

Charge calculations in molecular mechanics 7*: Application to polar π systems incorporating nitro, cyano, amino, C=S and thio substituents

Raymond J. Abraham and Paul E. Smith

Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX, U.K.

Received 24 November 1988

Accepted 25 February 1989

Key words: Charge calculations; π Systems; Nitro compounds; Cyano compounds; Amino compounds

SUMMARY

A previously described method for calculating partial atomic charges in molecules has been applied to a variety of different functional groups with π electrons. The π charges have been determined by varying the relevant Hückel coulombic and resonance integrals so as to reproduce the experimental dipole moments of known compounds. These include nitro, cyano, mercapto and thiocarbonyl compounds, anilines and a series of heterocyclic ring compounds involving nitrogen, oxygen and sulphur atoms. The calculated dipole moments are in good agreement with experimental values and are a considerable improvement on other calculated values, while requiring only a fraction of the computational time necessary for more rigorous methods. The resulting π densities compare favourably with other theoretical (CNDO, MNDO and STO-3G) methods.

INTRODUCTION

Molecular mechanics and molecular dynamics calculations have been shown to be useful tools for the investigation of many of the important features of molecules [1]. The calculation of relative conformational energies, energy barriers and interaction energies helps to determine specific properties of molecules and can be particularly helpful in the development of new and novel drugs [2, 3].

One of the major problems in the use of molecular mechanics has been the absence of a general method for the determination of the molecular charge distribution in molecules. This is of primary importance for all but nonpolar molecules. Ab initio and semiempirical methods are limited to the size of system amenable to calculation and thus several empirical charge schemes for the determination of partial atomic charges have been developed [4–6]. We have previously described a

*For part 6, see Ref. 7.

simple, quick and reliable method for the calculation of partial atomic charges of a wide variety of compounds (CHARGE2) [7–9].

The method is based on a series of one-, two- and three-bond effects which are related to the electronegativity difference between atom pairs and their atomic polarisabilities [8]. The scheme was extended to include π systems by inclusion of a Hückel procedure to determine the relevant π charges [9]. The program was then parameterised on known molecular dipole moments. Justification for this type of approach and the detailed description of the program has been presented previously [7–9]. The charges derived have been shown to give a good description of the charge distributions in several molecules of interest [7, 10].

Here, we describe the further development to include a wider range of π systems by parameterisation of the relevant Hückel coulombic and resonance integrals. The new parameters may be used for calculations on nitro, cyano, mercapto and thio compounds, anilines and a variety of nitrogen, oxygen and sulphur heterocycles.

A modification of the resonance integral to include nonplanar π systems has also been adopted [11]. The resonance integral decreases according to the following equation:

$$\beta = \beta_0 \cos \theta$$

Where β_0 is the standard resonance integral and β the resonance integral between two atoms of a π system which are rotated by θ degrees [11]. The effect of this modification on aniline can be seen in Table 1. Here $\theta = 0^\circ$ corresponds to coplanarity of the amino group and the phenyl ring, where both groups are fully conjugated. As rotation around the C1–N bond takes place the conjugation between the two groups is decreased until they are orthogonal to each other ($\theta = 90^\circ$), and no longer conjugated. Hence the excess π charges on the carbon atoms of the phenyl ring tend to zero as they approach the situation present in benzene.

Using the Hückel scheme [9, 11] in conjunction with the ω -technique [7, 11], the compounds contained in this paper have been parameterised against the experimental dipole moments by variation of the relevant coulombic and resonance integrals. The experimental molecular geometries have been used where possible, and are taken from Ref. 12 unless otherwise stated. The cor-

TABLE 1
CALCULATED π CHARGES (me) AND DIPOLE MOMENT (D) FOR AMINO GROUP ROTATION IN ANILINE

θ^a	C1	C2	C3	C4	N	μ^b
0	49	–52	2	–40	90	1.56
15	46	–49	2	–37	84	1.48
30	38	–40	2	–30	68	1.24
45	31	–32	2	–24	54	1.03
60	14	–14	1	–10	23	0.55
75	4	–4	0	–3	6	0.29
90	0	0	0	0	0	0.19

^a θ is the angle of rotation between the planar amino group and the phenyl ring.

^bTotal dipole moment.

responding experimental dipole moments have been taken from Ref. 13, unless otherwise stated. Compounds for which different values of the experimental dipole moment are given have not been used in the parameterisation procedure. The results for each class of compound will be discussed in turn.

NITRO COMPOUNDS

The nitrogen hybridisation state was assumed to be identical to that found in simple amides, i.e., $tr\ tr\ \pi^2$. Here the nitrogen donates two electrons to the π system, with each sp^2 -hybridised oxygen donating one electron. The four-electron π system has only one unknown π parameter, the sp^2O-sp^2N resonance integral. The two coulombic integrals present in the π system have already been determined in Ref. 9. Our initial attempts at parameterisation of the N–O resonance integral were not completely successful. In particular the carbon π charges obtained for pyridine-*N*-oxide did not show the predicted charge alternation pattern. The parameterisation procedure was modified slightly by including both the σ and π charges in the variational procedure. The σ charges were varied by modification of the σ bond parameter, a_{N-O} [8]. In this way both the charge alternation pattern and the dipole moments may be reproduced. Values of $k_{N-O} = 1.00$ and $a_{N-O} = 26.43$ were found to be satisfactory.

A comparison of the charges for nitrobenzene and pyridine-*N*-oxide is given in Table 2, with

TABLE 2
TOTAL (AND π) CHARGES FOR NITROBENZENE AND PYRIDINE-*N*-OXIDE

Atom	CHARGE2	CNDO	MNDO	STO-3G	Observed
<i>Nitrobenzene</i>					
N	594(511)	463(1048)	482(950)	143(769)	
O	–367(–263)	–334(–541)	–343(–501)	–201(–400)	
C1	60(16)	36(– 68)	–106(–160)	73(– 90)	
C2	– 60(– 2)	22(33)	27(83)	– 41(41)	
C3	– 86(0)	5(– 3)	– 80(– 14)	– 59(– 2)	
C4	– 90(1)	29(42)	1(74)	– 44(43)	
H2	94	29	95	99	
H3	91	10	77	77	
H4	91	8	71	78	
$\mu(D)$	3.95	5.31	5.59	4.25	3.99
<i>Pyridine-N-oxide</i>					
N	341(452)	288(931)	219(777)	– 23(745)	
O	–440(–288)	–428(–759)	–460(–681)	–251(–526)	
C2	– 41(– 42)	– 10(–112)	– 27(– 62)	8(–131)	
C3	– 79(– 5)	34(48)	– 54(18)	– 40(58)	
C4	–150(– 72)	– 22(– 44)	– 60(– 8)	– 89(– 73)	
H2	105	44	120	100	
H3	93	5	69	76	
H4	91	16	85	75	
$\mu(D)$	3.03	4.61	4.53	2.96	4.13

TABLE 3
OBSERVED AND CALCULATED DIPOLE MOMENTS (D) OF NITRO COMPOUNDS

Compound	Observed	Calculated	CNDO
MeNO ₂	3.46	3.62	4.06
EtNO ₂	3.23	3.40	3.74
<i>t</i> -PrNO ₂ ^a	3.76	3.49	3.83
<i>t</i> -BuNO ₂ ^a	3.74	3.58	3.97
CH ₂ =CH·NO ₂	3.70	3.75	4.33
2,3-Dinitrobut-2-ene (<i>cis</i>) ^b	5.16	6.55/6.19 ^c	6.34/7.28 ^c
CF ₃ ·NO ₂	1.44	1.39	1.48
CH ₂ Cl·NO ₂	2.91	3.19	3.57
CCl ₃ ·NO ₂	1.86	1.88	1.99
CBr ₃ ·NO ₂	1.97	2.13	—
Pyridine- <i>N</i> -oxide	4.13	3.03	4.61
PhNO ₂ ^d	3.99	3.95	5.31
4-Nitrobenzaldehyde	2.15	2.82	4.02

^aGeometry from nitroethane.

^bGeometry from nitroethene.

^cPlanar/perpendicular nitro groups.

^dStandard geometry (see Ref. 14).

the calculated dipole moments for a variety of nitro compounds given in Table 3. Examination of the total charges for both compounds shows fairly good agreement between the methods. In all cases, with the exclusion of the STO-3G calculation for pyridine-*N*-oxide, a substantial positive charge is assigned to the nitrogen atom. This is in agreement with the standard resonance forms for the nitro group and *N*-oxide [15], which also predict high negative charges for the corresponding oxygen atoms. Although the total charges are similar in both sign and magnitude, their π contributions are very different. CNDO, MNDO and STO-3G give extremely high positive π charges on the nitrogen atom supporting the classical view of $+1e^-$ on nitrogen and $-1/2e^-$ on both oxygens. The CHARGE2 π charges are far smaller in magnitude, and yet the total charges are in quite good agreement. The high positive charges found by the more sophisticated methods are compensated for by a large negative σ charge associated with nitrogen, and substantial positive σ charge associated with oxygen. The difference between these sophisticated methods and the CHARGE2 scheme is thus clearly demonstrated as due to the large interaction of the σ and π systems in these quantum mechanical methods, whereas there is essentially no direct interaction between them in CHARGE2. It would be perfectly feasible to introduce such a concept, but this is outside the scope of the present work.

The effect of the nitro group on the π densities around the ring is not well reproduced using the Hückel procedure. The CHARGE2 π densities are negligible for all atoms except C1, which is attached to the nitro group. The CHARGE2 π densities for the carbon atoms of pyridine-*N*-oxide are in good agreement with the other methods. Table 3 shows that CHARGE2 reproduces the observed dipole moments quite well. The large increase in the dipole moment going from MeNO₂ to *t*-BuNO₂ (3.46–3.74) is not reproduced by CHARGE2 or CNDO. Geometrical factors may explain some of this. The conjugated system of *cis*-2,3-dinitrobut-2-ene has been calculated for both

planar and orthogonal nitro groups, because of the close contacts between the nitro groups in the planar conformation. The orthogonal conformation gives the best agreement with experiment when using the CHARGE2 scheme, although CNDO calculations predict a higher, and correspondingly worse, dipole moment.

CYANO COMPOUNDS

Most of the problems encountered when trying to parameterise the scheme for cyano compounds were a direct result of the large number of unknown parameters for this system. There are four parameters which may be varied during the fitting procedure. These are the coulombic integrals for sp-hybridised carbon and nitrogen, the resonance integral for the C–N bond and the σ parameter a_{C-N} for the same bond. Therefore, it was necessary to assume values for several of these parameters. Originally this was achieved by using the default value for a_{C-N} [8], and the Hückel coulombic integrals found for the sp²-hybridised carbon and nitrogen atoms [9]. Therefore, $\alpha_C = 0.00$ and $\alpha_N = 0.33$ (nitrogen value taken from the parameters derived for pyridines) which left the resonance integral to be used in the fitting procedure. However, this resulted in calculated π densities which were rather large compared with other methods.

TABLE 4
TOTAL (AND π) CHARGES FOR HCN, MeCN and ANILINE

Atom	CHARGE2	CNDO	MNDO	STO-3G	Observed
<i>HCN^a</i>					
N	–470(–143)	–100(–98)	–100(–142)	–161(–56)	
C	293(143)	29(98)	–91(142)	11(56)	
H	177	71	191	150	
$\mu(D)$	3.50	2.45	2.51	2.45	2.99
<i>MeCN^a</i>					
N	–464(–143)	–160(–399)	–81(–136)	–196(–144)	
C	361(143)	88(113)	–119(105)	76(75)	
CH	–64	–24	140	–186	
H	55	32	20	102	
$\mu(D)$	3.58	3.05	2.65	3.06	3.92
<i>Aniline</i>					
N	–372(90)	–203(–424)	–226(471)	–404(337)	
C1	27(49)	135(59)	35(21)	110(41)	
C2	–121(–52)	–49(–67)	–97(–57)	–89(–66)	
C3	–88(2)	25(27)	–30(23)	–53(22)	
C4	–128(–40)	–23(–45)	–88(–31)	–80(–41)	
NH	215	82	116	179	
H2	94	–2	62	57	
H3	91	–7	59	64	
H4	91	–7	59	58	
$\mu(D)$	1.56	1.79	1.48	1.50	1.53

^a π Density from the two orthogonal π systems.

The second approach, which proved more satisfactory, involved a scaling of the π charges to reproduce the π charges calculated by the other methods, and subsequent variation of the a_{C-N} σ parameter to reproduce the dipole moments. The coulombic integrals for sp carbon and nitrogen were taken as before, and the resonance integral varied to reproduce the STO-3G calculated π density for the nitrogen atom in MeCN (a value of $-144me$, Table 4), to give a value for k_{C-N} of 1.14. Variation of a_{C-N} gave a good correlation between observed and calculated dipole moments. The parameterisation was achieved using the data set given in Table 5, but without the inclusion of HCN (see later). As some compounds in the data set have sp^2C-spC bonds, the resonance integral for this bond was also allowed to vary in the parameterisation. The final values of a_{C-N} and k_{sp^2C-spC} were 16.21 and 0.91, respectively. The results are shown in Table 5.

The π and total charges calculated for HCN and MeCN are shown in Table 4. Obviously the π densities are in quite good agreement while the total charges from the present scheme are significantly larger than for the other methods. There are two main reasons for this discrepancy. First, all the other methods calculate low values of the dipole moment for both HCN and MeCN which may be reflected in the respective point charges. Secondly, the presence of a lone pair on the nitrogen atom could contribute considerably to the total dipole moment. The present scheme does not

TABLE 5
OBSERVED AND CALCULATED DIPOLE MOMENTS(D) FOR CYANO COMPOUNDS

Compound	Observed	Calculated	CNDO
HCN	2.99	3.50	2.45
MeCN	3.92	3.58	3.05
EtCN	4.02	3.64	3.08
CH ₂ (CN) ₂	3.74	4.10	3.41
Me ₂ C(CN) ₂ ^a	3.97	4.44	3.61
<i>t</i> -Bu·CN	3.95	3.76	3.12
CH ₂ F·CN ^b	3.43 ^b	3.29	2.62
CH ₂ Cl·CN	2.97	3.31	2.76
CHCl ₂ ·CN ^c	2.51	2.82	2.23
CCl ₃ ·CN	1.99	2.26	1.27
CH ₂ =CH·CN	3.89 ^d	4.33	2.98
MeCH=CH·CN (<i>cis</i>)	4.08	4.33	3.14
MeCH=CH·CN (<i>trans</i>)	4.75	4.32	3.46
CH ₂ =CMeCN	3.69	4.32	2.97
CO(CN) ₂	0.70	1.36	0.11
MeCO·CN	3.45	3.17	2.86
PhCN	4.14	4.31	3.22
2-Cyanopyridine ^e	5.78 ^f	5.49	4.57
3-Cyanopyridine ^e	3.66 ^f	3.71	2.89
4-Cyanopyridine ^e	1.96 ^f	1.69	0.91

^aGeometry from dicyanomethane.

^bGeometry and dipole moment from Ref. 16

^cGeometry from chlorocyanomethane.

^dDipole moment from Ref. 17.

^eGeometry from pyridine (see Ref. 12).

^fDipole moment from Ref. 18.

take lone pair dipoles into account and normally compensates for this by increasing the electron density on the atom bearing the lone pair. This effect was also observed when the scheme was applied to pyridines [9]. The agreement with the observed dipole moments would be even better if explicit account were taken in CHARGE2 of the hyperconjugative effects of methyl substitution (cf. MeCN vs. HCN). Again this is beyond the scope of the present work. In general, the experimental dipole moments are well reproduced by the charge scheme. They are also an improvement on the CNDO-calculated values which are consistently lower than observed.

ANILINES

The degree of conjugation between the amino group and phenyl ring of aniline has been the subject of much investigation [19–21]. The amino group is pyramidal in these systems [19, 20, 22], suggesting only partial conjugation between the two groups. For our calculations the nitrogen atom was considered to donate two electrons to the π system (te^2 te te hybridisation), with the nitrogen coulombic integral and the sp^2C - sp^3N resonance integrals available for parameterisation. A large data set of substituted anilines yielded values of 1.48 for the coulombic integral and 0.83 for the resonance integral.

The corresponding charges for aniline are shown in Table 4, together with those calculated by other methods. All four methods give very similar total charges, resulting in similar dipole moments which are also in good agreement with experiment. The π charge associated with the nitrogen atom in the CNDO, MNDO and STO-3G calculations is not strictly a π charge because of the nonplanarity of the nitrogen group. A more realistic interpretation of the π density donated by the amino group lies in the π charges associated with the ring atoms. For these atoms CHARGE2 reproduces the π density distribution predicted by the other three methods, with the characteristic π donation to ortho and para positions being observed.

The CHARGE2 calculated dipole moments shown in Table 6 proved quite insensitive to the nitrogen hybridisation state in all but one compound. In the case of 2,6-dichloroaniline the dipole moment varied from 1.01D for the pyramidal form, to 0.10D for the planar form. Why this large variation was observed only for this compound proved impossible to determine, even on careful examination of the bond dipole contributions. The CNDO calculations displayed a far larger variation of dipole moment with amino group planarity, which generally reduced the calculated value.

The effect of *N*-methyl substitution on the dipole moments is negligible for both the observed and calculated values, with the series aniline, *N*-methylaniline to *N,N*-dimethylaniline all having dipole moments of $\approx 1.60D$. The *cis* and *trans* forms of 3-aminoaniline refer to the relationship between the two NH_2 groups. The average of the *cis* and *trans* dipole moments calculated by both CHARGE2 and CNDO gives good agreement with the observed value (CHARGE2 1.73, CNDO 1.85 and OBS 1.77).

MERCAPTO COMPOUNDS

All of these compounds possess an sp^3 -hybridised sulphur atom which can donate π electron density in an analogous way to an sp^3 -hybridised oxygen atom. The parameters required are the coulombic integral for sp^3 sulphur, and the resonance integral for sp^2C - sp^3S bonds. Values deter-

TABLE 6
 OBSERVED AND CALCULATED DIPOLE MOMENTS(D) OF AMINO COMPOUNDS

Compound ^a	Observed	Calculated ^b	CNDO ^b
Aniline	1.53	1.57/1.56	1.79/1.14
3-Aminoaniline (<i>cis</i>)	1.77	2.29	3.58
3-Aminoaniline (<i>trans</i>)	1.77	1.18	0.12
4-Aminoaniline (<i>cis</i>)	1.58	1.97	3.57
3,5-Dimethylaniline	1.41	1.54	1.78
3-Fluoroaniline	2.13–2.54	2.59	2.51
4-Fluoroaniline	2.34–2.66	2.91	2.53
2-Chloroaniline	1.61–2.73	1.70	2.89
3-Chloroaniline	2.25–3.06	2.62	2.91
4-Chloroaniline	2.35–3.39	2.96	3.13
3,5-Dichloroaniline	2.99	2.96	2.93
3,4-Dichloroaniline	3.84	3.85	4.24
2,6-Dichloroaniline	0.92	1.01/0.10	2.67/0.87
2,5-Dichloroaniline	1.63	1.61	1.85
2,4-Dichloroaniline	2.70	2.63	3.05
2,3-Dichloroaniline	2.86	3.02	4.14
2,4,6-Trichloroaniline	1.72	1.66	1.90
2,4,5-Trichloroaniline	2.86	2.93	2.97
3-Bromoaniline	2.65	2.54	—
4-Bromoaniline	3.01	2.87	—
<i>N</i> -Methylaniline	1.65	1.47	1.71
<i>N,N</i> -Dimethylaniline	1.60	1.40/1.38	1.56/0.87
3-Fluoro- <i>N,N</i> -dimethylaniline	2.79	2.43	2.30
4-Fluoro- <i>N,N</i> -dimethylaniline	2.77	2.73	2.27
3-Chloro- <i>N,N</i> -dimethylaniline	2.93	2.46	2.74

^aStandard geometries (see Ref. 14).^bWhere two calculated values are quoted, the first refers to a pyramidal nitrogen and the second to a planar nitrogen.
 TABLE 7
 TOTAL (AND π) CHARGES FOR THIOPHENE AND $H_2C=S$

Atom	CHARGE2	CNDO	MNDO	STO-3G	STO-3G*	Observed
<i>Thiophene</i>						
S	— 68(67)	—60(14)	90(174)	268(274)	126(232)	
C2	— 64(— 9)	—37(—29)	—141(— 58)	—181(—85)	—105(—68)	
C3	— 98(— 25)	38(22)	— 85(— 29)	— 86(—52)	— 83(—48)	
H2	102	27	100	71	65	
H3	94	2	81	62	60	
μ (D)	0.84	1.22	0.93	0.25	0.73	0.53
<i>H₂C=S</i>						
C	19(101)	—71(13)	104(308)	—224(70)	—111(77)	
S	—201(—101)	—27(—13)	—194(—308)	100(—70)	1(—77)	
H	91	49	45	62	55	
μ (D)	2.05	0.34	2.84	0.90	0.22	1.65

mined from parameterisation on the observed dipole moments were 1.27 and 0.30, respectively.

A comparison of different calculated charge distributions for thiophene is given in Table 7. The methods differ significantly with respect to the amount of π and total electron density associated with the sulphur atom. All predict a positive sulphur π charge but the exact π charge ranges from 14 me for CNDO to 274 me for STO-3G. CHARGE2 predicts the donation of π electron density from sulphur to the C3 position, with the C2 position essentially unchanged. The other four methods, however, predict a uniform distribution between C2 and C3, or a higher π density on the C2 positions. This type of effect in the CHARGE2 calculations was also observed for pyrrole (see Ref. 9), and is probably an artifact of the Hückel method. The total charges for thiophene predict both negatively and positively charged sulphur. All the methods which predict a positively charged sulphur, also predict a correspondingly high negative charge associated with the C2 positions. The addition of polarisation functions to the sulphur atom has no effect on the π electron densities, but reduces the positive total charge on sulphur, cf. STO-3G and STO-3G*.

The dipole moments calculated by CHARGE2 and CNDO are compared with the experimental values in Table 8. The agreement between CHARGE2 and the experimental values is good, and a substantial improvement on the CNDO values. The large difference in dipole moments between the two conformations of HCO·SH is well reproduced by CHARGE2, while CNDO predicts no change in the observed values. However, for substituted thiophenes, CHARGE2 does not reproduce the effect of methyl substitution at the C2 and C3 positions on the ring, although the observed differences are small.

TABLE 8
OBSERVED AND CALCULATED DIPOLE MOMENTS(D) FOR MERCAPTO COMPOUNDS

Compound	Observed	Calculated	CNDO
HCO·SH (<i>cis</i>) ^a	2.87 ^b	3.28	1.78
HCO·SH (<i>trans</i>) ^a	1.54 ^b	1.75	1.79
MeCO·SH (<i>cis</i>) ^c	—	3.50	2.41
MeCO·SH (<i>trans</i>) ^c	1.82 ^d	1.88	2.17
Thiophene	0.53	0.84	1.22
2-Methyl-thiophene ^c	0.67	0.61	0.61
3-Methyl-thiophene ^c	0.82	0.78	1.84
2-Chloro-thiophene ^c	1.48/1.60	1.74	2.62
2-Bromo-thiophene ^c	1.35	1.61	—
2-Nitro-thiophene ^c	4.22	4.93	5.24
Thiazole	1.61	1.29	1.32
CH ₂ =CH·SMe (<i>cis</i>)	1.14	1.32	1.83
CH ₂ =CH·SMe (<i>trans</i>)	—	1.47	1.91
PhSH ^e	1.07–1.33	1.24	2.38

^aGeometry from Ref. 23.

^bDipole moment from Ref. 24.

^cFrom parent compound.

^dDipole moment from Ref. 25.

^eStandard geometry (see Ref. 14).

THIOCARBONYL COMPOUNDS

Before any calculations on compounds containing sp^2 sulphur could be performed, values of the electronegativity and polarisability had to be determined. The electronegativity of sp^2 -hybridised sulphur as given by Hinze and Jaffe appears in terms of a σ and π contribution [26]. Rather than guessing the amount of σ and π character of the sulphur atom, the value of $E = 10.88$ quoted for the σ contribution was used, with the coulombic integral being used to account for any π contribution. The polarisability of sp^2 sulphur ($P = 1.984$) was taken from the method of Miller and Savchik [27], as previous calculations have done [28].

Using these values for the electronegativity and polarisability of sp^2 sulphur, the remaining Hückel coulombic and resonance integrals can be parameterised. The parameterisation gave values of 0.11 and 1.05 for the coulombic and resonance integrals, respectively. The calculated charges for the parent compound thioformaldehyde are given in Table 7. Although all the methods show a negative π charge associated with the sulphur atom, the total charge on sulphur varies from -201 me (CHARGE2) to 100 me (STO-3G). This variation can also be seen in the calculated dipole moments. As in the case of thiophene, polarisation functions located on sulphur have no effect on the π charges but decrease the total charge associated with sulphur.

Table 9 contains the observed, CHARGE2, and CNDO determined dipole moments of a small set of thio compounds. Due to its small size the data set gives only moderately good agreement between observed and CHARGE2 calculated values, albeit over a large range of dipole moments. This still represents an improvement over the CNDO-derived dipole moments.

HETEROCYCLIC COMPOUNDS

The inclusion of heterocyclic compounds into the scheme is particularly advantageous for calculations on many of the important drugs available today, or potential drugs of tomorrow. Their inclusion into the scheme has required the parameterisation of several resonance integrals (the rel-

TABLE 9
OBSERVED AND CALCULATED DIPOLE MOMENTS(D) FOR THIO COMPOUNDS

Compound	Observed	Calculated	CNDO
$H_2C=S$	1.65	1.89	0.34
$Me_2C=S^a$	2.41	1.87	1.25
$F_2C=S$	0.08 ^b	0.20	1.33
$Cl_2C=S^a$	0.28	0.30	1.93
$HC=S \cdot NH_2$	4.01 ^c	3.56	2.99
$(NH_2)_2C=S^d$	5.07	4.31	4.73
$CH_2=CH \cdot C=S \cdot H$ (<i>trans</i>) ^e	2.61 ^e	2.37	0.21
$MeC=S \cdot NH_2^d$	4.53/4.80	3.59	3.47

^aGeometry from thioformaldehyde.

^bDipole moment from Ref. 29.

^cDipole moment from Ref. 30.

^dGeometry from thioformamide.

^eGeometry and dipole moment from Ref. 31.

TABLE 10
OBSERVED AND CALCULATED DIPOLE MOMENTS(D) FOR HETEROCYCLES

Compound	Observed	Calculated	CNDO
1,2-Diazole	2.21	2.23	2.09
Isoxazole ^a	2.90	2.97	3.16
Isotiazole ^b	2.44	2.38	2.93
1-Methyl-1,2-diazole ^c	2.28	2.25	2.05
1,2,5- Oxadiazole	3.38 ^d	3.10	3.52
1,2,5-Thiadiazole	1.57 ^e	1.04	2.31
1-Methyl-1,2,5-triazole ^b	0.37 ^f	0.23	0.14
1,3,4-Oxadiazole	3.04 ^g	3.77	3.19
1,3,4-Thiadiazole	3.28	3.27	2.89
1-Methyl-1,2,3-triazole ^b	4.46 ^f	4.11	4.19
1,2,4-Triazole ^b	2.72	3.01	2.96
1,2,4-Oxadiazole ^b	1.2	1.59	1.19
1-Methyl-1,2,4-triazole ^c	3.50	3.11	2.93
1,2,3,4-Tetrazole ^b	5.30 ^h	5.19	5.31
1,2,3,5-Tetrazole ^b	2.19 ^h	2.00	2.08
Pyridazine ^b	4.09	3.60	3.74
3-Chloro-pyridazine ^c	4.42	3.95	4.47
Benzo-2,1,3-oxadiazole ⁱ	4.04 ^j	3.76	3.87
Benzo-2,1,3-thiadiazole ⁱ	1.79 ^j	1.25	2.32
Formaldoxime	0.44	0.83	0.32
Acetaldoxime (<i>cis</i>) ^k	0.85	0.82	0.64
Acetaldoxime (<i>trans</i>) ^k	0.94	0.91	0.77

^aGeometry from Ref. 32.

^bMNDO optimised planar geometry.

^cGeometry from parent compound.

^dDipole moment from Ref. 33.

^eDipole moment from Ref. 34.

^fDipole moment from Ref. 35.

^gDipole moment from Ref. 36.

^hDipole moment from Ref. 37.

ⁱGeometry from Ref. 38.

^jDipole moment from Ref. 39.

^kGeometry from Ref. 40.

evant coulombic integrals have already been parameterised) so as to cover a wide variety of heterocyclic compounds. The data set is shown in Table 10 and represents a selection of common heterocyclic rings.

The parameterisation gave values for the resonance integral of $sp^2N-sp^2N(py) = 0.73$, $sp^2N(py)-sp^2N(py) = 0.49$, $sp^3O-sp^2N(py) = 0.30$, and $sp^3S-sp^2N(py) = 0.30$, where the py refers to a pyridine type nitrogen ($tr^2 tr tr \pi$) as opposed to an amide type nitrogen ($tr tr tr \pi^2$). Using the above parameters, CHARGE2 gives very good agreement between the observed and calculated dipole moments over a range of more than 5 Debyes.

CONCLUSIONS

The extension of the scheme to include more polar systems has been achieved by parameterisation of the relevant Hückel coulombic and resonance integrals. The π charges calculated for the above systems are consistent with those derived by more rigorous methods. The correlation between the observed and CHARGE2 calculated dipole moments is very good (correlation coeff = 0.9560 and rms = 0.37D) and a significant improvement over the CNDO-calculated values (correlation coeff = 0.7904 and rms = 0.83D). With this in mind, the scheme may be applied to very polar systems of biological interest such as proteins and nucleic acids and, hopefully, the calculated charge distributions can be used, within the molecular mechanics framework, to aid in further investigation of these systems.

IMPLEMENTATION

The program CHARGE2 is written in FORTRAN77 and is compatible with mainframe (VAX, IBM) and also IBM PC systems. The CPU time is minimal for the molecules so far examined (up to 200 atoms).

ACKNOWLEDGEMENTS

We thank Dr. W.A. Thomas and Dr. A. Krohn of Roche Products Limited for much helpful discussion. We also acknowledge a S.E.R.C. CASE award (PES) and the use of the computing facilities at the University of Liverpool and Roche Products Limited.

REFERENCES

- 1 Burkert, U. and Allinger, N.L., *Molecular Mechanics*, American Chemical Society, Washington, DC, 1982, pp. 326.
- 2 Vinter, J.G., *Chem. Br.*, 21 (1985) 32–38.
- 3 Hassall, C.H., *Chem. Br.*, 21 (1985) 39–47.
- 4 Gastiger, J. and Marsili, M., *Tetrahedron*, 36 (1980) 3219–3228.
- 5 Singh, U.C. and Kollman, P.A., *J. Comput. Chem.*, 5 (1984) 129–145.
- 6 Mullay, J., *J. Comput. Chem.*, 9 (1988) 764–770.
- 7 Abraham, R.J. and Smith, P.E., *Nucleic Acids Res.*, 16 (1988) 2639–2657.
- 8 Abraham, R.J., Griffiths, L. and Loftus, P., *J. Comput. Chem.*, 3 (1982) 407–416.
- 9 Abraham, R.J. and Smith, P.E., *J. Comput. Chem.*, 9, (1988) 288–297.
- 10 Bakke, J.M. and Chadwick, D.J., *Acta Chem. Scand.*, B42 (1988) 223–230.
- 11 Streitwieser Jr., A., *Molecular Orbital Theory for Organic Chemists*, Wiley, London, 1961, pp. 489.
- 12 Hellwege, K.H. (Ed.), *Structure Data of Free Polyatomic Molecules* (Landolt-Bernstein, Vol. 7), Springer-Verlag, Berlin, 1976, pp. 393.
- 13 McClellan, A.L., *Tables of Experimental Dipole Moments*, Vol. 1, Freeman, London, 1963; Vol. 2, Rahara Enterprises, El Cerrito, CA, 1974, pp. 999.
- 14 Binkley, J.S., Pople, J.A. and Hehre, W.J., *J. Am. Chem. Soc.*, 102 (1980) 939–946.
- 15 Politzer, P., Lane, P., Jayasuriya, K. and Domelsmith, L.N., *J. Am. Chem. Soc.*, 109 (1987) 1899–1901.
- 16 Graybeal, J.D. and Roe, D.W., *J. Chem. Phys.*, 37 (1962) 2503.
- 17 Wilcox, W.S. and Goldstein, J.H., *J. Chem. Phys.*, 22 (1954) 516–518.
- 18 Ford, R.G., *J. Mol. Spectrosc.*, 58 (1975) 178–184.
- 19 Adams, D.B., *J. Chem. Soc., Perkin Trans. 2* (1987) 247–253.
- 20 Hehre, W.J., Radom, L. and Pople, J.A., *J. Am. Chem. Soc.*, 94 (1972) 1496–1504.

- 21 Politzer, P., Abrahmsen, L. and Sjoberg, P., *J. Am. Chem. Soc.*, 106 (1984) 855–860.
- 22 Lister, D.G., Tyler, J.K., Hogg, J.H. and Larsen, W., *J. Mol. Struct.*, 23 (1974) 253–258.
- 23 Hocking, W.H. and Winnewisser, G., *Z. Naturforsch.*, 31A (1976) 438–453.
- 24 Hocking, W.H. and Winnewisser, G., *Z. Naturforsch.*, 31A (1976) 995–1001.
- 25 Naito, T., Ohashi, O. and Yamaguchi, I., *J. Mol. Spectrosc.*, 68 (1977) 32–40.
- 26 Hinze, J. and Jaffe, H.H., *J. Am. Chem. Soc.*, 84 (1962) 540–548.
- 27 Miller, K.A. and Savchik, J.A., *J. Am. Chem. Soc.*, 101 (1979) 7206–7213.
- 28 Abraham, R.J. and Grant, G.H., *J. Comput. Chem.*, 9 (1988) 244–256.
- 29 Careless, A.J., Kroto, H.W. and Landsberg, B.M., *Chem. Phys.*, 1 (1973) 371–372.
- 30 Sugisaki, R., Tanaka, T. and Hirota, E., *J. Mol. Spectrosc.*, 49 (1974) 241–250.
- 31 Georgiou, K. and Kroto, H.W., *J. Mol. Spectrosc.*, 83 (1980) 94–104.
- 32 Stiefvater, O.L., *J. Chem. Phys.*, 63 (1975) 2560–2569.
- 33 Saegebarth, E. and Cox, A.P., *J. Chem. Phys.*, 43 (1965) 166–173.
- 34 Dobyns, V. and Pierce, L., *J. Am. Chem. Soc.*, 85 (1963) 3553–3556.
- 35 Mauret, P., Fayet, J.P., Fabre, M., Elguero, J. and Del Carmen Pardo, M., *J. Chim. Phys.*, 70 (1973) 1483–1486.
- 36 Bak, B., Nielsen, J.T., Nielsen, O.F., Nygaard, L., Rastrup-Andersen, J. and Steiner, P.A., *J. Mol. Spectrosc.*, 19 (1966) 458–460.
- 37 Krugh, W.D. and Gold, L.P., *J. Mol. Spectrosc.*, 49 (1974) 423–431.
- 38 Brown, N.M.D., Lister, D.G. and Tyler, J.K., *Spectrochim. Acta*, 26A (1970) 2133–2138.
- 39 Tobiason, F.L., Huetis, L., Chandler, C., Pedersen, S.E. and Peters, P., *J. Heterocyclic Chem.*, 10 (1973) 773–778.
- 40 Rogowski, R.S. and Schwendeman, R.H., *J. Chem. Phys.*, 50 (1969) 397–403.