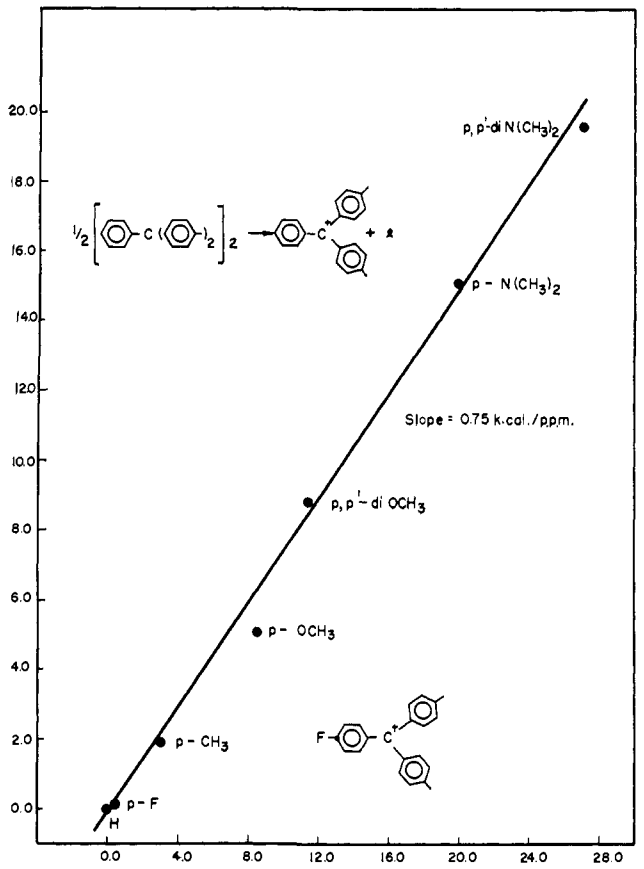

Figure 1. Relationship between effects of *para* substituents on stabilization energy and fluorine n.m.r. shielding for trityl cations. Ordinate: stabilization energy, kcal./mole, CH_3CN solutions; abscissa: δ_F, p.p.m., CH_3CN or H_2SO_4 solutions.

where R^+ is the *para*-substituted trityl cation, R_0^+ is the unsubstituted trityl cation, R–R is the symmetrical *para*-disubstituted hexaphenylethane, and R_0–R_0 is hexaphenylethane. It has been argued that $\Delta F_1^\circ \cong \Delta E^\circ_{\text{electronic}}$ and that $\Delta E^\circ_{\text{electronic}}$ is associated largely with the cation state.[7] The basis for the argument is the approximate equality of ΔF_1° with the corresponding ΔF_2° for the reaction at 298°K.

$$R^+ + R_0\text{–OH} \rightleftharpoons \text{R–OH} + R_0^+ \qquad (2)$$

where R_0–OH is triphenylmethanol and R–OH is the *para*-substituted triphenylmethanol. The approximate equality $\Delta F_1^\circ \cong \Delta F_2^\circ$ provides support for the argument, particularly since reaction 1 is measured in acetonitrile and reaction 2 in aqueous solutions.[7]

Preliminary measurements of the temperature coefficient of the Jenson cell have been carried out, and the results appear to provide even more convincing evidence that $\Delta F_1^\circ \cong \Delta E^\circ_{\text{electronic}}$. Table I lists values of ΔF_1° at 298°K. and the presently available values of the corresponding ΔH_1° obtained from e.m.f. measurements at 10 and at 25°. The observation that $\Delta F_1^\circ \cong \Delta H_1^\circ$ (or $\Delta S_1^\circ \cong 0$) provides evidence which apparently excludes[9] the possibility of any substantial contribution of solvent effects to values of ΔF_1°.

The relationship $\delta_F = C_1 E^\circ_{\text{electronic}} + C_2$ yields for a reaction series having a given state change between products and reactants: $\Delta\delta_F = C_1 \Delta E^\circ_{\text{electronic}}$. The approximate equality or proportionality between corresponding values of ΔF° and $\Delta E^\circ_{\text{electronic}}$ then leads us to anticipate linear shielding–free-energy relationships. The present discussion appears to provide some theoretical basis for recently reported[10] empirical relationships of this kind.

(9) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 80–84; (b) L. G. Hepler, *J. Am. Chem. Soc.*, **85**, 3089 (1963).

Table I. Enthalpy Stabilization Energies

para subst.	ΔF_1°,[a] kcal.	ΔH_1°,[b] kcal.
H,H,H	(0.0)	(0.0)
CH_3,CH_3,H	3.2	2.8
OCH_3,OCH_3,H	8.7	8.0
$N(CH_3)_2$,H,H	15.1	14.9

[a] At 298°K., experimental error ±0.1. [b] At 290°K., experimental error ±0.8.

(10) R. W. Taft, *et al.*, Preprints of Papers, Division of Petroleum Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. A19.

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Stabilization Energies of Substituted Methyl Cations. The Effect of Strong Demand on the Resonance Order[1]

Sir:

Lossing and students have found excellent correlation of the ionization potentials of *meta*- and *para*-substituted benzyl radicals[2] with Brown's σ^+ values.[3] This result coupled with applications of ionization and appearance potentials to condensed phase reactivities[4] and the previously known substantial effects of certain substituents on the appearance potential of the substituted methyl cation[4a] prompted us to a systematic investigation of the appearance potentials (A) of the general system

$$CH_3X_g + e \longrightarrow {}^+CH_2X_g + 2e + H$$

Table I summarizes the values of A for the substituted methyl cations which we have determined by the retarding-potential difference method[5] on a modified Bendix Model 14-101 time-of-flight mass spectrometer. The energy spread of the pseudo-monoenergetic electron beam was approximately 0.1 e.v. and Xe, Kr, and NO (depending on the A value) were used to calibrate the electron energy scale. The substituent effect of X is given as the stabilization energy relative to CH_3^+, S.E. $\equiv -(A_{CH_3X} - A_{CH_4})$. The effects obtained are unique in their magnitude; it seems unlikely that a larger range of substituent effects on energy will be found.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.
(2) A. G. Harrison, P. Kebarle, and F. P. Lossing, *J. Am. Chem. Soc.*, **83**, 777 (1961).
(3) H. C. Brown and Y. Okamoto, *ibid.*, **79**, 1913 (1957); **80**, 4979 (1958).
(4) (a) F. H. Field and J. L. Franklin, "Electron Impact Phenomena," Academic Press Inc., New York, N. Y., 1957, Chapter VI; (b) A. Streitwieser, Jr., *Progr. Phys. Org. Chem.*, **1**, 1 (1963).
(5) R. E. Fox, W. M. Hickam, and T. Kjeldaas, *Rev. Sci. Inst.*, **26**, 1101 (1955).

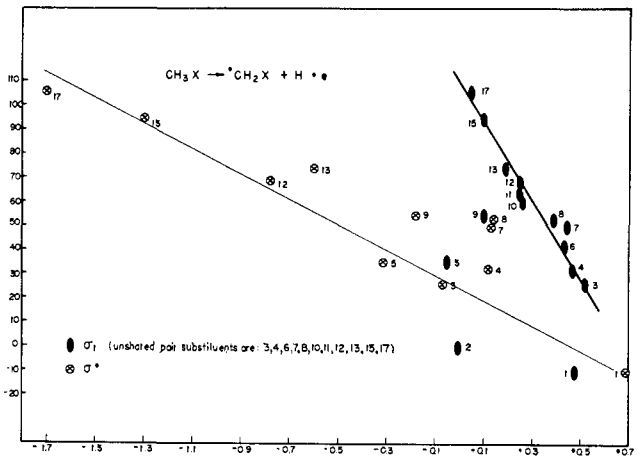

Figure 1. Relative stabilization energies for monosubstituted methyl cations. Ordinate: S.E., kcal./mole; abscissa: σ-value; ●, σ_I parameter; ⊗, σ^+ parameter.

Figure 1 plots S.E. of the methyl cations *vs.* corresponding σ^+ values. Points for X = NMe_2 (17), NH_2 (15), OMe (12), Me (5), F (3), and CN (1) follow a satisfactory linear correlation with σ^+. However, in contrast to the Lossing correlation the points for X = SMe (13), I (8), Br (7), and Cl (4) all give substantially larger S.E. then expected from their σ^+ values. No substantial improvement in correlation is obtained using parameters such as σ_p, $\sigma_R{}^+$, or $\sigma_p{}^\circ$.[6] Figure 1 also shows a plot *vs.* the inductive parameter,[6] σ_I. Although there is also no general correlation with σ_I, it appears significant that the stabilization energy effects of all of the *unshared-pair donor* substituents are correlated satisfactorily by the equation: S.E. (kcal.) = 110 − 164σ_I.

Table I. Relative Stabilization Energies of Monosubstituted Methyl Cations

	Ion	ΔA,[a] e.v.	S.E., kcal.[b]	σ_I
1	$^{+}CH_2CN$	+0.4	−10	+0.48
2	$^{+}CH_3$	(0.0)[c]	(0)	(0.00)
3	$^{+}CH_2F$	−1.1	26	+0.52
4	$^{+}CH_2Cl$	−1.4	32	+0.47
5	$^{+}CH_2CH_3$	−1.5[d]	35	−0.05
6	$^{+}CH_2SCN$	−1.8	42	+0.44
7	$^{+}CH_2Br$	−2.2	51	+0.45
8	$^{+}CH_2I$	−2.3	53	+0.39
9	$^{+}CH_2C_6H_5$	−2.4	55	+0.10
10	$^{+}CH_2OH$	−2.6	60	+0.26
11	$^{+}CH_2SH$	−2.8	64	+0.25
12	$^{+}CH_2OCH_3$	−3.0	69	+0.25
13	$^{+}CH_2SCH_3$	−3.2	74	+0.19
14	$^{+}CH_2P(CH_3)_2$	−3.4	79	...
15	$^{+}CH_2NH_2$	−4.1	95	+0.10
16	$^{+}CH_2NHCH_3$	−4.3	99	...
17	$^{+}CH_2N(CH_3)_2$	−4.6	106	+0.05

[a] $\Delta A = A_{CH_3X} - A_{CH_4}$, ±0.1 e.v. [b] S.E. = $-23.06\Delta A \pm 3$; evidence that the substituent effects are negligible in the neutral CH_3X compared to the cation state is presented in a subsequent publication. [c] Appearance potential 14.4 ± 0.1 e.v. [d] From ref. 4a.

The substituent X may stabilize the methyl cation through spatial σ- or π-bond interactions. The inductive parameter σ_I has been proposed as a quantitative measure of the former two.[6] In the present instance it cannot be doubted, however, that it is the R effect (from the π-bond interaction) which predominates.[7] The σ_I correlation shown in Figure 1 for the unshared-pair donor substituents evidently follows from an approximately linear relationship of the R effect with σ_I.

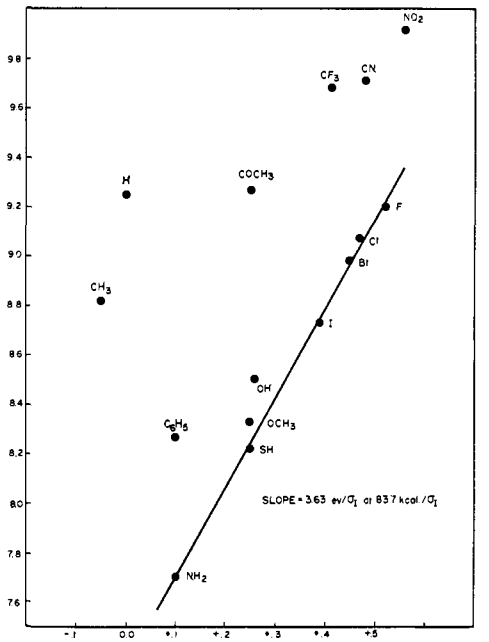

Figure 2. Relationship between ionization potential of substituted benzene and σ_I parameter. Ordinate: *I* for C_6H_5X, e.v.; abscissa: σ_I.

The present results are unprecedented in any of the aromatic σ *scales*,[6] where the order of electron-releasing R effect is I < Br < Cl < F and SCH_3 < OCH_3. For the methyl cations, the converse orders of stabilizing electron-releasing R effects I > Br > Cl > F and SCH_3 > OCH_3 are displayed (Table I). We note further that this latter order is not unique to nonaromatic systems. The ionization potentials for monosubstituted benzenes[4b] show the same order. In fact, Figure 2 displays the same kind of correlation (as Figure 1) between σ_I and the ionization potentials for benzene substituted with unshared-pair donor substituents.

Evidently the order of electron-releasing R effect of *unshared-pair donor* substituents depends upon the electronic demands placed upon the substituent. In the extreme demanding situations represented in methyl or phenyl cations simplification prevails apparently because the R effect involves only *one predominant interaction mechanism*, the C–X π(p–p) interaction. Under these conditions the I and the R effects are approximately linearly related (1) to one-another, (2) to their sum, and (3) to σ_I values. In the more weakly demanding situation represented by side-chain reactivities of benzene derivatives (including σ^+ reactivities) this simplification does not in general prevail.

Precise linear relationships between σ_I and the R

(6) *Cf.* R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960).

(7) This conclusion is supported by unpublished HMO calculations for UAFPD substituents (ref. 8) which reproduce the major trends of ΔA in Table I.

(8) R. W. Taft, *et al.*, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

effects of *meta* and *para* unshared-pair donor substituents in side-chain reactivities of benzene are restricted to elements of the first row in even the most favorable systems.[8] We suggest that these restrictions are to be associated with the intervention of additional interaction mechanisms in the R effects which arise because of the relatively weak electronic demands placed upon the substituent by the bonded phenyl function (which acts as an available electron source). That is, the additional orbital participation by the first atom of X, *e.g.*

$$=\ddot{\underset{\cdot\cdot}{\underset{\cdot\cdot}{I}}}:^{-}\ (\pi(p\text{-}d))^{9}\ \text{or}\ -\overset{+}{S}=C=N^{-}$$

which may then be involved precludes such unshared-pair donor substituents from displaying the $\pi(p\text{-}p)$ σ_I order of R effects. Therefore the aromatic side-chain reactivities require a minimum of two substituent parameters (*e.g.*, σ_I and σ_R or σ_m and σ_p) for generalized description.[10]

(9) J. R. Hoyland and L. Goodman, *J. Phys. Chem.*, **64**, 1816 (1960); *cf.* also ref. 6, footnote 38b.

(10) Evidently at least two substituent parameters are also required to describe substituent effects in general for the methyl cation stabilization energies or the substituted benzene ionization potentials (*i.e.*, to include substituents, *e.g.*, CH_3, C_6H_5, H, CN, etc., with the unshared-pair donor substituents).

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A Rapid Synthesis of Oligopeptide Derivatives without Isolation of Intermediates

Sir:

We wish to report a novel use of a water-soluble carbodiimide [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[1]] for the extremely rapid and facile synthesis of pure, protected oligopeptides (4–7 units) without isolation of intermediates.[2] By this technique, pure tetra- and pentapeptide derivatives (compounds **1–7**), corresponding to amino acid sequences in a strepogenin-active peptide isolated from acid digests of insulin[3] and at the active sites of certain enzymes, have been prepared in 2.5 to 3.5 days, typically in yields of 35–56% over-all. The peptides contained amino acids notoriously troublesome in peptide synthesis, including serine, threonine, methionine, and histidine.

For a typical coupling step, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.1 equiv.) was added to a solution of the N-carbobenzyloxyamino acid (1–1.1 equiv.), the amino acid ester hydrochloride or peptide ester hydrochloride (1 equiv., 5 or 10 mmoles), and triethylamine (1 equiv.) in methylene chloride (20 ml.). After 1 hr. at room temperature the solution was washed successively with water, dilute hydrochloric acid, water, sodium bicarbonate solution, and water. The dried solution was evaporated under reduced pressure and the solid (usually crystalline)

(1) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).

(2) Throughout this work the L-forms of amino acids were used.

(3) R. B. Merrifield and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 358 (1956).

Table I

No.	Compound	Over-all yield, %	Mol. formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	$[\alpha]_D$, deg.	Temp., °C.	Concn., %	Solvent
1	Z-Ser-His(Bzl)-Leu-Val-Glu-(OEt)$_2$[a]	40	$C_{44}H_{60}O_{11}N_7$	188–190	61.15	60.94	7.12	7.16	11.35	11.22	−22.7	25	2.0	DMF
2	Z-Ser-His-Leu-Val-Glu(OEt)$_2$[a–c]	11	$C_{37}H_{55}O_{11}N_7$	210–213	57.42	57.42	7.16	7.01	12.67	12.32	−47.0	25	3.0	Ethanol
3	Z-His(Z)-Leu-Val-Glu(OEt)$_2$[a]	42	$C_{43}H_{56}O_{11}N_6$	175–176	61.44	61.29	6.88	6.96	10.24	10.12	−12.6	26	2.0	DMF
4	Z-His(Bzl)-Leu-Val-Glu(OEt)$_2$[a]	54	$C_{41}H_{56}O_9N_6$	157–158	63.38	63.04	7.27	7.16	10.82	11.03	−21.5	25	2.2	DMF
5	Z-Glu(OBzl)-Ser-Ala-Gly-OEt[d]	56	$C_{30}H_{38}O_{10}N_4$	167–170	58.62	58.54	6.23	6.06	9.12	8.83	+2.7	25	2.0	DMF
6	BOC-Thr-Ser-Met-Ala-OEt[c,e]	9	$C_{22}H_{40}O_9N_5S$	100–105	49.22	49.29	7.51	7.63	10.44	10.66	−13.5	26	2.2	DMF
7	Z-Gly-Asp(OBzl)-Ser-Gly-OEt[f]	35	$C_{28}H_{34}O_{10}N_4$	135–137	57.33	57.18	5.84	5.81	9.55	9.42	−14.4	25	2.2	DMF

[a] Z, $C_6H_5CH_2OCO$; Bzl, $CH_2C_6H_5$; BOC, $(CH_3)_3COCO$; DMF, dimethylformamide. Peptide sequence in a strepogenin-active peptide isolated from acid digests of insulin.[3] [b] R. B. Merrifield and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 4646 (1956), report m.p. 213°, $[\alpha]^{27}D$ −46.3° (*c* 3, ethanol). [c] Low yield in final condensation. [d] Peptide sequence at active site of pseudocholinesterase and liver aliesterase (horse). [e] Peptide sequence at active site of subtilisin and mold protease. [f] Peptide sequence at active site of trypsin, chymotrypsin, thrombin, and elastase. [g] *Cf.* F. Sanger, *Proc. Chem. Soc.*, 76 (1963).