CIDEP for systems of homogeneously reacting radicals has been successfully explained by the radical-pair model[2,3] which considers the evolution of the electronic wave function for a pair of radicals during diffusive encounters and reencounters. In a single radical system the low field hyperfine lines usually tend toward emission[13] and this effect is explained by the theory if preferential reaction into the electronic singlet state of the product occurs. When two unlike radicals react, the difference in Zeeman energies caused by any *g* factor difference can act in the same way, producing emission for the radical of higher *g* factor. Trifunac and Thurnauer[15] seem to have observed such a behavior. A major difficulty arises in the case of e_{aq}^- in that the effect, emission from e_{aq}^- (and enhanced absorption for the counter radical with benzosemiquinone ion), is opposite to that described above. All of the counter radicals which lead to emission from e_{aq}^- (and indeed nearly all common radicals) have *g* factors considerably above that of e_{aq}^- (2.0003). Thus if the radical-pair model is to be used to explain the five cases showing emission it must be under the assumption that *reaction between* e_{aq}^- *and the counter radical occurs preferentially into the triplet state* of the product.

We believe that this proposed preference for the triplet state of the product molecule is correct and that it can be understood, qualitatively at least, on the basis of the arguments put forth by Henglein.[16] He has suggested that reactions of e_{aq}^- involve tunneling and that one must consider the matching of the energy levels which the electron will leave with those which it will occupy in the acceptor system, much as in the Franck-Condon principle. Henglein has placed the center of the occupied levels corresponding to e_{aq}^- at −1.7 eV with respect to the mobile electron. Because of the high ionization potential of the products in the systems used such as $CO_3\cdot^- - CO_3^{2-}$ or $C_6H_5\dot{O} - C_6H_5O^-$ the unoccupied ground state levels of the acceptor system will be at much more negative energies than −1.7 eV so that little reaction into the ground state is likely. If an excited state of the reactant system exists near the levels of e_{aq}^- then reaction can occur. Differences between various counter radicals can arise, therefore, because of their differing excited states. It would not be surprising if aromatics such as phenoxide ion and hydroquinone (the products with phenoxyl and benzosemiquinone ion radicals) had triplet excited states such that a reasonable match with e_{aq}^- occurred thus giving preferential rapid reaction into this triplet state.

Further work on the ESR of e_{aq}^- is being carried out in an attempt to account quantitatively for the time profile of the ESR signal using a modified Bloch equation[10] and to explore further the implications of the model suggested here to explain the preference for recombination to the triplet state.

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(7) The yields of e_{aq}^-, OH, and H are about 2.8, 2.8, and 0.6 radicals per 100 eV absorbed.

(8) As before[5] no field modulation was used so the spectra correspond directly to absorption. For determining the time profile, the ESR signal following each radiolysis pulse was digitized with a Biomation 8100 transient recorder and averaged by means of a PDP-8 minicomputer. The response time of the spectrometer was about 0.3 μsec. The magnetic field was also controlled by the computer.

(9) The reaction $e_{aq}^- + H_2O + N_2O \rightarrow OH + OH^- + N_2$ removes e_{aq}^- and converts it to additional OH. A corresponding increase in the ESR signal of the OH reaction product, $\dot{S}O_3^-$, is found in sulfite solutions saturated with N_2O.

(10) It is important to recognize that the slow *growth* of the ESR signal is a natural result of spin relaxation and in no way represents a chemical process. The detailed curve could be duplicated very closely by a calculation based on a modified Bloch equation similar to that employed earlier.[6]

(11) Optical pulse radiolysis experiments on similar solutions showed an electron half-life of about 35 μsec.

(12) The total radical concentration is estimated to be ~3 × 10^{-5} *M* under the dose conditions used. This value is consistent with the observed half-life being controlled by radical–radical reaction.

(13) Some of the decay of the signal of benzosemiquinone ion radical must be the result of radical–radical reaction. However, most of the radical does not react by this path as shown by the fact that the signal at 15 μsec is still nearly half that for the N_2O saturated solution (upper trace) where the yield is twice as large.

(14) That is, the low field-lines are weaker than the corresponding lines at high field. If the radical reaction rate is rapid enough as in pulse experiments[5] the low field lines actually appear in emission.

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Correlation of STO-3G Calculated Substituent Effects on the Proton Affinity of Benzene with σ^+ Parameters

Sir:

Linear free energy relationships have had an enormous impact on the direction which physical organic chemistry has taken in the last quarter century. Early attempts by Hammett and Taft among others to find a simple means of classifying the effects of substituents on chemical reactions have led directly to many of the now familiar concepts of bonding and structure.[1] Most of this multitude of reactions that have been correlated successfully by Hammett-Taft type schemes are entirely solution processes. Thus, interpretation of linear-free-energy correlations—or deviations therefrom—purely in terms of electronic arguments may at times be hazardous. With the advent of gas phase ion cyclotron resonance spectroscopy and of reliable nonempirical molecular orbital calculations—both of which may be used to provide energetic data on molecules and ions in their "dilute gas" phase—it should now be possible to separate the components of linear-free-energy correlations which are of a fundamental electronic origin from those that depend on the presence of solvent. Nevertheless, previous attempts to interpret electronic effects of substituents in quantitative terms by molecular orbital approaches have not been successful, undoubtedly because of the severe limitations of the semiempirical methods used.[2] In this communication we report the preliminary results of our ab initio theoretical investigations into the effects of meta and para substituents on the stability of protonated benzene.

The minimal basis set STO-3G method[3,4] was used to derive energies for the *isodesmic* process,[5] for comparison with the empirical σ^+ constants originally proposed by Brown and Okamoto[6] to correlate electrophilic aromatic substitution reactions. The STO-3G basis set has been shown previously to describe satisfactorily the energies of

Table I. Correlation of Proton Affinities and σ^+ Values for Para Substituted Benzenes

Substituent X	ΔE^a	σ^{+b}
	Para Substituents	
NO_2	−22.1	0.79
CN	−13.8	0.66
CF_3	−8.4	0.54
H	0.0	0.0
F	3.7	−0.073
Me	8.5	−0.311
Et	9.7	−0.295
i-Pr	10.8	−0.280
t-Bu	11.6	−0.256
OMe	15.7	−0.778
OH	16.0	-0.92^c
NH_2	27.2	-1.3^c
	Meta Substituents	
NO_2	−17.9	0.68
CN	−14.0	0.58
CF_3	−7.5	0.52
F	−7.5	0.352
OH	−5.3	$(0.04)^d$
H	0.0	0.0
NH_2	+0.6	-0.14^c
Me	2.0	−0.066
Et	2.4	−0.064
t-Bu	3.8	−0.059

[a] Energies (kcal mol^{-1}) of *isodesmic* processes (eq 1). [b] Reference 6 unless otherwise noted. [c] J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Chemistry", Wiley, New York, N.Y., 1963, p 204. [d] σ^+ values for non-hydroxylic solvents; R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

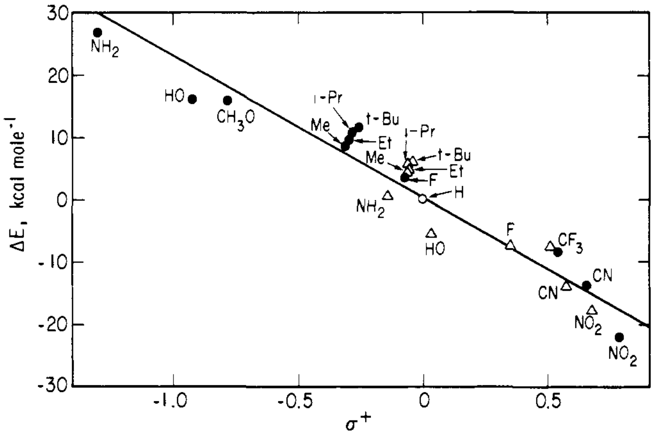
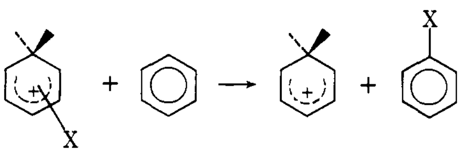


Figure 1. Correlation of ΔE values for isodesmic processes (eq 1) with σ^+ values. The least-squares regression line for all points except NH_2, OH, Et, *i*-Pr, and *t*-Bu is $\Delta E = (-22.83 \pm 1.63)\sigma^+ + (0.40 \pm 0.85)$. Circles correspond to para substituents, triangles to meta.

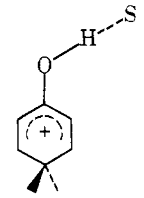


(1)

other isodesmic processes.[7] Both a "standard"[8,9] model and "partially optimized"[10] model were used for the Wheland intermediate with various substituents. Little difference was found for those several substituents calculated by both models. The STO-3G energies of neutral monosubstituted benzenes have already been reported.[11]

The data are summarized in Table I and presented in Figure 1. The overall results show a satisfactory correlation between the experimentally derived σ^+ values and the theoretical energy differences. For example, the electron-donating effect of *p*-F compared to the electron-attracting effect of *m*-F is well represented. Similarly, *m*-NH_2 is slightly electron donating in agreement with experiment. The *p*-NO_2 group is more deactivating than *m*-nitro.

Even systematic deviations are significant and explicable. For example, the progressive deviation of alkyl groups other than methyl from the linear correlation confirms the recent demonstration that the Baker-Nathan ordering of alkyl substituent effects in solution is entirely an artifact of the solvent.[9,12] That is, in the isolated molecule the larger *tert*-butyl group is better able to stabilize positive charge than are smaller alkyl groups. Also of interest is the observation that whereas a para hydroxy group is not as effective in stabilizing a positively charged center as its empirical substituent constant would seem to indicate, linear correlation between σ^+ and the energetic effect of methoxy is reasonable. Part of the difference no doubt stems from the possibility of hydrogen bonding of the hydroxy, but not the methoxy, substituent to the solvent, as originally suggested by Jaffe.[13]



The least-squares regression line, $\Delta E = -22.8\sigma^+ + 0.4$, does not differ significantly from those calculated for the separate meta and para substituents.[14] This correlation does not include the NH_2 or OH groups, in which hydrogen-bonding probably influences the empirical solution σ^+ values, and the alkyl groups other than methyl where ion solvation is apt to be hindered. The slope of the regression line corresponds to a value of ρ of −17 at 25°C to be compared with solution kinetic values for electrophilic aromatic substitution ranging from −6 to −12. The difference in ρ no doubt stems both from solvent participation and from the fact that substituent effects may be only partially developed in the transition states for aromatic substitution compared to those in protonated species.

The present results provide the important conclusion that minimum basis set ab initio calculations can quantitatively accommodate substituent effects in electrophilic aromatic substitution and that they afford a method complementing gas phase experimental results for distinguishing solvation effects from internal electronic effects. The results also provide a foundation for examining effects of various other types of substituents and for dissecting the electronic effects of substituents into changes in electron population and electron density functions. These further studies will be detailed in subsequent publications.

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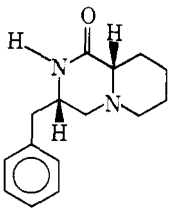
Structure and Synthesis of Verruculotoxin, a New Mycotoxin from *Penicillium verruculosum* Peyronel

Sir:

The fungus *Penicillium verruculosum* Peyronel, isolated from green peanuts, produces a toxic metabolite with an LD_{50} of 20 mg/kg (oral, 1-day-old cockerel).[1] Acute toxicity was characterized by ataxia, prostration, and complete lack of muscular coordination. In spite of these severe signs, the animals' eyes were open, and they appeared to be otherwise alert for the next hour. Isolation procedures, ir, NMR, MS, and uv data, for this metabolite have been reported in a preliminary paper, and the trivial name verruculotoxin was proposed.[1] We wish now to report the absolute stereostructure of verruculotoxin (**1**) from a combination of x-ray diffraction analysis and synthesis.



1

Verruculotoxin (**1**) crystallizes from CH_2Cl_2-heptane as large needles in the common and unambiguously determined space group $P2_12_12_1$ with a = 14.340 (1), b = 12.211 (1), and c = 7.896 (1) Å, and one molecule of $C_{15}H_{20}N_2O$ per asymmetric unit. All unique data with $2\theta \leq 114°$ were collected on a fully automated four-circle diffractometer using Cu radiation (λ 1.5418 Å). A total of 1048 reflections were measured and after correction for Lorentz, background, extinction, and polarization effects a total of 925 (88%) were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$). A multiple solution tangent formula approach[2] clearly showed 12 out of the 18 nonhydrogen atoms. A three-dimensional electron density synthesis revealed the remaining nonhydrogen atoms. Hydrogen atoms were located in a subsequent difference synthesis. Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms lowered the conventional crystallographic discrepancy index to 0.036 for the observed reflections.[3] Figure 1 is a computer generated drawing of the final x-ray model.

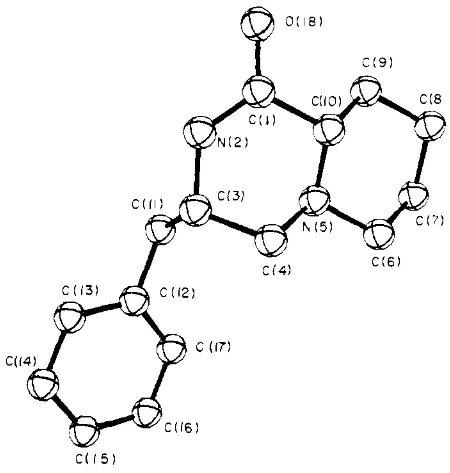
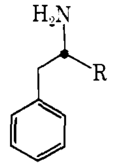


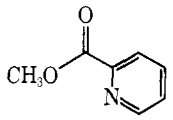
Figure 1. A computer generated perspective drawing of verruculotoxin **1**. The absolute configuration is as shown. Hydrogen atoms have been omitted for clarity.

Verruculotoxin (**1**) represents the first naturally occurring example of the octahydro-2*H*-pyrido[1,2-*a*]pyrazine system.[4] The piperazine ring of verruculotoxin (**1**) exists in a flattened chair conformation with the benzyl group in an axial position. Atoms C(10), C(1), O(18), N(2), and C(3) form a plane. The piperidine ring is also in a chair conformation and the bridgehead N(5) is puckered to give a trans ring junction. The phenyl group is planar, and no hydrogen bonds were detected in the crystal structure. Tables I–V which can be found in the supplementary material contain the fractional coordinates, important bond distances, important bond angles, temperature factors, and observed and calculated structure factors, respectively.

Verruculotoxin (**1**) can be viewed as a modified cyclic dipeptide of pipecolic acid and phenylalanine. A straightforward synthetic approach based on this dissection was undertaken. Phenylalinol (**4**)[5] was prepared from L-phenylalanine (**2**) by quantitative esterification with thionyl chloride in MeOH according to the procedure of Brenner and Huber[6] and reduction of the resulting methyl ester hydrochloride (**3**) with $NaBH_4$ in 50% aqueous EtOH (68%). A neat solution of equimolar amounts of phenylalinol (**4**) and methyl picolinate (**5**) was heated at 150° for 1 hr under a nitrogen atmosphere. The resulting amide **6** crystallized in near quantitative yield when placed under a vacuum for 12 hr. Recrystallization from hexane-ethyl acetate yielded a sample whose NMR, ir, and high resolution mass spectra were consistent with structure **6**. Alcohol **6** was smoothly transformed into chloride **7** by treatment with thionyl chloride in methylene chloride (96%). The NMR of **7** was consistent with the assigned structure but no further characterization was attempted. Chloride salt **8** was produced by refluxing a DMF solution of **7** for 9 hr and then precipitating **8** with acetone (64%). Hydrogenation of **8** in methanol



2, R = COOH
3, R = $COOCH_3$
4, R = CH_2OH



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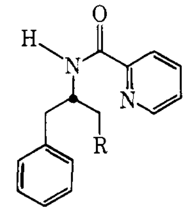

6, R = OH
7, R = Cl