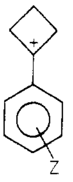
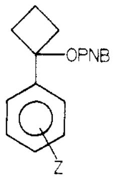
negative ρ^+ values. The C^+ shift data do not involve any bond making or bond breaking. Therefore, the bond opposition forces do not play any role in the NMR data, resulting in smaller changes in the ρ^{C^+} values compared to the ρ^+ values.

The ρ^{C^+} value for the 1-aryl-1-cyclobutyl cations (**21**) can be estimated to be −18.1 from the data reported by Olah and co-workers.[12] This is relatively more negative compared to the ρ^{C^+} values for the five–, six–, and seven-membered rings. Interestingly, the ρ^+ value observed for the solvolysis of the 1-aryl-1-cyclobutyl para nitrobenzoates (**22**) is also more negative than the ρ^+ values observed for the five-, six-, and seven-membered ring systems.[10] This relatively large negative ρ^+ value for the cyclobutyl system was attributed to the difficulty of incorporating an sp^2 atom into the ring, which makes the developing cationic center more electron demanding, resulting in relatively large electron supply from the aryl group and relatively large negative ρ^+ value.[10] The relatively large negative ρ^{C^+} value can also be accounted for on the basis of similar considerations.



21
ρ^{C^+} −18.1



22
ρ^+ −4.9

The ρ^{C^+} values of −16.3 and −16.0 for systems **8** and **9**, respectively, compare with the value of −17.0 observed for the arylcyclopentyl system, **5**. Although a safe conclusion for the differences in the ρ^{C^+} values for the systems **8** and **9** and the cyclopentyl system **5** cannot be reached because of the suggested anisotropy effects in bicyclic systems, the relatively less negative ρ^{C^+} values for the systems **8** and **9** may be attributed to additional C–C hyperconjugative and inductive stabilizations provided by the norbornyl moiety fused onto the cyclopentyl ring in the systems **8** and **9**.

Table III. Physical Constant Data for the Coumaranyl Alcohols 13-18

alcohol	mp or bp (mm), °C	alcohol	mp or bp (mm), °C
13	106-108 (0.1)[a]	16	77
14	126-128 (0.1)[a]	17	113-114
15	74	18	125

[a] The distillate was found to contain the corresponding olefins along with the alcohol (^1H NMR and ^{13}C NMR) and was used for the ion preparation without further purification. Satisfactory analytical data (C ± 0.37 and H ± 0.2%) were obtained for all the other compounds.

Experimental Section

Precursors. The tertiary alcohols **13–18** were synthesized by the reaction of the corresponding ketone with 5-lithiocoumaran (prepared from 5-bromocoumaran and *n*-butyllithium) as reported from our laboratories.[7] The physical constant data for these alcohols are summarized in Table III. The alcohols **13** and **14** were found to contain considerable amounts of the corresponding olefins (^1H NMR and ^{13}C NMR) after distillation. These alcohols were used for ionization to the corresponding cations without further purification. Satisfactory analytical data (C ± 0.3% and H ± 0.2%) were obtained for the alcohols **15–18**.

Carbocations. The ions were prepared by slow addition of the appropriate alcohol as a solution in SO_2ClF (alcohols **13** and **14**) or as a powder (alcohols **15–18**) to a solution of FSO_3H/SbF_5(1:1, mol/mol)/SO_2ClF cooled to −78 °C with rapid vortex mixing. The "magic acid", SbF_5/FSO_3H (1:1, mol/mol), concentration in the solution was 3 M. The concentration of the ion based on the alcohol added was ~0.5 M. Transfer of the solutions under nitrogen to 8-mm NMR tubes was achieved via a cooled double-ended syringe, as previously described.[13]

NMR Spectra. The ^{13}C NMR spectra were recorded at −70 °C on a Varian CFT-20 spectrometer, using 8-mm tubes containing a concentric 3-mm (outside diameter) capillary tube of completely deuterated acetone and tetramethylsilane, and using 8192 data points, a spectral width of 6500 Hz, and a pulse angle of 45°. Chemical shifts are reported in parts per million downfield from external tetramethylsilane.

Registry No. 2 (Z = *p*-OCH_2CH_2-*m*), 79816-06-1; 4 (Z = *p*-OCH_2CH_2-*m*), 79816-07-2; 6 (Z = *p*-OCH_2CH_2-*m*), 79816-08-3; 7 (Z = *p*-OCH_2CH_2-*m*), 79816-09-4; 8 (Z = *p*-OCH_2CH_2-*m*), 79827-17-1; 9 (Z = *p*-OCH_2CH_2-*m*), 79827-18-2; **13**, 79816-10-7; **14**, 79816-11-8; **15**, 79816-12-9; **16**, 79816-13-0; **17**, 79839-02-4; **18**, 79839-03-5.

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(12) Olah, G. A.; Berrier, A. L.; Arvanaghi, M.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1981**, *103*, 1122.

(13) Kelly, D. P.; Brown, H. C. *Aust. J. Chem.* **1976**, *29*, 957.

Hyperconjugation as a Parameter in Correlation Analysis

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Many years ago, Kreevoy and Taft suggested that hyperconjugation was an important factor in chemical reactivity and that a parameter which characterized hyperconjugation could be used together with other parameters to correlate log *k* values. A number of other groups of workers have extended this approach. A reexamination of the data shows that in all of the cases studied equally good results can be obtained by considering only electrical, steric, and polarizability effects. There is no need to involve hyperconjugation in order to satisfactorily account for the data. As all chemical reactivity data, including those studied here, can be described in terms of electrical and/or steric and/or polarizability parameters and as, at best, some data can be described in terms of hyperconjugation parameters, it is best to abandon the use of the unnecessary hyperconjugation parameters.

Kreevoy and Taft[1] proposed eq 1 for the correlation of

$$(Q_X/Q^\circ) = \rho^*\sigma^*_X + h(\Delta n_H) \qquad (1)$$

rate constants for the acid hydrolysis of substituted ethyl acetals and ketals, ΔG°_{333} values for the reaction of aldehydes and ketones with 2-propanol in toluene catalyzed

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(1) Kreevoy, M. M.; Taft, R. W. *J. Am. Chem. Soc.* **1955**, *77*, 5590; **1957**, *79*, 4011.

0022-3263/82/1947-0008$01.25/0

Table I. Data Used in the Correlations[f]

(1) X^1, X^2, k_r [$X^1X^2C(OEt)_2 + H_3O^+$ in 49.6% aqueous dioxane at 25 °C]:[a] Me, H, 0.248; *i*-Pr, H, 0.164; *t*-Bu, H, 0.188; *i*-Bu, H, 0.167; $HOCH_2$, H, 8.47×10^{-4}; Et, H, 0.267; $PhCH_2$, H, 8.70×10^{-3}; $ClCH_2$, H, 1.03×10^{-5}; Et_2CH, H, 0.312; $PhCH_2CH_2$, H, 2.88×10^{-2}; H, H, 4.13×10^{-5}; Me, Me, 7.52×10^2; CH_2-*t*-Bu, Me, 9.2×10^3; Et, Me, 7.2×10^2; PhVn, H, 1.52×10^2; $ClCH_2$, Me, 8.60×10^{-2}; $EtOCH_2$, H, 8.62×10^{-4}; $PhCH_2$, Me, 8.45×10; $PhOCH_2$, Me, 0.350; $HOCH_2$, Me, 1.16×10; $AcOCH_2$, Me, 0.228; $BrCH_2$, Me, 0.138; Ph, H, 7.07; MeVn, H, 2.98×10^2

(2) X^1, X^2, $\Delta\Delta G°_{333}$[g] [$X^1X^2C{=}O$ + *i*-PrOH in PhMe catalyzed by Al(O-*t*-Bu)$_3$]:[a] Me, H, −4.4; *i*-Bu, H, −4.2; *t*-Bu, H, −3.8; $MeOCH_2$, Me, −2.8; Ph_2CH, Me, −2.4; $PhCH_2$, Me, −0.5; Me, Me, 0; Et, Me, 0.3; cC_6H_{11}, Me, 0.6; iPr, Me, 0.3; tBu, Me, 0.4; $PhCH_2$; $PhCH_2$, −4.0; Et, Et, 0.9; Pr, Pr, 1.4; Bu, Bu, 1.4; iBu, iBu, 1.3; iPr, iPr, 1.4

(3) X^1, X^2, $\Delta\Delta H°_{355}$[g] [(*E*)-$X^1CH{=}CHX^2 + H_2(g)$]:[a] CH_2OH, H, −3.9; H, H, −5.2; $RO_2C(CH_2)_2$, H, −3.5; $ViCH_2$, H, −0.30; $ViCH_2CH_2$, H, −2.7; Me, H, −2.5; Et, H, −2.7; Pr, H, −2.6; Bu, H, −2.6; $BuCH_2$, H, −2.5; *i*-Bu, H, −2.5; *t*-$BuCH_2$, H, −1.9; *i*-Pr, H, −2.7; *sec*-Bu, H, −2.8; *t*-Bu, H, −2.7; RO_2CCH_2, Me, −2.0; Me, Me, 0.0; Et, Me, 0.0; Pr, Me, 0.0; *i*-Pr, Me, −0.2; Et, Et, 0.0

(4) X^1, X^2, $\Delta\Delta H°$[g] [(*E*)-$X^1CH{=}CHX^2 + H_2(g)$]:[a] H, H, −5.1, $ViCH_2$, H, −2.6; Me, H, −2.1; Et, H, −2.7; Pr, H, −2.5; Bu, H, −2.5; $BuCH_2$, H, −2.5; *i*-Bu, H, −2.5; *i*Pr, H, −2.2; sec-Bu, H, −2.6; *t*-Bu, H, −2.9; Me, Me, 0.0; Et, Me, −0.1; Pr, Me, −0.1; *i*-Pr, Me, 0.5; Et, Et, −0.1

sets 101–106[c] [substituent, log t'_R (relative retention time) of $CH_2{=}CHCH_2OAk$]: Me, 0.000, 0.000, 0.000, 0.000, 0.000, 0.000; Et, 0.224, 0.197, 0.205, 0.116, 0.099, 0.107; Pr, 0.503, 0.452, 0.429, 0.301, 0.298, 0.227; *i*-Pr, 0.386, 0.352, 0.301, 0.191, 0.170, 0.132; Bu, 0.787, 0.721, 0.686, 0.532, 0.487, 0.423; *i*-Bu, 0.643, 0.609, 0.529, 0.370, 0.337, 0.263; *sec*-Bu, 0.651, 0.626, 0.565, 0.403, 0.359, 0.291; *t*-Bu, 0.559, 0.541, 0.504, 0.326, 0.302, 0.241; Am, 1.071, 0.989, 0.979, 0.779, 0.694, 0.632; *sec*-Am, 0.915, 0.855, 0.753, 0.605, 0.548, 0.468; *i*-Am, 0.947, 0.895, 0.781, 0.667, 0.567, 0.492; *t*-Am, 0.871, 0.816, 0.694, 0.573, 0.532, 0.414; CH_2-*t*-Bu, 0.724, 0.690, 0.524, 0.376, 0.313, 0.180; Hx, 1.366, 1.239, 1.167, 1.016, 0.899, 0.782; Hp, 1.651, 1.495, 1.425, 1.250, 1.099, 0.974; Oc, 1.935, 1.741, 1.659, 1.463, 1.302, 1.177

set 111[d] [substituent, σ^*_c constants]: Me, 0.0; Et, −0.101; Pr, −0.116; *i*-Pr, −0.195; Bu, −0.131; *i*-Bu, −0.124; *sec*-Bu, −0.210; *t*-Bu, −0.288; Am, −0.145; CH_2-*i*-Bu, −0.140; MePrCH, −0.223; Et_2CH, −0.222; *sec*-$BuCH_2$, −0.140; *t*-Am, −0.305; Me-*i*-PrCH, −0.220; CH_2-*t*-Bu, −0.130; Hx, −0.159; MeBuCH, −0.237; EtPrCH, −0.235; $CH_2CHMePr$, −0.153; CH_2CH_2-*sec*-Bu, −0.156; $(CH_2)_3$-*i*-Pr, −0.155; CMe_2Pr, −0.317; Me-*sec*-BuCH, −0.235; Me-*i*-BuCH, −0.231; Et-*i*-PrCH, −0.213; $MeEt_2C$, −0.319; CH_2CHEt_2, −0.154; CH_2CMe_2Et, −0.147; CMe_2-*i*-Pr, −0.317; CHMe-*t*-Bu, −0.226; Hp, −0.173; CHMeAm, −0.251; CHE-*t*-Bu, −0.249; $CHPr_2$, −0.248; CH_2CMe_2Pr, −0.159; CH(*i*-Pr)$_2$, −0.238; CEt_3, −0.333; Oc, −0.187; CHMeHx, −0.265; $CH_2CHEtBu$, −0.179; CH_2CHEt-*i*-Bu, −0.173

set 121[e] [Ak^1, Ak^2, and k_{rel} for $Ak^1CO_2Ak^2 + H_2$ at 300 °C over 3% Rh on activated charcoal]: Me, Me, 0.12; Me, Et, 0.35; Me, Pr, 1.42; Me, Bu, 4.65; Me, *i*-Bu, 1.94; Me, Am, 7.46; Me, *i*-$BuCH_2$, 5.88; Et, Me, 0.36; Et, Et, 0.68; Et, Pr, 2.58; Et, Bu, 10.4; Et, *i*-Bu, 3.02; Pr, Me, 1.00; Pr, Et, 1.51; Pr, Pr, 4.39; Pr, Bu, 13.6; Pr, *i*-Bu, 6.97; *i*-Pr, Me, 0.88; *i*-Pr, Et, 1.03; *i*-Pr, Pr, 2.77; *i*-Bu, Me, 1.31; *t*-Bu, Me, 1.65; *i*-Bu, Pr; 6.21; *t*-Bu, Pr, 4.67

[a] Reference 1. [b] Excluded from the correlation. [c] Values of log t'_r for sets 101–106 are given consectively after the substituent. Column packings are as follows: set 101, Apiexon L; set 102, SE-30; set 103, Vcon polar; set 104, Carbowax 20M; set 105, XF-115; set 106, DEGS.[4] [d] Reference 10. [e] Reference 5. [f] Abbreviations: Vi = vinyl, Vn = vinylene, Hx = hexyl, Hp = heptyl, Oc = octyl. [g] In kilocalories per mole per degree.

by Al(O-*t*-Bu)$_3$, and $\Delta H°_{355}$ and $\Delta H°_0$ values for the hydrogenation of *trans*-1,2-disubstituted ethylenes in the gas phase. The n_H value in eq 1 is given by eq 2, n_α is the sum

$$n_H = 6 - n_\alpha \tag{2}$$

of the α-hydrogen atoms in the substituents. Many reports have appeared in the literature since then in which hyperconjugation has been used, directly or indirectly, as a parameter in the correlation of chemical reactivity or physical properties. Thus, Hancock[2] and Palm[3] have used "corrected" steric parameters which have been modified by the inclusion of factors which were intended to account for hyperconjugation effects. Fellous, Luft, and their coworkers[4] have used eq 3 which results from eq 1 on the

$$Q_{Ak} = \rho^*\sigma^*_{Ak} + E_{S,Ak} + h(n - 3) \tag{3}$$

introduction of a steric term (Ak = alkyl) to correlate the logarithms of retention times for AkY (Y = $OCH_2CH{=}CH_2$, CO_2Me, Ac, SH, CN). Zdrazil and Kraus[5] have used an equation analogous to eq 1 to correlate relative reactivities for esters of the type $Ak^1(CO)OAk^2$ with hydrogen on rhodium.

We have shown[6] that alkyl group steric effects upon chemical reactivity and physical properties are a function of the branching equation given by eq 4, where n_i repre-

$$Q_X = \sum_{i=1}^{m} a_i n_i + a_0 \tag{4}$$

sents the number of C–C bonds to the *i*th carbon atoms in the alkyl group, the C atom bonded to the rest of the molecule being numbered 1. We have modified the branching equation by the inclusion of the variables n_c and n_c^2, where n_c is the total number of carbon atoms in the alkyl group, to give the bioactivity branching equation shown in eq 5 and have shown that this equation is gen-

$$Q_X = a_1n_1 + a_2n_2 + a_3n_c + a_4n_c^2 + a_0 \tag{5}$$

erally applicable to the biological activity of alkyl-substituted data sets.[7] We have examined most of the steric parameters for alkyl groups reported in the literature by correlation with eq 4. The results show that these parameters differ only in their dependence on branching at C^1, C^2, and C^3. The dependence on branching at the various positions in the alkyl group can be expressed by the relationship shown in eq 6a or by the ratio ϕ_{ij}. The

$$P_i = |a_i|100/\sum_{i=1}^{m}|a_i| \tag{6a}$$

$$\phi_{ij} = a_i/a_j \tag{6b}$$

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(2) Hancock, C. K.; Meyers, E. A.; Yager, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 4211. Hancock, C. K.; Falls, C. P. *Ibid.* **1961**, *83*, 4214. Hancock, C. K.; Yager, B. J.; Falls, C. P.; Schrack, O. O. *Ibid.* **1963**, *85*, 1297.

(3) Palm, V. "Grundlagen der Quantitativen Theorie Organischen Reaktionen"; Akademie-Verlag: West Berlin, 1971; p 168.

(4) Fellous, R.; Lizzani-Cuvelier, L.; Luft, R.; Rabine, J. P.; Rouillard, M. *Bull. Chem. Soc. Fr.* **1974**, 2482.

(5) Zdrazil, M.; Kraus, M. *Collect. Czech. Chem. Commun.* **1974**, *29*, 3515.

(6) Charton, M. *J. Org. Chem.* **1978**, *43*, 3995.

(7) Charton, M.; Charton, B. I. 3rd Congress of the Hungarian Pharmacological Society, 1979; Akademiai Kiado, Budapest, 1980; Symposium Volume, p 210.

major difference between the E_S° steric parameters of Hancock or the E_S^c steric parameters of Palm, both of which are supposed to include a hyperconjugation correction, and the E_S parameters of Taft or our υ parameters is that the former are more dependent on branching at C^1 than are the latter. Thus, it is possible to account for better correlation with E_S^c or E_S° in some cases purely in terms of a different dependence of the steric effect on geometry due to differences in the steric demand of the property being correlated. In the case of chemical reactivity, for example, the difference could be due to a difference in transition-state geometry. There is no need, then, to invoke hyperconjugation to explain the results. We felt that it would be useful, therefore, to reexamine the data sets studied by Kreevoy and Taft in order to determine whether the use of the hyperconjugation parameter in these correlations was unequivocal.

Results and Discussion

Work of Kreevoy and Taft. All of the data studied by Kreevoy and Taft are for systems of the type X^1X^2Y, in which X^1 and X^2 are substituents and Y is the active site (the site at which the measurable phenomenon takes place). Let X^1 and X^2 be $Z^1Z^2Z^3C$ or H. In the general case, some measurable chemical or physical property, *Q*, of the active site can be correlated with eq 7 (LDS). If

$$Q_{X^1X^2} = L\sum\sigma_{IX} + D\sum\sigma_{DX} + S\sum\upsilon_X + h \qquad (7)$$

the range in σ_D is small, as is usually the case for $CZ^1Z^2Z^3$ ($CZ_3{}^i$) groups, the average value of σ_D, $\bar{\sigma}_D$, will represent the value of σ_D (which will be essentially constant). In this event, there are only three possible values that the delocalized electrical effect term ($D_2\sigma_{DX}$) in eq 7 can have: (1) if $X^1 = X^2 = H$, then as $\sigma_{DH} = 0$, $D\sum\sigma_{DX} = 0$; (2) if $X^1 = H$ and $X^2 = CZ^1Z^2Z^3$, then $D\sum\sigma_{DX} = D\bar{\sigma}_D$; (3) if $X^1 = X^2 = CZ^1Z^2Z^3$, then $D\sum\sigma_{DX} = D2\bar{\sigma}_D$. As σ_D is constant, the term $D\sum\sigma_{DX}$ can be replaced by $D'n$, where *n* is the number of $CZ^1Z^2Z^3$ groups and may take on the values 0, 1, or 2. Then,

$$Q_{X^1X^2} = L\sum\sigma_{IX} + D'n + S\sum\upsilon_X + h \qquad (8)$$

We have shown elsewhere[8] that for ZCH_2 groups,

$$\sigma_{I,ZCH_2} = a_1\sigma_{IZ} + a_{01} \qquad (9)$$

If in the sets studied $Z^2 = Z^3 = H$, then

$$Q_{X^1X^2} = L\sum(a_1\sigma_{IZ} + a_{01}) + D'n + S\sum\upsilon_X + h \qquad (10)$$

$$= La_1\sum\sigma_{IZ} + 2La_{01} + D'n + S\sum\upsilon_X + h \qquad (11)$$

$$= L'\sum\sigma_{IZ} + D'n + S\sum\upsilon_X + h \qquad (12)$$

If S is negligible, or ν_X is constant

$$Q_{X^1X^2} = L'\sum\sigma_{IZ} + D'n + h \qquad (13)$$

In order to compare the results of correlations with eq 12 or 13 and those with the Taft–Kreevoy equation (eq 1), we must include the compounds for which X^1 and/or X^2 = H. For this purpose we may calculate an effective σ_{IZ} value for X = H($\sigma_{IZ(H)}$) as follows:

$$X^1 = X^2 = H \text{ as } \sigma_{IH} \equiv \sigma_{DH} \equiv \upsilon_H \equiv 0; \text{ from eq 7, } Q_{HH} = h \qquad (14)$$

When $X^1 = X^2 = CH_2X$, eq 11 applies. If $X^1 = X^2 = H$, then $n = \nu = 0$, and eq 11 becomes eq 15. Equating 14

$$Q_{HH} = La_1\sigma_{IZ(H)} + 2La_{01} + h \qquad (15)$$

and 15 gives eq 16. As, $a_1 = 0.416$, $a_{01} = -0.0103$,[8] we can

$$La_1\sigma_{IZ(H)} = -2La_{01} \qquad (16)$$

calculate a value of 0.05 for $\sigma_{IZ(H)}$. This value is not significantly different from 0.

Table II. Electrical and Steric Effect Substituent Constants[a]

X	σ_{IZ}	σ_{RX}	σ^+_{RX}	υ_X
H	0	0	0	0
Me	0	−0.16	−0.16	0.52
Et	−0.01	−0.14	−0.14	0.56
Pr	−0.01	−0.16		0.68
i-Pr	−0.02	−0.16	−0.16	0.76
Bu	−0.01	−0.16		0.68
i-Bu	0.01	−0.16	−0.16	0.98
sec-Bu	−0.02	−0.16		1.02
t-Bu	−0.03	−0.18	−0.13	1.24
Am	−0.01	−0.16		0.68
Et_2CH	−0.02		−0.16	1.51
t-$BuCH_2$	−0.01	−0.17	−0.16	1.34
c-Hx	−0.02	−0.15		0.87
$ViCH_2$	0.11	−0.14		0.69
$ViCH_2CH_2$	0.02	−0.15		0.75
$PhCH_2$	0.12	−0.13	−0.13	0.70
Ph_2CH	0.24	−0.13		1.25
$PhCH_2CH_2$	0.03		−0.15	0.70
$ClCH_2$	0.47		−0.05[b]	0.60
$BrCH_2$	0.47		−0.09[b]	0.64
$HOCH_2$	0.24	−0.07	−0.15	0.53
$MeOCH_2$	0.30	−0.10		0.63
$EtOCH_2$	0.28		−0.08[b]	0.61
$PhOCH_2$	0.40		−0.06[b]	0.74
$AcOCH_2$	0.38		−0.07[b]	0.63
EtO_2CCH_2	0.30	−0.11		0.76[c]
$EtO_2CCH_2CH_2$	0.15	−0.13		0.68[c]

[a] Set 1 was correlated by using σ^+_R and sets 2–4 by using σ_R constants. All electrical effect constants are from ref 8 or were estimated as described therein unless otherwise noted. Unless otherwise noted, all υ constants are from: Charton, M. In "Design of Biopharmaceutical Properties Through Prodrugs and Analogs"; Roche, E. B., Ed.; American Pharmaceutical Soc.: Washington, DC, 1977; p 228. [b] Calculated from the pK_a's of the corresponding 4-substituted pyridinium ions in water by using the regression equation in ref 8. [c] Assumed equal to the values for CH_2CO_2H and $CH_2CH_2CO_2H$ given in: Charton, M. *J. Theor. Biol.*, 1981, *91*, 115.

Finally, all of the $CZ^1Z^2Z^3$ groups studied by Taft and Kreevoy are of the CH_2Z type with the exception of the *i*-Pr, Et_2CH, and *t*-Bu groups. For these groups we have assumed that as they are $CZ_3{}^i$ groups (see eq 17). We have

$$\sigma_{IZ} = \sum\sigma_{IZ^i} \qquad (17)$$

correlated the sets studied by Kreevoy and Taft with eq 12 and 13. The data and substituent constants are in Tables I and II; results of the correlations are reported in Tables III and IV. In three of the sets studied, best results were obtained with eq 13 (LD sets). In sets labeled D, best results were obtained with eq 18. Equation 18 results

$$Q_X = D'n + h \qquad (18)$$

when σ_{IZ} is constant or when $L = 0$. We can calculate values of *L* and *D* from the observed *L* and *D* values by means of the relationships shown in eq 19a,b. Values of

$$L = L'/a_1 \qquad (19a)$$

$$D = D'/\bar{\sigma}_D \qquad (19b)$$

$\bar{\sigma}_D$ were calculated from the values of $(\sigma_{DX^1} + \sigma_{DX^2})/2$ for each data point in the set. The $\bar{\sigma}_D$ values had standard errors of 0.03 or less, proving the constancy of σ_D (Table IV). It is convenient to describe the composition of the electrical effect in terms of P_D (eq 20), the percent delo-

$$P_D = |D|100/(|L| + |D|) \qquad (20)$$

calized (resonance) effect. Values of *L*, *D*, and P_D are reported in Table V. Clearly, the substituent effect in-

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[8] Charton, M. *Prog. Phys. Org. Chem.* **1980**, *13*, 119.

Table III. Results of Correlations with Eq. 12 and 21[x]

set	X_1	X_2	X_3	X_0	R^a	F^b	$r_{12}{}^c$	$r_{13}{}^c$	$r_{23}{}^c$	$S_{est}{}^d$	$S_1{}^d$	$S_2{}^d$	$S_3{}^d$	$S_0{}^d$	f^e	$100R^2\,{}^f$	n^g	eq
1-LDS	−8.77	3.84	0.181	−4.76	0.9928	391.7	0.386^m	0.286	0.117	0.294	0.401	0.125	0.217^r	0.212	0.133	98.57	21	12
2-LDS	−13.4	4.57	0.507	−9.25	0.9663	61.12	0.212	0.119	0.549^l	0.633	1.47	0.490	0.559^q	0.796	0.294	93.38	17	12
3-LDS	−5.62	2.49	0.147	−5.20	0.9895	264.7	0.095	0.146	0.079	0.221	0.554	0.0926	0.181^r	0.173	0.161	97.90	21	12
4-LDS	−0.598	2.60	−0.174	−4.99	0.9900	196.6	0.147	0.150	0.153	0.239	1.994	0.109	0.233^r	0.203	0.163	98.01	16	12
101B	0.305	−0.109	−0.112	−0.274	0.9949	386.7	0.112	0.416	0.174	0.0568	0.00942	0.0189	0.0215	0.0457	0.117	98.98	16	21
102B	0.274	−0.0848	−0.0877	−0.252	0.9957	458.1	0.112	0.416	0.174	0.0470	0.00780	0.0156	0.0178	0.0378	0.107	99.13	16	21
103B	0.267	−0.106	−0.130	−0.219	0.9900	197.1	0.112	0.416	0.174	0.0685	0.0114	0.0228	0.0260	0.0551	0.163	98.01	16	21
104B	0.249	−0.122	−0.140	−0.248	0.9924	259.4	0.112	0.416	0.174	0.0554	0.00919	0.0184	0.0210	0.0446	0.142	98.48	16	21
105B	0.220	−0.101	−0.126	−0.218	0.9883	167.6	0.112	0.416	0.174	0.0606	0.0100	0.0201	0.0230	0.0487	0.176	97.67	16	21
106B	0.203	−0.110	−0.149	−0.187	0.9869	150.1	0.112	0.416	0.174	0.0586	0.00972	0.0195	0.0222	0.0472	0.186	97.40	16	21
111B	−0.0144	−0.0820	0.00347	0.00972	0.9990	6293.0	0.191	0.491^h	0.100	0.00323	0.000377	0.000678	0.00618	0.00203		99.80	42	21

[a] Multiple correlation coefficient. [b] F test; the superscript indicates the confidence level (CL). In the absence of a superscript, CL = 99.9%. [c] Partial correlation coefficient of the *i*th independent variable on the *j*th independent variable. The superscript indicates the CL. In the absence of a superscript, CL = <90%. [d] Standard errors of the estimate and the regression coefficients. The superscript indicates the CL of the Student's *t* test for the significance of the regression coefficient. In the absence of a superscript, CL = 99.9%. [e] The standard error divided by the root mean square of the dependent variable. [f] The percent of the variance of the data accounted for by the regression equation. [g] The number of data points in the set. [h] 99.5% CL. [i] 99.9% CL. [j] 98.0% CL. [k] 97.5% CL. [l] 95.0% CL. [m] 90.0% CL. [q] 60.0% CL. [r] 50.0% CL. [s] 40.0% CL. [t] 30.0% CL. [u] 20.0% CL. [v] 10.0% CL. [w] <10.0% CL. [x] For eq 12, $X_1 = L'$, $X_2 = D'$, $X_3 = S$ and $X_0 = h$; for eq 21, $X_1 = a_c$, $X_2 = a_1$, $X_3 = a_2$, $X_0 = a_0$.

Table IV.[w] Results of Correlations with Eq 1, 13, 18, 21, 24, and 25

set	X_1	X_2	X_0	R^a	F^b	$r_{12}{}^c$	$S_{est}{}^d$	$S_1{}^d$	$S_2{}^d$	$S_0{}^d$	f^e	$100R^2\,{}^f$	n^g	eq.
1LD	−8.89	3.87	−4.65	0.9926	597.3	0.386^m	0.292	0.371	0.120	0.166	0.132	98.52	21	13
2LD	−13.4	4.81	−9.03	0.9642	92.46	0.212^m	0.629	1.46	0.409	0.752	0.292	92.96	17	13
3LD	−5.69	2.49	−5.10	0.9891	404.4	0.095	0.219	0.542	0.0913	0.122	0.159	97.82	21	13
4LD	−0.405	2.59	−5.10	0.9895	305.1	0.147	0.234	1.94^v	0.106	0.144	0.160	97.91	16	13
4D		2.59	−5.10	0.9895	654.9		0.226		0.101	0.139	0.155	97.91	16	18
121B	0.369	−0.120	−1.45	0.9490	95.21	0.289	0.168	0.0268	0.0413^i	0.136		90.06	24	21
121C	0.347		−1.46	0.9279	136.3		0.194	0.0297		0.157	0.389	86.10	24	24
1KT	−3.86	−0.628	3.40	0.9912	503.1	0.170	0.317	0.163	0.0375	0.148	0.143	98.24	21	1
2KT	−6.43	0.532	−2.60	0.9776	151.1	0.019	0.499	0.397	0.0888	0.351		95.57	17	1
3KT	−2.56	0.424	−2.37	0.9917	536.9	0.514^l	0.191	0.141	0.0299	0.119		98.35	21	1
4KT	−2.81	0.395	−2.15	0.9844	203.7	0.722^h	0.285	0.335	0.0596	0.234		96.91	16	1

[a-i,m,v] See the corresponding footnotes in Table III. [w] For eq 13, $X_1 = L'$, $X_2 = D'$, and $X_0 = h$; for eq 18, $X_2 = D'$ and $X_0 = h$; for eq 21, $X_1 = a_c$, $X_2 = a_1$, and $X_0 = a_0$; for eq 24, $X_1 = a_c$ and $X_0 = a_0$; for eq 25, $X_1 = a_c$, $X_2 = a_{11}$, and $X_0 = a_0$. For eq 18 and 24, footnote *a* indicates the simple correlation coefficient.

cludes a large delocalized component in all four of the sets studied.

We have also correlated the data with the Taft–Kreevoy equation (sets labeled KT in Table IV). We may compare correlations with eq 13 or 18 and those with eq 1 by examining the values of *F*, *S*, and $100R^2$.

It must be noted that we have included the points for the CH_2OH group in sets 1, 3, and 4 although we have noted elsewhere[8] that substituents which contain the OH group have substituent constants which are very strongly medium dependent. This type of substituent should generally be included only when it has been shown that inclusion does not significantly change the constants in the regression equation. We have included it in this work because it was included in the original correlations of Kreevoy and Taft. We must also point out that both we and Kreevoy and Taft have excluded the phenyl, 1-propenyl, and styryl groups.

The results obtained in the correlations were comparable to those reported by Kreevoy and Taft. The hyperconjugation effect proposed by these authors can be accounted for by a delocalized electrical (resonance) effect.

Table V. Values of *L*, *D*, P_D, *D* and S_D for Sets 1-4

set	$-L$	$-D$	P_D	$\bar{\sigma}_D$	$S\bar{\sigma}_D$
1	21.4	28.7	57.3	−0.135	0.0306
2	32.2	31.0	49.1	−0.155	0.0126
3	13.7	16.7	54.9	−0.149	0.0240
4	*a*	16.5	100.0	−0.157	0.0105

[a] σ_{IZ} is approximately constant for set 4. *L'* and *D'* values are from sets 1LD, 2LD, 3LD, and 4D in Table IV.

Chromatographic Retention Times. The relative retention times, t_r, for gas chromatography of alkyl allyl ethers studied by Fellous, Luft, and co-workers are presumably a function of intramolecular forces between the column packing surface and the substrate and of steric effects. As only alkyl groups vary in this data, we may apply a modification of eq 4 in the form of eq 21, where

$$Q_X = \sum_{i=0}^{p} a_i n_i + a_c n_c \qquad (21)$$

Table VI.[a,b] Results of Correlations with Eq 21 (P = 4 or 6) and 23

set	X_1	X_2	X_3	X_4	X_5	X_6	X_0	R	F
101A	0.311	-0.115	-0.118	-0.0206			-0.274	0.9950	274.7
102A	0.274	-0.0853	-0.0881	-0.00150			-0.252	0.9957	315.0
103A	0.273	-0.112	-0.135	-0.0192			-0.220	0.9902	138.2
104A	0.254	-0.127	-0.144	-0.0163			-0.248	0.9925	182.2
105A	0.226	-0.108	-0.132	-0.0223			-0.218	0.9887	119.2
106A	0.206	-0.115	-0.152	-0.0138			-0.187	0.9871	104.6
111A	-0.0157	-0.0805	0.00469	0.00173	0.00208	0.000363	0.0106	0.9991	3108.0
121A	0.383	-0.106	-0.0812	-0.0849	-0.0176	0.143	-1.47	0.9669	151.0

set	r_{12}	r_{13}	r_{14}	r_{15}	r_{16}	r_{23}	r_{24}	r_{25}	r_{26}
101A	0.112	0.416	0.572^l			0.174	0.261		
102A	0.112	0.416	0.572^l			0.174	0.261		
103A	0.112	0.416	0.572^l			0.174	0.261		
104A	0.112	0.416	0.572^l			0.174	0.261		
105A	0.112	0.416	0.572^l			0.174	0.261		
106A	0.112	0.416	0.572^l			0.174	0.261		
111A	0.191	0.491^h	0.499^h	0.512^h	0.396^j	0.100	0.335^l	0.347^l	0.170
121A	0.289	0.339	0.560^j	0.642^h	0.315	0.000	0.222	0.214	0.370

set	r_{34}	r_{35}	r_{36}	r_{45}	r_{46}	r_{56}	S_{est}	S_1	S_2
101A	0.068						0.0583	0.0133	0.0221
102A	0.068						0.0491	0.0112	0.0186
103A	0.068						0.0709	0.0162	0.0269^i
104A	0.068						0.0573	0.0131	0.0217
105A	0.068						0.0622	0.0142	0.0236
106A	0.068						0.0609	0.0139	0.0231
111A	0.073	-0.113	0.121	0.450^i	0.221	0.349^l	0.00325	0.00123	0.00143
121A	0.114	0.0370	0.158	0.605^i	0.277	0.207	0.151	0.164^l	0.163^s

set	S_3	S_4	S_5	S_6	S_0	f	$100R^2$	n	eq.
101A	0.0238	0.0340^s			0.0469	0.120	99.01	16	21
102A	0.0200^i	0.0287^w			0.0395	0.112	99.13	16	21
103A	0.0289^i	0.0414^t			0.0570^i	0.168	98.05	16	21
104A	0.0233	0.0334^t			0.0461	0.147	98.51	16	21
105A	0.0254	0.0363^s			0.0500^i	0.181	97.75	16	21
106A	0.0248	0.0355^u			0.0489^i	0.193	97.44	16	21
111A	0.00127	0.00141^p	0.00180^p	0.00265^u	0.00232		99.82	42	21
121A	0.167^t	0.189^t	0.174^w	0.190^r	0.349		93.49	24	23

[a] For eq. 21, $X_1 = a_c$, $X_2 = a_1$, $X_3 = a_2$, $X_4 = a_3$, $X_5 = a_4$, $X_6 = a_5$, and $X_0 = a_0$. For eq. 23, $X_1 = a_c$, $X_2 = a_{11}$, $X_3 = a_{12}$, $X_4 = a_{21}$, $X_5 = a_{22}$, $X_6 = a_{23}$, and $X_0 = a_0$. [b] For all other footnotes in this table, see the corresponding footnotes in Table III.

p = 3, n_i accounts for the steric effect as a function of branching, and n_c is proportional to the group polarizability and therefore provides a measure of the London (included dipole–induced dipole) force.[9] This force should be the major constituent of the intermolecular forces. Although these molecules have dipole moments, the magnitude of the dipole moment is not greatly affected by variations in the alkyl group. Excellent correlations of log t_r were obtained with eq 21 where p = 2.

The results of the correlations with eq 21 when p = 3 are reported in Table VI (sets labeled A), and those obtained with eq 21 when p = 2 are given in Table IV (sets labeled B). Values of P_c, P_1, P_2, ϕ_{12} and S_ϕ are set forth in Table VII. The P_c values show that polarizability alone accounts for from 40% to 60% of the substituent effect. Branching at C^2 is slightly more important than at C^1. As all of the ϕ_{21} values are not significantly different from the mean value, $\bar{\phi}_{21}$ = 1.17, we may conclude that the composition of the steric effect is the same on all of the column packings studied.

In a later paper, Fellous, Luft, and Rabine[10] have defined a set of chromatographic substituent constants, σ^*_c, from eq 22. In this equation log $t_{R,AkZ}$ is the reduced relative retention time of some compound AkZ in which Z is a constant functional group and Ak is a variable alkyl group, n_H is the number of H atoms bonded to the alkyl carbon atom to which Z is attached, and ρ and h are constants. The authors state that σ^*_c is a function of group contributions. We have correlated these σ^*_c constants with eq 21 with p = 4. Results are set forth in Table VII (set 111A). As a_3 and a_4 were not significant, correlation was carried out with eq 21 with p = 2. An excellent result was obtained (Table VI, set 111B). Values of P_c, P_1, P_2, ϕ_{21}, and S_ϕ are reported in Table VII. They show that more than 60% of the σ^*_c is due to polarizability and that with regard to the steric effect, branching at C^1 is far more important than branching at C^2. Clearly, then, the data can be accounted for very effectively in terms of steric effects and polarizability, and *it is not necessary to invoke hyperconjugation.*

$$\sigma^*_c \equiv {}^1\!/_\rho[\log t_{R,AkZ} - h(n_H - 3)] \qquad (22)$$

Table VII. Values of P_1, P_c, ϕ_{21}, and S_ϕ

set	P_C	P_1	P_2	ϕ_{21}	S_ϕ
101	58.0	20.7	21.3	1.03	0.266
102	61.4	19.0	19.6	1.03	0.283
103	53.1	21.1	25.8	1.23	0.360
104	48.7	23.9	27.4	1.15	0.240
105	49.2	22.6	28.2	1.25	0.337
106	43.9	23.8	32.3	1.35	0.313
111	14.4	82.1	3.5	-0.0423	0.00208
121	75.5	24.5^a			

[a] This is the P_{11} value.

Hydrogenolysis. We have also studied the relative reactivities reported by Zdrazil and Kraus[5] for the hy-

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(9) Charton, M.; Charton, B. I. *J. Org. Chem.* **1979**, *44*, 2284.

(10) Fellous, R.; Luft, R.; Rabine, J. P. *J. Chromatogr.* **1977**, *140*, 137.

drogenolysis of $Ak^1CO_2Ak^2$ over rhodium. As this presumably again involved some degree of intermolecular interaction between the rhodium surface and the ester and steric effects and, once more, as only alkyl groups were varied, we carried out correlations with a modification of eq 21 (eq 23). The data used are given in Table I, and results of the correlations are in Table VII.

$$Q_{X^1X^2} = a_{11}n_{11} + a_{12}n_{12} + a_{21}n_{21} + a_{22}n_{22} + a_{23}n_{23} + a_cn_c + a_0 \tag{23}$$

A significant correlation was obtained, accounting for 93.49% of the variance of the data. Unfortunately, n_{22} and n_{12} were both highly linear in n_c, as was n_{12} in n_{22}. We cannot determine with certainty, therefore, the extent to which steric effects are important in this reaction. Clearly, however, polarizability is a major factor. Thus, correlation with eq 24 gave very good results, accounting for 86.10%

$$Q_{X^1X^2} = a_cn_c + a_0 \tag{24}$$

of the variance of the data (set 121C, Table IV). Inclusion of a term for branching at C^{11} gave improved results (set 121B, Table IV), accounting for 90.07% of the variance of the data (see eq 25). Thus, steric effects do make small

$$Q_{X^1X^2} = a_cn_c + a_{11}n_{11} + a_0 \tag{25}$$

but significant contributions. Values of P_c and P_{11} are reported in Table VI. They are uncertain due to the collinearity of n_c with n_{12} and n_{22} noted above.

Conclusion

A long-held tenet in the philosophy of science is the use of the simplest explanation which will account for the observations. This is the essence of Occam's razor. In terms of correlation analysis, this may be interpreted as the use of the smallest possible number of parameters which will account for the data. We believe that we can account for most, if not all, chemical reactivities and physical properties in terms of localized (field and/or inductive) and delocalized (resonance) electrical effects, steric effects, and group polarizabilities. It is not necessary to invoke hyperconjugation parameters to account for physical or chemical phenomena, and therefore it is undesirable to do so.

Syntheses and Conformational Analyses of Isomeric Cocaines: A Proton and Carbon-13 Nuclear Magnetic Resonance Study

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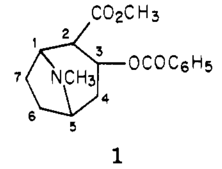
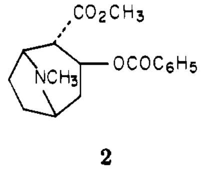
The ^1H and ^{13}C NMR spectra of cocaine (1), pseudococaine (2), allococaine (3), allopseudococaine (4), and the hydrochloride salts of 1, 2, and 4 have been recorded. The conformation of the piperidine ring in all four isomers, including the orientation of the *N*-methyl substituent, was determined from analysis of the data. Vicinal, geminal, and long-range coupling constants strongly suggest a chair conformation for the piperidine ring of all the compounds studied. Comparison of the ^1H and ^{13}C chemical shift data suggests that 2 and 4 have a larger population of axial *N*-methyl substituents than 1 and 3, respectively. Improved procedures for the synthesis of 2, 3, and 4 are reported. In particular, a stereoselective route to 4 is presented.

Cocaine (1), a natural component of coca leaves (*Erythroxylum coca*), is a potent central nervous system stimulant and is a major drug of abuse.[1] As one isomer of 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester, cocaine (1) has three diastereoisomers known as pseudococaine (2), allococaine (3), and allopseudococaine (4). The structure and stereochemistry of these isomers are well characterized and are as depicted. They can be viewed as *N*-methylpiperidines with an ethano bridge across the 2,6 positions, *N*-methylpyrrolidines with a propano group bridging the 2,5 positions, or as cycloheptanes containing a methylamino bridge. For the purposes of this paper we have viewed 1–4 as *N*-methylpiperidine derivatives.



1



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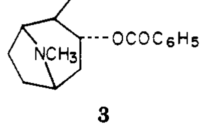

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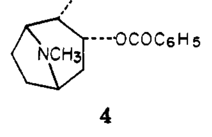
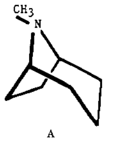


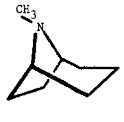
4

In principle, the tropane system can exist in four conformations. The *N*-methyl group can be either syn (A, C) or anti (B, D) to the ethano bridge, and in addition, the piperidine ring can adopt either chair (A, B) or boat (C, D) conformation. Single-crystal X-ray structure determination of cocaine (1) hydrochloride has shown a chair conformation for the piperidine ring with the *N*-methyl group syn to the ethano bridge (A).[2] Examination of the ^1H NMR spectra of 1–4 has led Beyerman and co-workers[3]

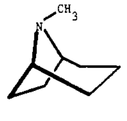


A

B



C



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