the meta and para position hardly differs; this is inexplicable, at least for the present. In fact, we find it both frustrating and amusing that the TMA have a resonance contribution, $R = 64\%$ in Table II, just like any other family, *e.g.*, $R = 59\%$ for benzyl chloride and $R = 49\%$ for phenols. If it is admitted that the TMA cannot make a resonance contribution according to the Swain–Lupton formulation,[4] one might be puzzled. This can be resolved simply by saying that reactivity parameters F and R are theoretically unsuitable for interpreting δ and denying

(11) (a) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963); (b) H. H. Jaffé, *ibid.*, **53**, 191 (1953).

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(13) (a) P. R. Wells, S. Ehrenson, and R. W. Taft, *Progr. Phys. Org. Chem.*, **6**, 147 (1968); (b) Y. Yukawa and Y. Tsuno, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 71 (1966).

(14) J. M. Haigh and D. A. Thornton, *Tetrahedron Lett.*, 2043 (1970).

(15) (a) Y. Yukawa, Y. Tsuno, and H. Yamada, *Mem. Inst. Sci. Ind. Res. Osaka Univ.*, **23**, 79 (1966); (b) Y. Yukawa and H. Yamada, *Nippon Kagaku Zasshi*, **85**, 501 (1964); (c) M. Charton, *J. Org. Chem.*, **36**, 266 (1971).

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that their correlation has anything but empirical validity. In our view, Charton's analyses of pmr data and the ortho effect is subject to the same limitations.[15c]

δ–δ Correlation.—It appeared to us that a logical precondition for the Hammett or Swain–Lupton correlations, eq 1 and 2, might be closer to the data. That is, δ^0 of one family of compounds might be related to δ^0 of another family (eq 3). Such an approach is inefficient in that it can involve several systems in numerous cross comparisons. The virtue of eq 3, and perhaps its regressive feature too, is that the δ–δ comparison is direct and involves no assumptions, adjustments, or hypotheses.

There have been a few reports on different δ–δ comparisons, *e.g.*, two solutes in a series of solvents,[17] or pairs of chemical shifts within one family of compounds,[18] or SCS of two families under the same conditions.[3,19] Sample plots are given in the thesis[1a] and in the citations.[3,17–19] The results for a number of δ–δ comparisons are given in Table III, where we emphasize r as the criterion of fit; the slope parameter, occasionally given in brackets, seems less important at this stage. That is, if the fits are poor, both the "theory" and applications of eq 3 become superfluous.

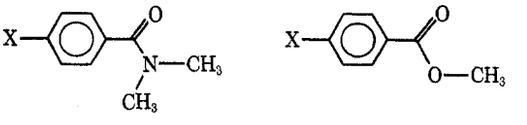
Initially, we found many systems which had significantly larger r (and often N) in their δ–δ than in their Hammett correlations. As we added to the number tested, the average r of the δ–δ relations tended to decline. One could, of course, become selective and reject problem systems. By deleting the families $ArNH_2$ in C_6H_{12} and $ArCH{=}CH_2$ in $CDCl_3$ from Table III, we would immediately raise the average r above 0.90. In so doing, however, we would discard some fair (r = 0.90–0.95) correlations along with the poor ($r <$ 0.90) ones.

Perhaps the most significant point to make about Table III is that there are no large blocks or extended series of values of $r > 0.95$. Thus, even if there were a rationale for eq 3, there is not much practical incentive to speculate on it. Theoretically, the slopes of eq 3 also do not relate to structure in any obvious way; this may be evident, if one considers the toluenes (Table III, column 3) compared with other aryl families, *e.g.*, $ArOCH_3$, ArCHO, $ArSCH_3$, etc., in which the SCS were measured in a single solvent, carbon tetrachloride. All of this is significant, if disappointing, because the pure and unadulterated pmr property is contained in eq 3.

Comments on Pmr Correlations.—At the outset, it would seem desirable to avoid adventitious medium effects or to keep them constant.[12j] In pmr correlations, differential influences of association, *e.g.*, hydrogen bonding or ion pairing, of anisotropy, *e.g.*, aryl solutes and solvents,[20] or of any other concentration-dependent effects are usually minimized when SCS are taken at infinite dilution in an "inert" solvent. Since this has not been a standard practice, discrepancies in published work on the same compounds are not uncommon.[3] As for the choice of a solvent, this is often dictated by other necessities; in any case, there are systems for which even carbon tetrachloride is not inert enough.[21] It is probable that δ^0 of this study are probably free of residual specific effects, because the dilution plots of most compounds were essentially parallel. This was far from the case with the benzyl halides.[3] The existence of unsystematic concentration-dependent effects at infinite dilution should, in fact, be used as an early criterion to disqualify any family from correlations of the type 1–3.

Suppose now that a sufficient and representative number of compounds in a family have been examined. On this point statistical criteria may be explicit, but out of prudence we have recommended $N > 10$.[3] Suppose further that one could settle on the scale to use, *e.g.*, σ, σ^-, σ^+, or F and R, etc. It has been shown previously that, even if eq 1 was acceptable, the magnitude of ρ could not be related in any way to the chemical structure it was intended to characterize.[3] Equally, the demands of precision and significance were not met in general by the δ–δ relation 3. Finally, though the Swain–Lupton surface 2 may store δ^0 well, it is of dubious significance. In short, all three relations appear to have no theoretical basis.

There have been several signs that SCS can be extraordinarily sensitive to their environment. From "outside" of the molecule a change in solvent can change the Hammett ρ substantially and often drastically: for $ArCH_2CH_2\mathbf{H}$, ρ = 6.8 in carbon tetrachloride and 4.6 in acetone; for $ArO\mathbf{H}$, ρ = 67 in carbon tetrachloride and 110 in HMPA.[2,3] From "within" the molecule there are the marked changes in ρ when aryl families differ only in their geometry, *e.g.*, syn and anti anils or cis and trans cinnamic acids.[2,3] Relative motion within the molecular framework leads to obvious effects on SCS, when barriers are high, but even in low barrier systems, *e.g.*



the broadening of δ (~0.8–1.4 Hz) has been observed.[22] In fact, most protons on side chains, except for those in cylindrically symmetrical groups, *e.g.*, CH_3, $N(CH_3)_3^+$, $C(CH_3)_3^+$, or those in rigid or severely hindered systems, will be mobile. Differential mobilities in these families make for variable magnetic effects. All of this suggests that the mutual interaction of a side chain proton with a remote substituent may be incompletely represented in eq 1–3.

Some time ago a phenomenological relation was proposed to account for the chemical shift. Equation 10 contained at least five "contributions" and some of

$$\delta = \sum_i \Delta\delta_i \qquad (10)$$

these were or could be composite.[23] Portions of this equation have been used occasionally in SCS cor-

(17) S. H. Marcus and S. I. Miller, *J. Phys. Chem.*, **73**, 453 (1969).

(18) (a) B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Aust. J. Chem.*, **21**, 1853 (1968); (b) Y. Nomura, Y. Takeuchi, and N. Nakagawa, *Tetrahedron Lett.*, 639 (1969); (c) W. Drenth and A. Loewenstein, *Recl. Trav. Chim. Pays-Bas*, **81**, 635 (1962).

(19) (a) C. Brown and D. R. Hogg, *J. Chem. Soc. B*, 1315 (1968). (b) K. D. Bartle, D. W. Jones, and P. M. G. Bavin, *J. Chem. Soc. B*, 388 (1971).

(20) E. M. Engler and P. Laszlo, *J. Amer. Chem. Soc.*, **93**, 1317 (1971).

(21) T. Schaefer, B. Richardson, and R. Schwenk, *Can. J. Chem.*, **46**, 2775 (1968).

(22) G. P. Schiemenz and G. Stein, *Tetrahedron*, **26**, 2007 (1970).

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TABLE III

CORRELATION COEFFICIENTS IN SAMPLE δ–δ RELATIONS (EQUATION 3)

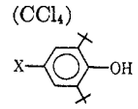
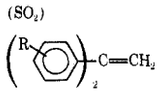
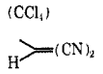
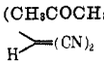
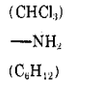
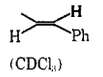
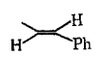
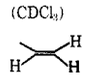
Site x[a,b] (solvent)	Code/ ref[c]	Site y[a,b]: $-CH_3$ (CCl_4)	$-OH$ ($DMSO$)[d]	($CDCl_3$)	 ($CDCl_3$)	 ($CDCl_3$)	NH_2 (C_6H_{12})	$N^+(CH_3)_3$ (CH_3CN)	SCH_3 (CCl_4)	Avg $r \times 10^3$
$-N(CH_3)_2$	76	[0.94]	[7.80]	0.979	0.960	0.897	0.935	0.990(9)	0.953	958
($CHCl_3$)		0.994(7)	0.958(10)							
$-OCH_3$	*e*	[1.39]	[11.8]							
(CH_3CN)		0.992(11)	0.981(10)	0.972	0.929	0.885	0.903	0.976	0.835	934
$-OCH_3$	14	[0.83]	[6.8]							
(CCl_4)		0.988(9)	0.956(10)	0.981	0.964	0.888	0.959	0.960	0.870	946
	8	[0.179]	[1.66]							
(CCl_4)		0.986	0.988(8)	0.997	0.972	0.857	0.987	0.979	0.996	970
$-SCH_3$	16	[1.52]	[11.8]							
(CCl_4)		0.979(9)	0.917(10)	0.992(7)	0.997(7)	0.829(7)	0.463	0.974		876
$-N^+(CH_3)_3$	*f*	[2.15]	[16.1]							
(CH_3CN)		0.968(12)	0.917(12)	0.966	0.934	0.765	0.834		0.974	908
$-CH_3$	2		[7.90]						[0.63]	
(CCl_4)			0.938(13)	0.960(10)	0.947(10)	0.828(10)	0.573	0.968	0.979(9)	885
$-N^+(CH_3)_3$	*f*	[1.68]	[13.2]	[2.3]	[1.8]	[0.65]		[0.829]	[1.6]	
(D_2O)		0.967(12)	0.927(12)	0.940(8)	0.888(8)	0.739(8)	0.805	0.989(19)	0.972(6)	903
$-CH_2F$	*g*	[0.76]	[5.6]							
(CCl_4)		0.982	0.948(10)	0.979	0.957	0.848	0.861	0.987(8)	0.995	945
$-CH_2Cl$	*g*	[1.30]	[9.07]					[0.57]		
(CCl_4)		0.963	0.854(10)	0.891	0.867	0.887	0.488	0.934(8)	0.874	845
$-H$	*h*	[0.31]	[2.38]							
(CCl_4)		0.953(7)	0.969(6)							
$-OH$	9	[0.10]	[0.966]							
($DMSO$)		0.950(12)	0.992(11)	0.975	0.863	0.508	0.893	0.905	0.855	868
$-OH$	*d*	[0.111]		[0.19]	[0.15]	[0.055]	[0.21]	[0.052]	[0.071]	
($DMSO$)		0.938(13)		0.977(10)	0.920(10)	0.720(10)	0.704(11)	0.917(12)	0.917(10)	870
$-C\equiv CH$	23	[0.61]	[5.08]	[0.89]	[0.67]	[0.29]		[0.31]	[0.39]	
(CCl_4)		0.950(10)	0.997(10)	0.980(8)	0.907(8)	0.753(8)	0.874	0.912(7)	0.881(8)	907
$-NH_2$	*i*	[0.11]	[1.03]							
($DMSO$)		0.871	0.988(11)	0.870	0.854	0.767	0.845	0.789	0.874	857
$-NH_2$	7	[0.18]	[1.47]	[0.28]	[0.21]	[0.09]		[0.082]	[0.12]	
(CH_3CN)		0.924	0.974(18)	0.952(10)	0.898(10)	0.708(10)	0.849	0.876(9)	0.954(8)	892
 (FSO_3H)	86	[0.90] 0.959(11)	[7.25] 0.970(11)	0.977	0.921	0.678	0.927	[0.43] 0.984(9)	0.996	926
 (SO_2)	*j*	[0.87] 0.880	[7.5] 0.961(11)	0.956	0.889	0.556	0.929	[0.39] 0.854(8)	0.984	876
 (CCl_4)	*k*	[0.443] 0.966	[3.68] 0.967(11)	0.981	0.931	0.663	0.980(11)	0.945	0.833	908
 (CH_3COCH_3)	*l*	[0.60] 0.953(11)	[3.26] 0.913(11)	0.959	0.931	0.636	0.926	0.941	0.845	888
 ($CHCl_3$)	11a	[0.80] 0.941	[4.33] 0.836(11)	0.918	0.928	0.746	0.728	0.961	0.784	855
 (C_6H_{12})	6a	[0.21] 0.573	[2.4] 0.704(11)	0.953	0.763	0.236		0.834	0.463	647
 ($CDCl_3$)	66	[0.82] 0.950(15)	[6.38] 0.939(13)	0.963	0.935	0.738	0.819	0.946(9)	0.838	891
 ($CDCl_3$)	41	[1.9] 0.794	[14.9] 0.723(13)	0.702	0.783	0.988	0.205	0.756	0.690	705
 ($CDCl_3$)	*m*	[0.670] 0.960(10)	[4.98] 0.977(10)		0.977(12)	0.734(12)	0.953	0.966	0.992(7)	937

TABLE III (*Continued*)

Site x[a,b] (solvent)	Code/ ref[c]	Site y[a,b]: –CH₃ (CCl₄)	–OH (DMSO)[d]	(CDCl₃)	 (CDCl₃)	 (CDCl₃)	NH₂ (C_6H_{12})	$N^+(CH_3)_3$ (CH_3CN)	SCH_3 (CCl_4)	Avg $r \times 10^3$
($CDCl_3$)	*m*	[0.81] 0.947(10)	[5.77] 0.920(10)	0.977(12)		0.814(12)	0.763	0.934	0.975(7)	904
($CDCl_3$)	*m*	[1.17] 0.828	[9.38] 0.720(10)	0.733(12)	0.814(12)		0.236	0.765	0.829(7)	704
–CHO (CCl_4)	5	[0.59] 0.919	[3.43] 0.843(8)	0.944(8)	0.936(8)	0.418(8)	0.872	0.959	0.994(5)	861
average *r*		0.929	0.918	0.946	0.916	0.758	0.830	0.929	0.892	

[a] Each system may be represented as XC_6H_4TH, where **H** is the site and **T** the transmitting group. Unless the whole structure is indicated, each system is designated by the site. The average number of substituents was N = 10–11, and the range was N = 6–16. Each entry consists of the correlation coefficient r, sometimes preceded by the slope parameter [s] and followed by (N). [b] The sites listed horizontally supply the δ_{yi} values for eq 3; the vertically listed sites supply δ_{xi}. Since δ_y entries are also included among the δ_x entries, citations are given with the latter set. [c] A number in this column refers to systems coded in ref 2 and 3, where citations are also given. [d] Reference 16. [e] R. Tanaka, this laboratory. [f] This study. [g] Reference 3. [h] Footnote *i*, Table II. [i] B. M. Lynch, B. C. MacDonald, and J. G. K. Webb, *Tetrahedron*, **24**, 3595 (1968). [j] D. A. Tomalia and H. Hart, *Tetrahedron Lett.*, 3389 (1966). [k] Reference 15a. [l] M. A. Weinberger, R. M. Heggie, and H. L. Holmes, *Can. J. Chem.*, **43**, 2585 (1965). [m] Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967).

relation studies.[15,24] Having recognized that their version of eq 2 was inadequate, Yukawa and Tsuno attempted modifications.[15] Most recently, they have taken certain terms from eq 10, and with appropriate scaling have identified two with polar and resonance effects and utilized another to correct for substituent magnetic anisotropy.[5] The latter takes into account the nature and geometry of the substituent and must be applied individually in any given aryl family. For the several meta-substituted aryl families whose SCS were correlated, the number of substituents was rather small ($N \simeq$ 6–9). And, as was the case with eq 2, it is difficult to see what the polar term means in terms of the chemical structure and there appear to be problems with halogen substituents. It must be conceded, however, that, according to the goodness of fit, the correlations are impressive ($r > 0.99$).[5]

In order to obtain satisfactory correlations of SCS of an aryl family, at least one more term must be added to eq 2. Whatever virtue simplicity has, we have lost it. The question of using extended and/or modified versions of eq 1–3 *vs.* eq 10 for investigating the effect of structure on δ becomes academic and perhaps irrelevant as the two approaches move closer together.

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The Isolation, Structure, Synthesis, and Absolute Configuration of the Cactus Alkaloid Macromerine[1,2]

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(−)-Macromerine has been isolated as the major alkaloid of the cactus *Coryphantha macromeris* and its structure determined to be *N*,*N*-dimethyl-2-hydroxy-2-(3′,4′-dimethoxyphenyl)ethylamine (**3**) from spectral and analytical measurements. Two independent syntheses of racemic macromerine and one of (+)-macromerine (**3a**) were developed. The absolute configuration of (−)-macromerine was shown to be *R* by relating it to (*R*)-(−)-adrenaline (**8**).

Coryphantha macromeris is one of the more alkaloidiferous species found in our recent phytochemical surveys of cacti.[3,4] Chromatography of the crude base fraction on alumina affords the crystalline major alkaloid, macromerine, in 0.16% yield.[5] The molecular weight by mass spectroscopy (225) and the elemental analysis point to a molecular formula of $C_{12}H_{19}NO_3$ for macromerine.

The nmr spectrum in $CDCl_3$ indicates the presence of three aromatic hydrogen atoms, two methoxyl groups, an OH group, and two *N*-methyl groups (downfield shift in acid[6]). The presence of the hydroxyl group is substantiated by the infrared spectrum

(1) Taken from the (a) Masters Thesis and (b) Ph.D. Dissertation of S. D. Brown, Texas Christian University, 1965 and 1969, respectively.

(2) Partially communicated in (a) S. D. Brown and J. E. Hodgkins, 22nd Southwest Regional Meeting of the American Chemical Society, Albuquerque, N. Mex., Dec 1966, Abstracts p 60A; (b) J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Lett.*, 1321 (1967).

(3) S. D. Brown, J. L. Massingill, Jr., and J. E. Hodgkins, *Phytochemistry*, **7**, 2031 (1968).

(4) S. D. Brown, J. E. Hodgkins, and M. G. Reinecke, unpublished results.

(5) Subsequent to our initial reports,[2] macromerine also was isolated from *Coryphantha runyonii* by L. E. Below, A. Y. Leung, J. L. McLaughlin, and A. G. Paul, *J. Pharm. Sci.*, **57**, 515 (1968).

(6) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).