SUBSTITUENT EFFECTS IN MONOSUBSTITUTED BENZENES: SEMI-EMPIRICAL SCF STUDIES OF THE HAMMETT CONSTANTS

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Semi-empirical SCF calculations using the AM1 Hamiltonian were shown to account for the Hammett σ constants and other properties of a representative series of 22 monosubstituted benzenes in terms of the atomic charges at the *ipso*, *ortho*, *meta* and *para* positions. The trends of the correlations with experimental σ constants were found to follow the normal expectations of physical organic chemistry. Additional support for the AM1 charge distributions was obtained in correlations with the ^{13}C chemical shifts of 12 of the test molecules. On the other hand, no correlations were found between σ constants and computed force constants for bending peripheral H atoms out of the plane of the aromatic ring, supporting the view that Hammett σ constants reflect charge distributions and not secondary effects expressed in the stiffness of bonds.

INTRODUCTION

In a semi-empirical SCF study of the energy costs for twisting tetra-*meso*-substituted pyridyl rings on porphyrins about the bonds attaching them to the macrocycle ring, undertaken to explore the energetically possible conformations of porphyrin–DNA complexes,[1–3] it was found that while moderate (say 10–30°) twisting away from the equilibrium angles[4,5] could be achieved at minimal energy cost – a few kJ at most – approaching a dihedral angle of 0° with respect to the macrocycle bond system meets energy barriers of many tens of kJ and induces large-scale distortion of the macrocycle ring itself.[6] Binding energies of porphyrin–DNA complexes, however, can be large, and because this interaction could form the basis for useful spectroscopic DNA probes or drugs,[7,8] it is of interest to investigate the origin of the the ring twisting barriers at a fundamental level. We elected to focus on substituted tetraphenylporphyrins (TPP) rather than on substituted pyridylporphyrins in order to simplify the problem. As noted long ago,[9,10] *meso*-substituted porphyrins are of interest not only as useful macrocycles, but also as test cases for theories of chemical bonding and reactivity. We were thus led to compute, using the Ampac programs and the AM1 Hamiltonian, the effects upon the energy barriers to ring twisting of variously substituted TPPs, the substituents being chosen so as to span a range of electronic effects.[11] Indeed, it proved to be the case that the nature of the substituent affected the barrier to ring twisting.[12] At the molecular size of substituted TPPs, however, the computational expense and the difficulty of achieving proper geometric convergence are such that extensive explorations become unwieldy. We were thus led to consider a still simpler set of questions, namely, how the semi-empirical quantum mechanical approach relates to the classical accounting for substituent effects in phenyl rings. Initially this entailed searches for correlations between semi-empirical values for atomic charges and experimentally derived values for the Hammett constants.[11] We later expanded the search to test for substituent effects upon ^{13}C chemical shifts[13–15] and force constants for out-of-plane bending of ring hydrogens, the former as an independent measure of electron distribution and the latter because interference with hydrogens *ortho* to the attachment carbon is the primary steric barrier to twisting TPP rings toward coplanarity with the macrocycle.

A variety of molecular orbital studies of substituent effects in monosubstituted benzenes have been reported before, ranging from simple π-electron calculations to

Table 1. Experimental values of Hammett constants, ^{13}C chemical shifts (δ), atomic charges (Q) and ring-H dihedral bending constants for monosubstituted benzenes[a]

Species	σ_p	σ_m	δ (ppm) ipso	ortho	meta	para	QC_{ipso}	QC_{ortho}	QCH_{ortho}	QC_{meta}	QCH_{meta}	QC_{para}	QCH_{para}	Q_{carbon}	Q_{phenyl}	k_{meta}
NC₂H₆	-0.83	-0.16	22.6	0	1.0	-11.5	0.0929	-0.0541	0.0127	-0.0612	-0.0010	-0.0588	0.0017	-0.1965	0.1179	39.26
NH₂	-0.66	-0.16	19.2	-12.4	1.3	-9.5	0.1317	-0.093	-0.0308	-0.0344	0.0244	-0.0860	-0.0253	-0.2090	0.0936	39.55
OH	-0.37	0.12	26.9	-12.6	1.8	-7.9	0.195	-0.1146	-0.0461	-0.0231	0.0369	-0.0962	-0.0345	-0.1766	0.1419	40.63
OCH₃	-0.27	0.12	30.2	-15.5	0.0	-8.9	0.1587	-0.0717	-0.0013	-0.0490	0.0125	-0.0670	-0.0051	-0.1498	0.1759	39.61
CH₃	-0.17	-0.07					-0.0606	-0.0409	0.0163	-0.0640	-0.0043	-0.0531	0.0066	-0.3236	-0.0299	39.11
C₂H₅	-0.15	-0.07					-0.0366	-0.0437	0.0130	-0.0636	-0.0040	-0.0540	0.0062	-0.3052	-0.0124	39.10
C₆H₅	-0.01	-0.06					-0.0025	-0.0386	0.0220	-0.0650	-0.0049	-0.0528	0.0072	-0.2625	-0.0388	39.19
H	0.00	0.00	0.0	0	0.0	0	-0.0593	-0.0593	0.0000	-0.0593	0.0000	-0.0593	0.0000	-0.3558	-0.0593	39.36
CH₂OH	0.00	0.00	12.3	-1.4	-1.4	-1.4	-0.0656	-0.0265	0.0328	-0.0689	-0.0086	-0.0463	0.0138	-0.3027	-0.0033	39.17
COO⁻	0.00	-0.10					0.005	-0.1085	0.0397	-0.1657	-0.0648	-0.1615	-0.0642	-0.7050	-0.1093	38.10
CH₂CN	0.18	0.16					-0.0801	-0.0306	0.0300	-0.0634	0.0008	-0.0424	0.0209	-0.3105	0.0024	39.29
F	0.06	0.34	35.1	-14.1	1.6	-4.4	0.2335	-0.0874	-0.0090	-0.0364	0.0292	-0.0709	-0.0057	-0.0849	-0.2682	39.94
PF₂	0.59	0.49					-0.4356	0.0237	0.0880	-0.0804	-0.0132	-0.0137	0.0510	-0.5627	-0.2350	39.37
Br	0.23	0.39	-5.4	3.3	2.2	-1	-0.0581	-0.027	0.0473	-0.0620	0.0037	-0.0447	0.0194	-0.2810	-0.0633	39.76
Cl	0.23	0.37	6.4	0.2	1.0	-2	0.04	-0.0395	0.0382	-0.0565	0.0101	-0.0505	0.0146	-0.2026	0.1512	39.94
COOH	0.45	0.37					-0.0818	-0.0089	0.0582	-0.0680	-0.0015	-0.0325	0.0323	-0.2681	-0.0639	39.56
PCl₂	0.61	0.54					-0.3991	0.0278	0.0970	-0.0786	-0.0080	-0.0060	0.0616	-0.5068	-0.1594	39.43
COCH₃	0.50	0.38	7.9	-0.3	-0.3	2.9	-0.1162	-0.02	0.0423	-0.0650	-0.0009	-0.0405	0.0227	-0.3267	-0.0106	39.11
CF₃	0.54	0.43					-0.1755	0.0082	0.0848	-0.0730	-0.0014	-0.0159	0.0531	-0.3212	0.0446	40.26
NH₃⁺	0.60	0.86					-0.1486	-0.0083	0.0778	-0.0347	0.0674	0.0229	0.1244	-0.2116	0.2662	41.22
CN	0.66	0.56	-19.0	1.4	-1.5	1.4	0.0006	-0.0127	0.0569	-0.0699	-0.0022	-0.0298	0.0361	-0.1944	0.1461	39.60
POF₂	0.89	0.81					-0.3964	0.0245	0.0921	-0.0801	-0.0113	-0.0105	0.0556	-0.5181	-0.1791	39.36
NO₂	0.78	0.71	19.6	-5.3	0.8	6	-0.0634	-0.0008	0.0858	-0.0627	0.0123	-0.0223	0.0500	-0.2126	0.1828	40.40

[a] Hammett constant data from Ref. 11; NMR chemical shifts in ppm referred to benzene, with upfield being negative, taken from Refs 13–15; atomic charges as computed from the AM1 Hamiltonian using the density matrix procedure of Ampac 2.10; bending force constant k_{meta} derived from the Ampac 2.10 standard enthalpy of formation values at 0 and ±15° dihedral angles of a meta hydrogen, with the dihedral referred to the ipso, ortho and meta carbons between the substituent and the bent bond.

ab initio studies at the STO–3G basis set level. The results were generally similar to the semi-empirical results presented here. Reviews of the relevant literature can be found in Refs 16 and 17.

EXPERIMENTAL

A cautious attitude is required in attributing substituent effects to physical causes, for benzene by itself cannot provide a large enough database to differentiate among the various sources of substituent effects that have been discussed in the literature.[18] As part of our caution we elected not to compare computed results directly with laboratory measurements, as this would imply arbitrarily selecting material from the vast experimental literature on substituent effects. Instead, we chose to take as a primary measure the values of Hammett σ constants in a standard tabulation,[11] for which the authors undertook a balanced evaluation of the literature of the field. It was still necessary to make choices among the 530 substituents for which σ constants are tabulated. We did this by adopting a list of 15 from an organic chemistry textbook,[19] augmenting it to provide additional examples at the extremes of the Hammett σ constant scale, and ending with a list of 22 substituents for the calculations (Table 1).

All calculations were done with the Ampac Version 2.10 program and the AM1 Hamiltonian.[20,21] For some of the calculations, symmetry constraints were applied; tests indicated that none of the results presented here were affected thereby, in particular, the computed standard enthalpies of formation with and without symmetry constraints differed by less than 1 kcal mol^{-1} (1 kcal = 4·184 kJ). Because of the low barriers to rotation of some of the substituents, it was not always possible to attain geometric convergence to low gradient norm values; again, none of the results presented here were affected. Atomic charge values presented here are those derived from the density matrix in the Ampac Version 2.10 program. Bending force constants were computed by fitting to a quadratic equation the standard enthalpy of formation values computed while the dihedral angle for a ring hydrogen was scanned twice in 5° increments over a reaction coordinate extending 15° above and below the plane of the aromatic ring. Spot checks showed no systematic dependence of the force constant on the manner of calculation.

RESULTS AND DISCUSSION

As often noted, the Hammett constants σ_m and σ_p correlate strongly with one another. This inescapable colinearity between the two prevents one from distinguishing between different sources of substituent effects on the basis of *meta* and *para* effects. The σ_m/σ_p correlation for the particular 22 substituents studied here, which has an R^2 value of 0·79, is less steep than

the $R^2 = 0·89$ correlation found for the tabulated set of 530 Hammett constants.[11] It was indeed found in separate trials that the correlations, or lack thereof, that appeared in plots against σ did not differ qualitatively from correlations in plots against σ_m.

Correlation of Hammett constants with charge distribution

Atomic charges computed at the *ipso*, *ortho*, *meta* and *para* positions and for the benzene ring – both for the carbon atom alone and for the sum of the carbon and
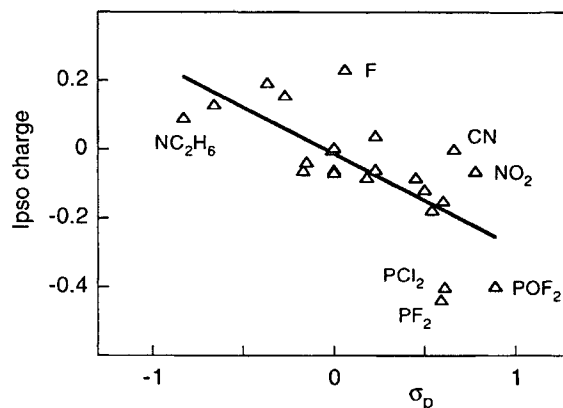

Figure 1. Correlation between AM1 atomic charges at the *ipso* carbon atom for 22 substituted benzenes (Table 1) and their σ_p values from Ref. 11. The correlation coefficient is $R = 0·70$; the corresponding correlation with σ_m has $R = 0·54$
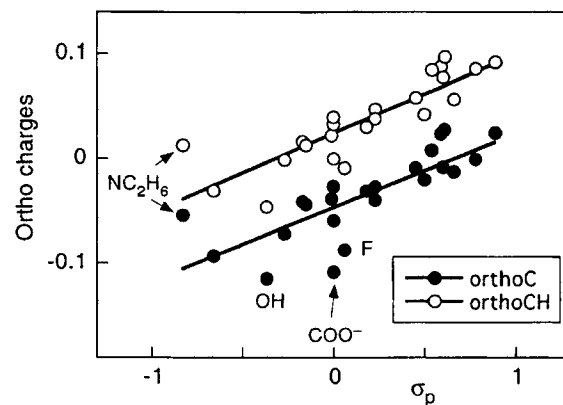

Figure 2. Correlation between AM1 *ortho* position atomic charges and σ_p values. The ordinate gives the atomic charges for the carbon atom alone (*ortho*C) and for the sum of the charges of the *ortho* carbon and its adjacent hydrogen (*ortho*CH). The correlation coefficient for the carbon atom alone is 0·78 and that for the sum of the carbon and hydrogen charges is 0·85; the corresponding correlations with σ_m have R values of 0·75 and 0·70

adjacent hydrogen atom charges – are shown as functions of σ_p and σ_m in Figures 1–5. Strong correlations exist for the *ortho* and *para* positions, but no significant dependence is found at the *ipso* or *meta* carbons or for the ring as a whole. The slopes of the correlation lines are listed in Table 2.

There are definite outliers on the correlation lines: NC_2H_6, OH, COO^- and F at the *ortho* position, COO^- and NH_3^+ at the *meta* position, NC_2H_6, COO^- and
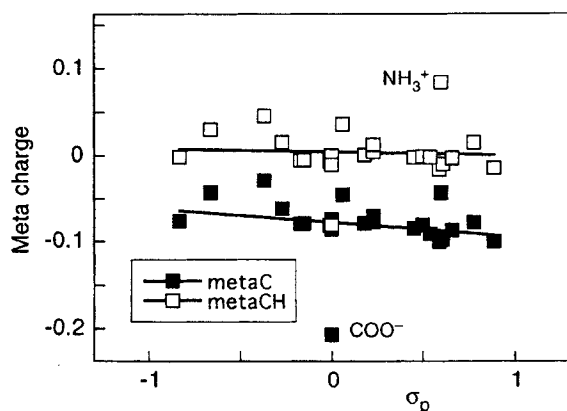
Figure 3. Correlation between AM1 *meta* position atomic charges and σ_p values for the carbon atom alone (*meta*C) and for the carbon atom and its adjacent hydrogen together (*meta*CH). The correlation coefficient for the carbon atom alone is 0·22 and that for the sum of the carbon and hydrogen charges is 0·06; the corresponding correlations with σ_m have R values of 0·09 and 0·31
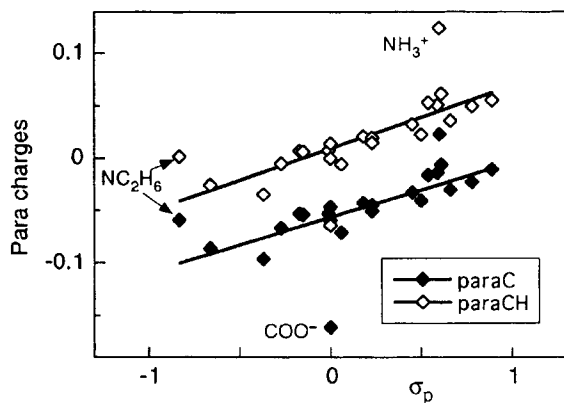

Figure 4. Correlation between AM1 *para* position atomic charges and σ_p values for the carbon atom alone (*para*C) and for the carbon atom and its adjacent hydrogen together (*para*CH). The correlation coefficient for the carbon atom alone is 0·65 and that for the sum of the carbon and hydrogen charges is 0·72; the corresponding correlations with σ_m have R values of 0·81 and 0·74
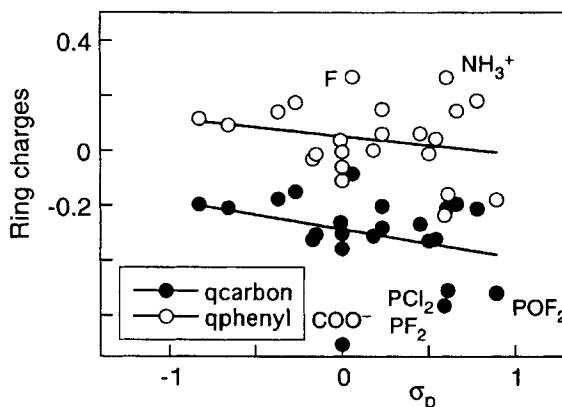

Figure 5. Correlation between AM1 total ring charges and σ_p values for the carbon atoms alone (qcarbon) and for the sum of carbon and hydrogen charges (qphenyl). The correlation coefficient for the carbon atoms alone is 0·33 and that for the sum of the carbon and hydrogen charges is 0·22; the corresponding correlations with σ_m have R values of 0·04 and 0·08

Table 2. Slopes of least-squares regression lines for correlations of atomic charges, normalized to single positions, versus Hammett σ_p values

	ortho	meta	para	ring
C only	+0·070	−0·003	+0·051	−0·0109
C plus H	+0·076	−0·013	+0·060	−0·0172

NH_3^+ at the *para* position and F, NH_3^+, COO^-, PF_2 and POF_2 for the ring as a whole. Detailed inspection of the output from the calculations did not suggest specific causes for this behavior. Despite the large values of the correlation coefficients for the regressions of these data, it is clear from the scatter around the regression lines that both descriptors of the substitutent effects – AM1 atomic charges and Hammett constants – offer only estimations of the individual properties of the test molecules. It is possible that more stringent tests of the same correlation could be made by comparing directly with the experimental measurements underlying the tabulated Hammett constants.

In undertaking a more stringent tests, however, it would have to be recognized that molecular electrostatic potentials should be more faithful indicators of relative reactivities at different sites of molecules than charge distributions derived directly from wavefunctions.[22-24] Semi-empirical wavefunctions appear to be as useful for the purpose of evaluating such potentials as *ab initio* ones, although it is still an open question whether the MNDO or the AM1 method gives preferable results.[25-27]

NMR chemical shifts

Independent correlations with the atomic charges at specific ring carbons may be expected for NMR chemical shifts, which should be differently affected by whatever particular chemical effects lead to the experimental Hammett constants. The fundamental theory of the chemical shift is thought to be well understood, and *ab initio* SCF explorations of the connection between nuclear shielding tensors and molecular structures have been undertaken.[28-32] For the most part these studies have dealt with small molecules, although some efforts to deal with ones the size of substituted benzenes have appeared.[33] For a review, see Ref. 34.

Carbon-13 shifts have been evaluated for 12 of the molecules in the study group.[13-15] As recognized already in the original report,[13] for these molecules there is indeed a correlation between ^{13}C chemical shifts at the *para* position (correlation coefficient of the linear regression $R = 0.95$) and Hammett σ_p values, while significant correlations are not present for the *ipso*, *ortho* or *meta* carbons, which have correlation coefficients of only 0.52, 0.40 and 0.34 (Figure 6). The large scatter of the mostly downfield shifts for the *ipso* carbon and the intrinsically very small shifts at the *meta* carbon obscure the correlation in those cases.

One can then ask whether correlations between AM1 atomic charges and chemical shifts may be overshadowed by the scatter in the intermediate correlation with the Hammett constant. That this is indeed the case is shown in Figures 7–9, where the ^{13}C chemical shifts are shown as functions of the AM1 atomic charges at the corresponding carbon. Within the scatter of the data there are correlations for all four ring positions, the
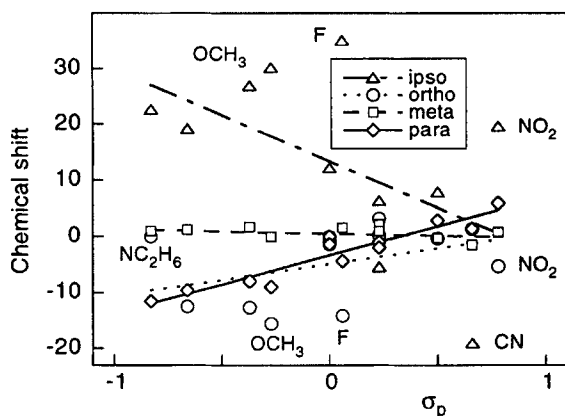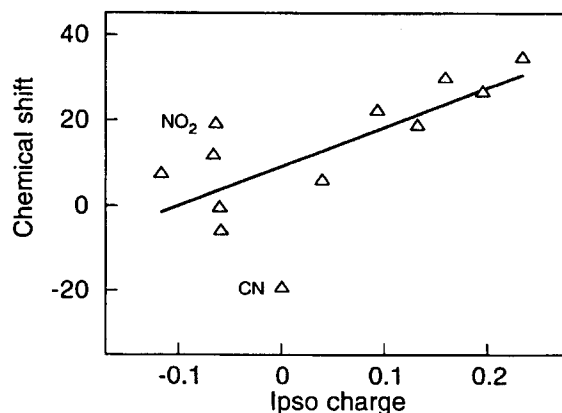
Figure 7. Correlation of ^{13}C chemical shifts (in ppm, upfield negative) at the *ipso* position with AM1 *ipso* charges
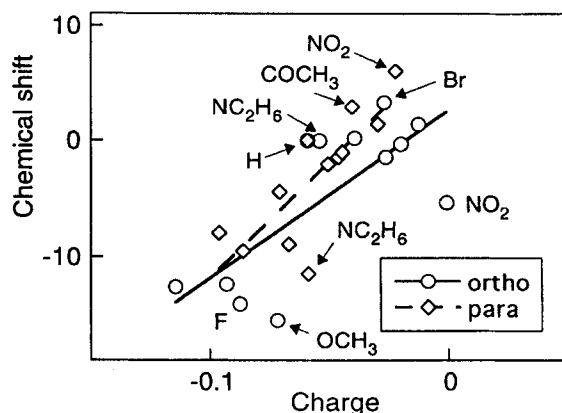
Figure 8. Correlation of ^{13}C chemical shifts (in ppm, upfield negative) at the *ortho* and *para* positions with AM1 *ortho* and *para* charges

Figure 6. Correlation of ^{13}C chemical shifts (in ppm, upfield negative) at the *ipso, ortho, meta* and *para* positions with σ_p values. The regression lines are $13.4 - 16.4\sigma_p$ $(R = 0.52)$, $-4.9 + 5.6\sigma_p$ $(R = 0.40)$, $0.6 - 0.8\sigma_p$ $(R = 0.34)$, and $-3.3 + 10.3\sigma_p$ $(R = 0.95)$ for the *ipso, ortho, meta* and *para* positions, respectively
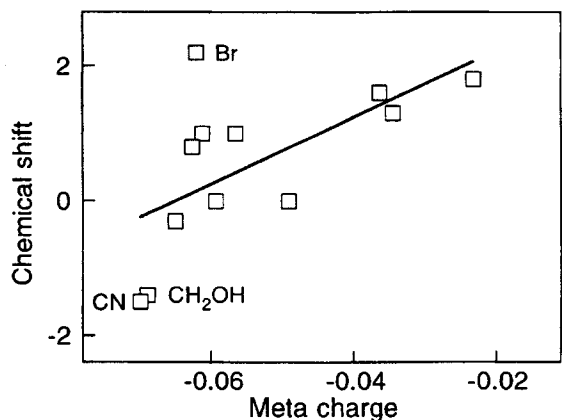
Figure 9. Correlation of ^{13}C chemical shifts (in ppm, upfield negative) at the *meta* position with AM1 *meta* charges

values of the shifts and the strength of the charge dependences varying from position to position. Proton NMR shifts for substituted benzenes correlate with ^{13}C shifts, at least at the *para* position,[13,35-37] and since the correlation between C and H charges in the AM1 calculations is also strong, the same degree of accounting for proton shifts also occurs at the *para* position.

If the correlation between AM1 atomic charge and chemical shift is a valid one, then aside from the *ipso* shifts it should be independent of ring position. That this is indeed the case is shown in Figure 10. The correlations with AM1 atomic charges are comparable to those with the Hammett constants, having R^2 values of 0·55 and 0·64 for the *ortho* and *para* shifts, respectively, compared with 0·56 and 0·63 for the correlation of the atomic charges with the Hammett σ_p values for the same 12 molecules. Indeed, the linear least squares fit to all of the data, including the *meta* shifts, is hardly different from the individual fits to the *ortho* and *para* data (Figure 9).

It is well known in the theory of chemical shifts that σ- and π-electrons contribute differently to the nuclear shielding tensor.[34] Because it is awkward to search for what semi-empirical SCF theory can say about this distinction through testing for correlations among substituents, we investigated the question by an artificial perturbation of electron donation to the ring system. For the three halogenated benzenes in the test set we forced the C—X distance to vary on both sides of the equilibrium separation and compared the resulting effects upon the total charges and the π-electron densities at the various ring positions. The results for C—F and C—Br stretching were qualitatively identical to the C—Cl

Figure 11. Effect of stretching the Cl—C bond of chlorobenzene on the electronic charge distribution of the phenyl ring. Assignment of symbols to ring positions as in Figures 1–4; crosses refer to Cl. Open symbols denote atomic charge and filled symbols denote π-electron density. The π-electron density for Cl was reduced by 0.4 to bring its value onto the scale of the ring atoms

stretching results shown in Figure 11. Figure 11 shows that the electronic distribution varies in a reasonable way over the phenyl ring and that the AM1 atomic charges and π charges are fully correlated with one another, independent of position. Separation of π and σ effects on the electronic properties that determine chemical shifts therefore cannot be effected from the results of the semi-empirical calculations. Nonetheless, the atomic charges provided by the semi-empirical method do capture the basic NMR trends at all positions. It would be of interest to look for a predictive ability in a more comprehensive way for a set of aliphatic test molecules, where ability to account for chemical shifts would be more useful than in the case of aromatics.

H-atom bending forces

The substituent effect of primary interest in our porphyrin study was upon the barriers to phenyl twisting in *para*-substituted TPPs, which is readily seen from the molecular structure to derive from steric interference between the hydrogens *ortho* to the carbons bonded to the macrocycle. It is therefore of interest to inquire whether the force constant for keeping this hydrogen in the plane of the phenyl ring shows a substituent effect. For this purpose we computed the energy required to force the one hydrogen out of the plane with all other atoms left free to relax. The energy cost, taken from the AM1 enthalpy of formation values, proved to be very close to purely parabolic in dihedral bend angle out to 30° twist, no matter what constraints were held during the enforced twist. Force constants for bending *meta* and *para* H-atom dihedral angles of each of the molecules in the test set were calculated from the AM1
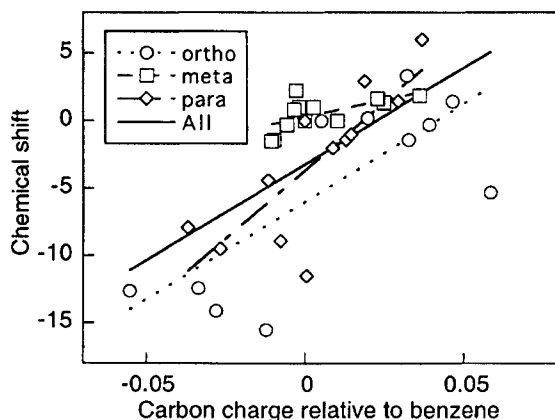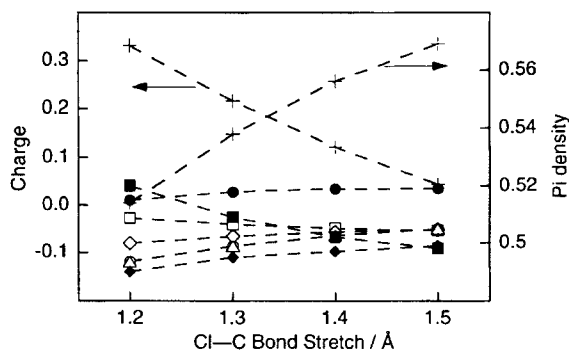

Figure 10. Correlation of ^{13}C NMR shifts with AM1 charges relative to benzene for *ortho, meta* and *para* positions. The solid regression line for all positions together is $-3·2 + 142q$ ($R = 0·65$). The *ortho* regression line is $-6·0 + 144q$ ($R = 0.74$), the *meta* regression line is $0·3 + 49q$ ($R = 0·62$) and the *para* regression line is $-3·7 + 210q$ ($R = 0·80$)

enthalpy of formation values at 165, 180 and 195° and assumed pure parabolic dependence. The ambiguity of establishing reference points for these results led us to test various options for defining the dihedral bend angle and constraining the molecular geometry, as set forth in the caption of Figure 12.

The results presented in Figure 12 show that there are no correlations between any of the derived bending force constants and the Hammett σ_p value. Moreover, there are no significant differences between the force constants at the positions *meta* and *para* to the substituents, no matter how the phenyl ring is constrained. The bending force constants are much higher if the phenyl ring geometry is held fixed during the bending process, which is not surprising. The apparent differences between force constants that arise from different definitions of dihedral are artificial, as the ring geometry itself is fully free to relax independent of the enforced out-of-plane bend. Distortion of phenyl rings has been shown to be much more facile than commonly thought, and it has been confirmed that values of ring distortion energies computed by the AM1 Hamiltonian
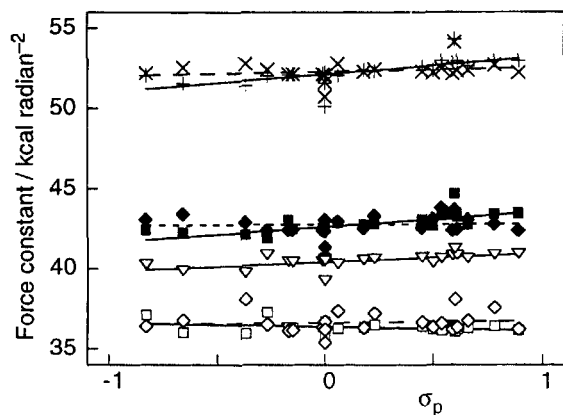

Figure 12. Dihedral bending force constants for substituted benzenes as a function of σ_p values. Dashed lines are regression lines for *meta* H-atom bending and solid lines are for *para* H-atom bending. ×, *meta* H-atom bend, phenyl ring geometry otherwise fixed; +, *para* H-atom bending, phenyl ring geometry otherwise fixed. Filled squares and diamonds are for *para* and *meta* H-atom dihedral bending, respectively, with the dihedral taken with respect to the three carbon atoms nearest to the out-of-plane H-atom; open squares and diamonds are for *para* and *meta* H-atom dihedral bending, respectively, with the dihedral angle being defined by the plane of the carbons *ipso, ortho* and *meta* with respect to the out-of-plane H-atom; the phenyl ring geometry was otherwise free to relax during the forced dihedral bending. ∇, *para* H-atom bend with the phenyl structure free to relax except for the H-atom dihedrals, which were forced to remain at 180°; the *para* H-atom dihedral was defined as for the open diamonds. The main outliers from all lines are the two charged substituents.

are well supported by the crystallographic literature.[38] Indeed, the energy costs for distorting benzene carbon ring dihedrals are similar to the costs for distorting the H-atom dihedrals. One can thus consider that the values of the force constants shown in Figure 12, in the range 40 ± 5 kcal rad^{-2} independent of position and substituent, should be realistic guides to the energy costs involved when out-of-plane H-atom motions are involved in larger structural changes, as in distorted macrocycles[12] or in chemical reactions. One would expect a limit of around 30°, corresponding to an energy cost of about 10 kcal, to be the most distortion energy that could be afforded in ordinary circumstances.

Outliers

It is of interest to inquire about the degree to which the correlations found are limited by the semi-empirical SCF method itself, i.e., about how well the AM1 atomic charges as computed by Ampac 2.1 can be trusted for such a wide range of substituent types. Support for attributing part of the scatter in the correlations to the limitations of the semi-empirical SCF approach can be found in the fact that the charged substituents COO$^-$ and NH$_3^+$ are often found among the extreme outliers for all three effects investigated; charged or highly electronegative substituents generally do present intrinsic difficulties to SCF methods. This does not account for all of the scatter, however, because in many instances the outliers are for substituents that are among the ordinary organic chemistry groups for which the AM1 Hamiltonian was parameterized. At least part of the scatter could be due to ambiguities inherent in deriving the Hammett constants also.[11] It is open to question whether stronger correlations would be found using more elaborate procedures for assigning atomic charges than that provided by Ampac 2.1.

CONCLUSION

The semi-empirical SCF method has been shown to account in a straightforward way for the general trends observed in the Hammett constants for substituted benzenes. In accord with normal expectations in physical organic chemistry, the correlations of Hammett constants with computed charge at the various phenyl ring positions were found to be strong at the *ortho* and *para* positions, weak at the *meta* position, and subject to large scatter reflecting the particular characteristics of individual molecular types. The semi-quantitative correctness of the atomic charge distributions computed with the AM1 Hamiltonian was supported by the correlations found between the AM1 atomic charges and ^{13}C chemical shifts at all ring positions. That the substituent effects expressed by Hammett constants are direct electronic effects rather than manifestations of

alterations in molecular flexibility is confirmed by the failure to find significant substituent effects or positional effects on the force constant for dihedral bending of the phenyl hydrogens.

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