

COSMIC(90): An improved molecular mechanics treatment of hydrocarbons and conjugated systems

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SUMMARY

Four modifications to the COSMIC molecular mechanics force field are described, which greatly increase both its versatility and the accuracy of calculated conformational energies. The Hill non-bonded van der Waals potential function has been replaced by a two-parameter Morse curve and a new H–H potential, similar to that in MM3, incorporated. Hydrocarbon energies in particular are much improved.

A simple iterative Hückel pi-electron molecular orbital calculation allows modelling of conjugated systems. Calculated bond lengths and rotational barriers for a series of conjugated hydrocarbons and nitrogen heterocycles are shown to be as accurate as those determined by the MM2 SCF method.

Explicit hydrogen-bonding potentials for H-bond acceptor-donor atom pairs have been included to give better hydrogen bond energies and lengths. The van der Waals radii of protonic hydrogens are reduced to 0.5 Å and the energy well depth is increased to 1.0 kcal mol⁻¹.

Two new general atom types, N_{sp}⁺ and O_{sp}⁻, have been introduced which allow a wide variety of charged conjugated systems to be studied. A minimum of parameterisation is required, as the new types are easily included in the Hückel scheme which automatically adjusts bond and torsional parameters according to the defined bond-order relationships.

INTRODUCTION

The COSMIC molecular mechanics force field, described previously [1], is the potential energy function which forms the basis for the COSMIC integrated molecular modelling sys-

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tem*. Throughout the 15-year period of this software development, force-field energy functions, parameters and atom types have been kept as simple as possible and have not been optimised on any one particular class of molecule. Whilst this approach of keeping the COSMIC force field as general as possible has the advantage that it can be used to model a diverse range of chemical structures, several shortcomings can be identified. These include applications to:

a) Saturated hydrocarbons. The relative conformational energies of saturated hydrocarbons such as n-butane and methylcyclohexane are poorly reproduced, and are not up to the standards of other force fields (e.g. MM2 [2]). The non-bonded van der Waals potential has been shown to be at fault [3].

b) Conjugated systems. There is no provision whatsoever for performing calculations on molecules containing conjugated pi-systems other than phenyl rings. Other force fields either provide a simple MO calculation to cope with the pi-system (MM2 [4]) or supply many more specific atom types to cover common conjugated functional groups (CVFF [5a], AMBER [6], CHARMM [7]).

c) Charged species. The specified list of atom types does not allow modelling of such entities as charged amino-acid residues and carboxylate and phenoxide ions.

d) Hydrogen bonding. The relatively simple treatment of hydrogen bonds, which involves setting the van der Waals radius of protonic hydrogens to zero, can lead to H-bonding distances which are much too short, and can even allow fusion with the acceptor atom [6a].

In this paper we report modifications to the COSMIC force field which address the above four areas, and demonstrate that these lead to major improvements both in calculated conformational energies and in the range of molecular structures that can be studied.

1. NON-BONDED VAN DER WAALS POTENTIAL

COSMIC previously used a potential function based on the Hill curve [8] ('6-exp') to model van der Waals non-bonded interactions (Eq. 1.1).

$$E_{\text{vdW}} = f[-2.25/rr^6 + 8.28 \times 10^5 \cdot \exp(-rr/0.0736)] \quad (1.1)$$

where: rr is r_{ij}/r_{ij}^* ; r_{ij} , distance between atoms i, j ; and r_{ij}^* , sum of vdW radii of atoms i, j .

A similar function is used in MM2 [2], whereas many of the other force fields (CVFF [5], AMBER [6], CHARMM [7]) use a Lennard-Jones '6-12' potential.

It has recently been shown [3] that the COSMIC non-bonded parameters differ considerably from other force fields, particularly for hydrogen, resulting in the inability of COSMIC to reproduce experimental energies for molecules with significant H-H interactions. Hydrogens in COSMIC are both small (low van der Waals radius) and 'hard' (steep repulsive curve and deep energy well), which has two main effects: conformations containing H-H interactions at or

* The complete COSMIC software system (VAX/VMS version), including the latest version of the force field, is available to academic institutions through the COSMIC Users Group at the Nottingham address given above. A fully supported version of the COSMIC(90) force field is also incorporated in the Nemesis molecular modelling package (Apple Macintosh and IBM PC versions) available from Oxford Molecular, Terrapin House, South Parks Road, Oxford OX1 3UB, U.K.

around the van der Waals contact distance, such as *gauche* n-butane, are over-stabilised, whereas conformations with very close range repulsive H–H interactions, such as planar benzophenone, are given too high a steric energy. The modification proposed earlier [3] was to replace the Hill potential function with a two-parameter Morse curve and to use a new H–H non-bonded potential similar to that in MM3 [9], in which the hydrogens are much larger and softer. All other potentials were left unchanged, but converted to Morse format.

Method

We have implemented and extensively validated these proposed amendments, and have found substantial improvements in conformational energies, particularly for hydrocarbons. The exact changes made are as follows:

- (i) The Hill potential (Eq. 1.1) has been replaced by a Morse curve (Eq. 1.2 and Fig. 1).

$$E_{\text{vdW}} = -E_{\text{min}} [z^2 - 2z] \quad (1.2)$$

where: z is $\exp[b(1 - (r_{ij}/r_{\text{min}}))]$; E_{min} , energy minimum; r_{min} , internuclear separation at energy minimum ($= r_{ij}^*$); r_0 , internuclear separation when $E_{\text{vdW}} = 0$; and $b = \ln(2) \cdot r_{\text{min}} / (r_{\text{min}} - r_0)$.

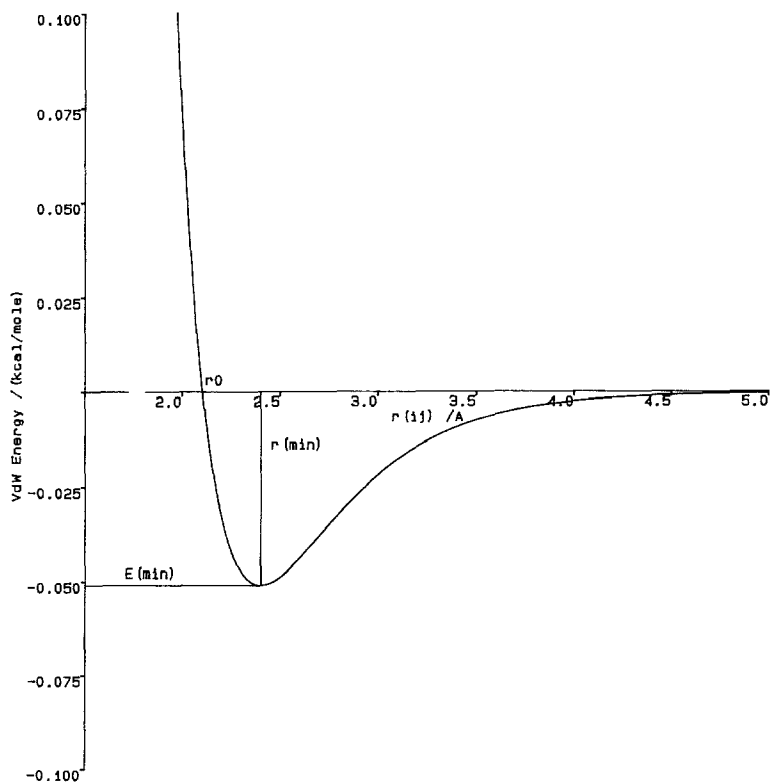


Fig. 1. Parameters defining a Morse curve.

Although a Morse potential is fully described by three parameters (r_0 , r_{\min} , E_{\min}), r_0 and r_{\min} can be related by a steepness parameter, b , which is a constant for a given Hill function [3]. Using a two-parameter function has the advantage of reducing the required changes to the source code to a minimum, as the existing arrays for r_{ij}^* and f can be utilised, albeit with slightly different meanings.

(ii) Initially, all Hill parameters were converted to Morse parameters by a simple graphical fitting [3]. E_{\min} can be read directly from the graph, whilst r_{\min} is equivalent to r_{ij}^* . The value for the steepness parameter ($b = 5.643$) was derived from the MM3 H-H potential.

(iii) For H-H interactions only, the van der Waals radius of hydrogen has been increased from 1.20 Å to 1.595 Å, giving $r_{\min} = 3.19$ Å, and $-E_{\min}$ has been reduced from 0.051 to 0.022 kcal mol⁻¹. This gives an H-H potential very similar to that found in MM3. For all other H-X interactions the existing vdW's parameters are still used.

(iv) The van der Waals radius of carbon has been increased from 1.70 Å to 1.91 Å for all C-H and C-X interactions. This was found necessary to compensate for the larger hydrogen.

In theory, similar improvements could have been made by re-parameterising the Hill potentials; the decision to convert to a Morse format was made for two reasons: i) we have found that the Morse potential function is significantly faster to compute than the Hill function (up to 23% improvement using optimised code on an Apollo DN 10000); and ii) the Hill function becomes attractive at short range, and thus requires an alternative function to be used below a distance of approximately 1.0 Å. The Morse curve does not suffer from this defect.

Results

n-Alkanes

Relative conformational energies for ethane, n-butane, n-pentane and n-hexane, calculated using the old and the new COSMIC force fields, are listed in Table 1. These are compared with literature experimental and ab-initio values, and with the MM2 and MM3 force fields. The two key hydrocarbon parameters, namely the rotational barrier in ethane and the *gauche/anti* n-butane energy difference, which were previously grossly underestimated, are now calculated satisfactorily. It was necessary to make minor adjustments to the C_{sp³}-C_{sp³} bond length (increased from 1.52 Å to 1.526 Å) and the C_{sp³}-C_{sp³} torsional barrier (increased from 0.10 to 0.14 kcal mol⁻¹) to achieve these results. The *anti/syn* energy difference in butane (5.56 kcal mol⁻¹) appears to be overestimated when compared with the experimental value of 4.60 kcal mol⁻¹, derived from extrapolation of spectroscopic data [12]. However, there is considerable uncertainty over the accuracy of the extrapolation, indeed, recent ab-initio calculations give a much higher barrier to rotation (6.34 kcal mol⁻¹) [11]. It has also been noted that MM2, which is set to closely reproduce the experimental value, cannot reproduce barriers to rotation in crowded alkanes unless the torsional barrier is increased to 5.2 kcal mol⁻¹ [11]. We therefore feel that the calculated COSMIC barrier represents a reasonable compromise, when this evidence is taken into account. Conformational energies for pentane and hexane show good agreement with the experimental and ab-initio values, and are much improved in comparison to the old force field.

Mono-substituted cyclohexanes

Calculated and experimental data for a series of mono-substituted cyclohexanes are summar-

TABLE 1
RELATIVE CONFORMATIONAL ENERGIES^a AND ROTATIONAL BARRIERS OF n-ALKANES

Molecule	Conformation	COSMIC		Expt./ ab initio	MM2/3
		Old ^b	New ^c		
Ethane	staggered	0.00	0.00	0.00	0.00
	eclipsed	1.88	2.90	2.88 ^d	2.41 ^e
n-Butane	anti	0.00	0.00	0.00	0.00
	gauche	0.22	0.91	0.89 ^f	0.81 ^e
	120°	2.20	3.25	—	3.30 ^e
	syn (0°)	3.22	5.56	4.60 ^g	4.83 ^e
n-Pentane	aa	0.00	0.00	0.00	0.00
	ag	0.19	0.89	0.76 ^h	0.86 ^e
	g ⁺ g ⁺	0.32	1.70	1.36 ^h	1.62 ^e
	g ⁺ g ⁻	1.46	3.24 ⁱ	3.33 ^{h,j} 3.61 ^{h,j}	3.51 ^{e,j}
n-Hexane	aaa	0.00	0.00	0.00	0.00
	aag	0.17	0.88	0.77 ^h	0.89 ^k
	aga	0.17	0.88	0.77 ^h	0.94 ^k
	ag ⁺ g ⁺	0.26	1.64	—	1.62 ^k
	g ⁺ ag ⁺	0.31	1.70	1.60 ^h	1.71 ^k
	g ⁺ ag ⁻	0.42	1.86	—	1.89 ^k
	g ⁺ g ⁺ g ⁺	0.32	2.39	1.91 ^h	2.30 ^k
	ag ⁺ g ⁻	1.40	3.20	—	3.25 ^k
	g ⁺ g ⁺ g ⁻	1.37	3.92	—	3.94 ^k
	g ⁺ g ⁻ g ⁺	2.50	5.49	—	5.58 ^k

^a Energies in kcal mol⁻¹.

^b Using force field in Ref. 1.

^c This work.

^d Expt., Ref. 10.

^e MM3, Ref. 9.

^f Consensus of experimental gas-phase values, Ref. 11.

^g Expt., Ref. 12.

^h Ab initio 6-31G*/MP3, Ref. 11.

ⁱ Unsymmetric (C_i) conformation.

^j Symmetric (C_s) conformation.

^k Calculated using MM2(87), Ref. 2b.

ised in Table 2. The axial/equatorial energy difference in methylcyclohexane is now well calculated. Axial methylcyclohexane contains two *gauche*-butane-type interactions, and therefore the destabilisation of the axial form is expected to be approximately double that found in butane. Cyclohexanol and methoxycyclohexane are also satisfactorily calculated. The energy difference in phenylcyclohexane is overestimated, but this was also found using MM2.

In the halocyclohexanes, the experimental axial/equatorial energy difference increases as the group is descended from fluoro- to bromo-. This is correctly reproduced by MM2, but in both the old and new COSMIC force fields the trend is reversed. The crucial parameters governing these energy differences are the H-X van der Waals potentials. In COSMIC the halides are much smaller and harder in comparison with MM2 and it seems likely that the vdW parameters will have to be modified to make the halides both larger and softer. Work is in progress to this effect.

TABLE 2
AXIAL—EQUATORIAL ENERGY DIFFERENCES^a FOR MONO-SUBSTITUTED CYCLOHEXANES (C₆H₁₁X)

X	COSMIC		Expt.	MM2
	Old ^b	New ^c		
CH ₃	0.40	1.73	1.75 ^d , 1.9–2.0 ^e	1.78 ^f
OH	0.23	0.60	0.4–0.5 ^g	0.55 ^h
OCH ₃	0.37	0.71	0.45 ⁱ	0.57 ^h
Ph	2.29	4.08	2.70 ^j	4.84 ^h
F	0.60	0.83	0.16–0.26 ^k	0.16 ^k
Cl	0.48	0.79	0.34–0.51 ^k , 0.65 ^l	0.43 ^k
Br	0.41	0.72	0.38–0.72 ^k , 0.50 ^l	0.47 ^k

^a Energies in kcal mol⁻¹.

^b Using force field in Ref. 1.

^c This work.

^d In solution, Ref. 13.

^e Gas-phase, Ref. 14.

^f Ref. 2a.

^g Ref. 15.

^h Calculated using MM2(87), Ref. 2b.

ⁱ Ref. 16.

^j High-temperature NMR, Ref. 17.

^k Summarised in Ref. 18a.

^l Gas-phase ED, Ref. 18b.

Ethers

Three ethers were considered: dimethylether (DME), methylethylether (MEE) and tetrahydrofuran (THF). Several of the existing ether force-field parameters were found to be too inaccurate for quantitative modelling. New values for the C_{sp³}–O_{sp³} bond length and force constant ($l_0 = 1.41$ Å, $1/2k = 320$ kcal mol⁻¹ Å⁻²) were taken directly from the AMBER [6b] force field to replace the old parameters (1.47 Å, 309.5 kcal mol⁻¹ Å⁻²). The C_{sp³}–O_{sp³} torsional barrier was reduced from 0.60 to 0.38 kcal mol⁻¹ (also from AMBER). It was also necessary to reduce the C_{sp³}–O_{sp³}–C_{sp³} bond angle from 114.8° to 109.5°.

With these changes in place, the agreement with experiment is excellent (Table 3). The rotational barriers in both DME and MME are correctly calculated as is the *anti/gauche* energy difference in MEE. In THF, the C_s ('envelope') form is predicted to be slightly more stable (0.09 kcal mol⁻¹) than the C₂ ('half-chair') conformer. The experimental results reverse the order but again the difference in stability is very slight (0.1 kcal mol⁻¹) [21]. It is interesting that, using the old COSMIC force field, the C₂ form of THF is not a valid minimum on the potential surface, and therefore no energy comparison is possible. The energy of the C_{2v} planar transition state is overestimated at 4.21 kcal mol⁻¹ above the C₂ conformer (expt. 3.5 kcal mol⁻¹) [21].

Alkyl halides

Calculated and experimental energies for 1,2-difluoroethane, 1,2-dichloroethane, 1-chloropropane and 1,3-dichloropropane are summarised in Table 4. There is generally poor agreement between COSMIC and experiment, with the exception of dichloroethane in which the *anti/gauche* energy difference is correctly predicted. Rather surprisingly, experimental results [18a] indicate that chloropropane has a preference for the *gauche* conformation, in contrast to both COSMIC and various MM2 calculations [18a] which all favour the *anti* form. In dichloropropane, although the predicted order of the conformations is correct, the *ag* and *aa* conformers are given too low

TABLE 3
RELATIVE CONFORMATIONAL ENERGIES^a AND ROTATIONAL BARRIERS OF ALIPHATIC ETHERS

Molecule	Conformation	COSMIC		Expt.
		Old ^b	New ^c	
Dimethyl ether	staggered	0.00	0.00	0.00
	eclipsed	3.87	2.68	2.70 ^d
Methyl ethyl ether	anti	0.00	0.00	0.00
	gauche	0.36	1.41	1.40 ^e
	syn (0°)	5.39	6.22	(5.90) ^f
Tetrahydrofuran	C ₂ 'half chair'	—	0.00	0.00
	C _s 'envelope'	—	−0.09	0.10 ^g
	C _{2v} planar	—	4.21	3.50 ^g

^a Energies in kcal mol^{−1}.

^b Using force field in Ref. 1.

^c This work.

^d Ref. 19.

^e Ref. 20.

^f MM2 calculation, See Ref. 6b.

^g Ref. 21.

a relative energy. However, these results are almost identical to calculations performed using a modified MM2 force field with empirical partial atomic charges [18a].

1,2-Difluoroethane is an interesting molecule in that the *gauche* conformation is more stable than the *anti* form, the so-called 'gauche effect'. COSMIC fails to calculate this correctly, predict-

TABLE 4
RELATIVE CONFORMATIONAL ENERGIES^a OF ALKYL HALIDES

Molecule	Conformation	COSMIC		Expt. ^d
		Old ^b	New ^c	
1,2-Difluoroethane	anti	0.00	0.00	0.00
	gauche	1.94	2.10	−0.60 to −1.76
1,2-Dichloroethane	anti	0.00	0.00	0.00
	gauche	1.22	1.35	1.05 to 1.09
1-Chloropropane	anti	0.00	0.00	0.00
	gauche	0.23	0.41	−0.05 to −0.36
1,3-Dichloropropane	g ⁺ g ⁺	0.00	0.00	0.00
	ag	0.18	0.05	1.10
	aa	0.57	0.27	1.50
	g ⁺ g [−]	2.19	2.36	—

^a Energies in kcal mol^{−1}.

^b Using force field in Ref. 1.

^c This work.

^d Summarised in Ref. 18a.

ing the *anti* conformer to be over 2 kcal mol⁻¹ more stable. In this case, the problem cannot be easily overcome by modifying the vdW potential as the *gauche* F–F non-bonded interaction will always be destabilising, due to repulsion of like charges. The standard way of incorporating the *gauche* effect into molecular mechanics calculations is to introduce V_1 and V_2 (one-fold and two-fold) terms into the torsional potential, and optimise these parameters to fit the experimental data. As this would involve a major change to the COSMIC force field, we do not feel this is justified at present.

Carboxylic acids and esters

Formic acid and acetic acid were considered along with their methyl esters (Table 5). The C_{sp²}–O_{sp³} bond length was found to be in error (1.31 Å), and a suitable replacement was taken from AMBER [6b] ($l_0 = 1.364$ Å, $\frac{1}{2}k = 450$ kcal mol⁻¹Å⁻²) to give a better fit with the experimental C–O bond length in acetic acid (1.361 Å) [22].

The relative E–Z energy difference is overestimated in the acids but underestimated in the ester forms. The barrier to rotation around the C–O bond is approximately correct in all four cases. The origin of the E–Z difference is not completely understood, as the obvious explanation, intramolecular hydrogen bonding in the Z configuration, does not explain the higher energy differences in the esters [22]. The larger difference in methylacetate compared with methylformate is largely a steric effect involving the two methyl groups; this is mirrored by the COSMIC calculations, although the absolute energy differences are approximately one-third of the experimental values.

2. HÜCKEL CALCULATION FOR CONJUGATED SYSTEMS

It is well known that molecules containing delocalised or conjugated pi-systems pose particular difficulties for molecular mechanics calculations [23]. The basic problem can be appreciated from a consideration of 1,3-butadiene, in which all three C–C bonds lie between sp²-hybridised carbons, yet where the central bond is longer than the outer two and is associated with a much lower barrier to rotation. At the molecular mechanics level, where each carbon atom is simply defined

TABLE 5
RELATIVE CONFORMATIONAL ENERGIES^a AND ROTATIONAL BARRIERS OF CARBOXYLIC ACIDS AND METHYL ESTERS

Molecule	E _E –E _Z		Rotational barrier	
	COSMIC		COSMIC	Expt. ^d
	Old ^b	New ^c	New ^c	
Formic acid	6.50	6.90	15.6	12–13
Acetic acid	6.18	6.91	15.1	12–13
Methylformate	1.56	1.60	11.4	12–13
Methylacetate	1.97	2.99	11.0	8–10

^a Energies in kcal mol⁻¹.

^b Using force field in Ref. 1.

^c This work.

^d Summarised in Ref. 22.

as C_{sp^2} , there is no obvious way of easily distinguishing between these two types of C_{sp^2} - C_{sp^2} bonds.

In principle, the problem can be addressed in one of two ways. The first is to define an ever-increasing number of atom types with associated parameter sets for each atom in the conjugated system. In the case of specialised force fields covering well-defined conjugated systems, this has the advantage of allowing a highly accurate parameter set to be developed. With generalised force fields, however, the need to keep atom types to a minimum requires that a more general method is used. The most notable examples of the latter method are MM2 [4], and earlier related programs [24], in which a preliminary SCF molecular-orbital calculation is performed on the pi-system, and the theoretical bond orders are then used to modify the force field parameters. In this way bond lengths, stretching force constants and torsional barriers can be determined individually for each bond in the pi-system, as they occur.

The overall COSMIC philosophy, of using the minimum number of general atom types, has led us to develop a similar modification to the COSMIC force field and associated software to allow modelling of conjugated systems, based on an iterative Hückel calculation.

Method

The standard Hückel molecular orbital (HMO) model [25] for hydrocarbons requires only two input parameters: a Coulomb integral (α_0) representing the energy of an electron in an isolated carbon p-orbital, and a resonance integral (β_0) which represents the energy of interaction of two p-orbitals. Heteroatoms can be included by defining Coulomb and resonance integrals relative to the carbon atom and the C-C bond in benzene, respectively (Eqs. 2.1 and 2.2).

$$\alpha_X = \alpha_0 + h_X \beta_0 \quad (2.1)$$

$$\beta_{XY} = k_{XY} \beta_0 \quad (2.2)$$

This method was implemented initially, using Streitweiser's recommended values for h_X and k_{XY} [25]. After solving the Hückel matrix, pi-bond orders are obtained by a simple Mulliken population analysis. However, the calculated bond orders were found to be too inaccurate for our purposes, particularly in 'single' bonds such as the central bond in 1,3-butadiene, in which the bond order is considerably overestimated.

The HMO model can be much improved by the introduction of an iterative procedure whereby the resonance integrals are allowed to vary according to the calculated bond order from the previous cycle [26,27]. A number of relationships between the resonance integral and the pi-bond order have been proposed utilising parabolic [25] and exponential [26,27] functional forms. However, these were not found to yield significantly more accurate bond orders than a simpler linear relationship, which was therefore implemented (Eq. 2.3).

$$k_{i+1} = k_{\min} + \rho_i (k_{\max} - k_{\min}) \quad (2.3)$$

where: k_{\min} and k_{\max} are the minimum and maximum resonance integrals for single and double bonds, respectively (determined empirically); ρ_i , the pi-bond order from cycle i ; and k_{i+1} , the new resonance integral for cycle $i+1$.

The iterative method has only currently been parameterised for carbon–carbon bonds; in all other bond types the resonance integrals remain fixed. The procedure is continued until no further change is observed in the new resonance integrals which, in practice, takes less than ten cycles. The full set of Hückel parameters for each COSMIC pi-atom type and bond type are listed in Table 6.

A further enhancement allows the algorithm to handle anti-aromatic compounds such as cyclo-octatetraene. Because all the C–C resonance integrals are initially set to the same value (1.0), the standard HMO method calculates aromatic bond orders for this system, even with the iterative improvement, contrary to the experimentally observed alternating single and double bonds. However, by perturbing each initial resonance integral by ± 0.001 , sufficient asymmetry is introduced to set up the correct bond alternation, which is then further improved by each iteration cycle. Obviously, if the system *is* aromatic the bond orders converge back to an aromatic state.

The Hückel method employed takes no account of non-planar pi-systems, that is, the resonance integrals are not related to the dihedral angles across each pi-bond. Whilst this can lead to slight inaccuracies in bond lengths in non-planar systems, it has the important advantage that the calcu-

TABLE 6
HÜCKEL PARAMETERS USED IN COSMIC
a) Coulomb integrals (h_X)

Atom type	$n_{\text{pi}a}$	h_X	Atom type	$n_{\text{pi}a}$	h_X
2,3	1	0.00	16	2	3.00 ^b
8	1	0.50 ^b	17	2	2.00 ^b
9	2	1.50 ^b	18	2	1.50 ^b
10	2	2.00 ^b	22	1	1.00 ^b
11	1	1.00 ^b	25	1	1.50 ^e
12	2	1.27 ^c	26	2	1.00 ^e
13	1	0.11 ^c			

b) Resonance integrals (k_{XY})

Atom type 1	Atom type 2	k_{XY}	Atom type 1	Atom type 2	k_{XY}
2,3	2,3	1.00 ^{b,d}	2,3	25	0.80 ^e
2,3	8	1.00 ^b	2,3	26	1.00 ^e
2,3	9	0.80 ^b	8	8	0.49 ^c
2,3	10	0.80 ^b	8	9	0.73 ^c
2,3	11	1.00 ^b	8	10	0.30 ^c
2,3	12	0.30 ^c	8	12	0.30 ^c
2,3	13	1.05 ^c	9	22	0.70 ^b
2,3	16	0.70 ^b	25	11	0.70 ^e
2,3	17	0.40 ^b	25	26	0.70 ^e
2,3	18	0.30 ^b			

^a Number of pi-electrons donated.

^b From Ref. 25.

^c From Ref. 28.

^d k varied from 0.54 to 1.23 by iterative procedure (see text).

^e Integrals for charged atom types taken from neutral parents (see text).

lated bond orders are geometry-independent, thus necessitating no changes to any of the energy-minimisation routines.

The algorithm has been implemented in such a way as to allow separate evaluation of each pi-system in the molecule, as opposed to one large single calculation. This has the effect of both increasing the calculation speed and reducing the potentially heavy memory requirements for large molecules. The limiting factor is then the size of any one pi-system, and not the total number of pi-type atoms, which in the case of a peptide or protein may be significant. Pi-atoms and conjugated systems do not have to be explicitly defined by the user, as is the case with MM2, but are picked up automatically by the program on the basis of the COSMIC atom types. Only pi-systems containing three or more atoms are included in the treatment, with the exception of amide and ester groups, which are specifically excluded as they can be adequately parameterised using the existing atom types. All Hückel parameters and bond-order relationships are read from external files to allow easy modification, without the need to recompile source code.

Force field parameters and bond-order relationships

Bond lengths and stretching-force constants have been defined as linear functions of the calculated pi-bond order. The torsional barrier to rotation is considered to be proportional to the square of the bond order, a similar relationship to that used in the MMP1 [24] force field. Thus, a total of five parameters are required for each type of pi-bond: ideal 'single' (zero pi-bond order) and 'double' (pi-bond order of 1) bond lengths and stretching-force constants, and a double-bond rotational barrier. The rotational barrier for a pure sp^2-sp^2 single bond is assumed to be zero (see Appendix for a full list of pi-bond parameters).

Carbon-carbon

Parameters for carbon-carbon bonds were derived first in the following manner: The C-C double-bond length and force constant were taken from the existing $C_{sp^2}-C_{sp^2}$ double-bond parameters for ethylene ($l_0 = 1.335 \text{ \AA}$, $\frac{1}{2}k = 670.0 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$). The value for the $C_{sp^2}-C_{sp^2}$ single-bond length (1.503 \AA) was chosen to reproduce the experimental bond length in benzene (pi-bond order 0.6667, $l = 1.399 \text{ \AA}$) [4a]. The associated force constant ($\frac{1}{2}k = 359.3 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$) was determined by assuming a linear relationship between bond length and force constant and interpolating between the values for the $C_{sp^2}-C_{sp^2}$ double bond and the existing $C_{sp^3}-C_{sp^3}$ bond parameters. The torsional barrier ($\frac{1}{2}V_2$) was set to $8.2 \text{ kcal mol}^{-1}$, giving a total barrier height in agreement with the experimental barrier in ethylene of 65 kcal mol^{-1} [29].

The remaining two parameters for carbon-carbon bonds are the minimum and maximum resonance integrals for single and double bonds, respectively, used in the iterative Hückel procedure. These are linked by the requirement that the resonance integral for benzene must equal 1.000, this being the standard bond in the HMO model. The values of k_{\min} and k_{\max} were adjusted empirically to give the best RMS agreement of calculated bond lengths with experimental X-ray data, for a range of planar aromatic hydrocarbons (benzene, naphthalene, anthracene, phenanthrene, pyrene, chrysene, triphenylene, perylene). This yielded $k_{\min} = 0.54$, $k_{\max} = 1.23$.

Carbon-nitrogen

Both $C_{sp^2}-N_{sp^2}$ bonds (pyridine type) and $C_{sp^2}-N_{tri}$ (pyrrole type) bonds have been considered.

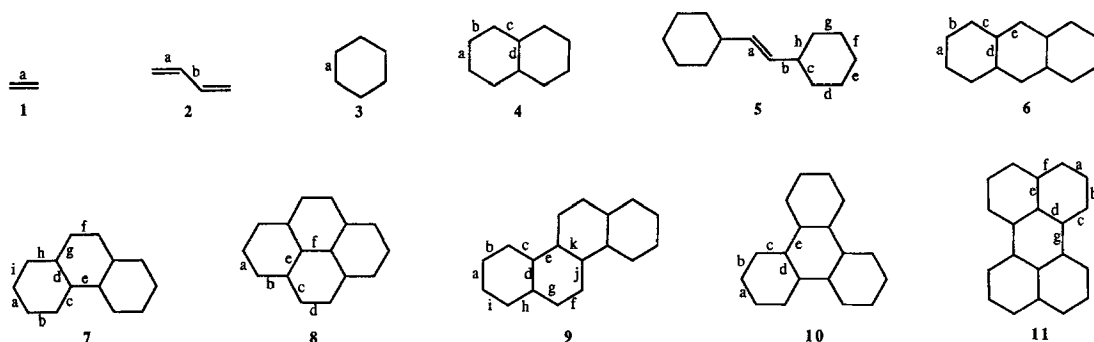


Fig. 2. Skeletal structures of conjugated hydrocarbons used to validate Hückel procedure (see Table 7).

Stretching-force constants for both bond types were taken from the existing $C_{sp^1}-N_{tri}$ (single bond) and $C_{sp^2}-N_{sp^2}$ (double bond) parameters. The bond-length range for each type of C–N bond was fixed at 0.196 Å (taken from MM2 [30]), and the upper and lower limits optimised to best fit observed X-ray bond lengths in methyleneimine, pyridine, pyrazine, pyrimidine, pyrrole, imidazole and purine. Torsional barrier heights were chosen to give a total barrier to rotation around each bond of 60 kcal mol^{−1}, in approximate agreement with the calculated barrier height in methyleneimine of 57 kcal mol^{−1}[31].

Others

Parameters for the following bond types have also been included: $C_{sp^2}-O_{sp^2}$; $C_{sp^2}-O_{sp^3}$; $C_{sp^2}-S_{sp^2}$; $N_{sp^2}-N_{sp^2}$; $N_{sp^2}-N_{tri}$. Bond lengths and stretching-force constants were taken directly from the MM2 force field [2b]. Torsional parameters were assigned to give a double-bond rotational barrier of 60 kcal mol^{−1} in each case. In some instances, for example $C_{sp^2}-O_{sp^3}$, this is a fairly arbitrary value, as pure double bonds of this type do not exist.

Results

Bond lengths

Calculated and experimental bond lengths for eleven aromatic hydrocarbons (Fig. 2) and seven aromatic nitrogen heterocycles (Fig. 3) are listed in Tables 7 and 8, respectively. The mean, RMS and maximum bond-length errors in the hydrocarbons are 0.007 Å, 0.009 Å and 0.021 Å. These compare favourably with errors in published bond lengths, using MM2, of 0.007 Å, 0.009 Å and 0.025 Å [4a]. In the nitrogen compounds, the errors are 0.008 Å, 0.012 Å and 0.035 Å compared with MM2 values of 0.008 Å, 0.011 Å and 0.030 Å [30].

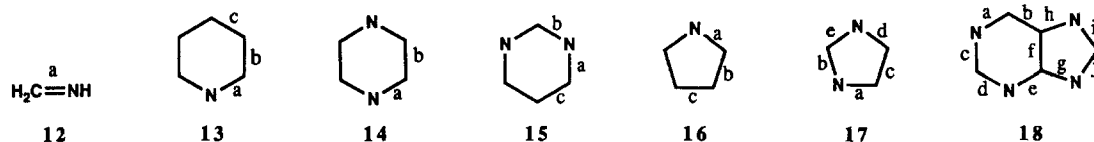


Fig. 3. Skeletal structures of conjugated nitrogen heterocycles used to validate Hückel procedure (see Table 8).

TABLE 7
CALCULATED AND EXPERIMENTAL BOND LENGTHS IN CONJUGATED AND AROMATIC HYDROCARBONS

Molecule	Bond ^a	Bond length (Å)		Expt.–Calc.
		Expt. ^b	Calc.	
Ethylene (1) ^c	a	1.337	1.337	0.000
1,3-Butadiene (2)	a	1.344	1.345	–0.001
	b	1.467	1.456	0.011
Benzene (3)	a	1.399	1.397	0.002
Naphthalene (4)	a	1.412	1.419	–0.007
	b	1.371	1.379	–0.008
	c	1.422	1.423	–0.001
	d	1.420	1.415	0.005
<i>trans</i> -Stilbene (5)	a	1.338	1.359	–0.021
	b	1.473	1.460	0.013
	c	1.406	1.405	0.001
	d	1.393	1.395	–0.002
	e	1.393	1.396	–0.003
	f	1.391	1.396	–0.005
	g	1.390	1.395	–0.005
	h	1.402	1.407	–0.005
Anthracene (6)	a	1.418	1.427	–0.009
	b	1.375	1.372	0.003
	c	1.444	1.431	0.013
	d	1.433	1.426	0.007
	e	1.405	1.403	0.002
Phenanthrene (7)	a	1.394	1.407	–0.013
	b	1.401	1.386	0.015
	c	1.409	1.417	–0.008
	d	1.420	1.415	0.005
	e	1.465	1.451	0.014
	f	1.350	1.365	–0.015
	g	1.453	1.436	0.017
	h	1.423	1.414	0.009
	i	1.386	1.384	0.002
Pyrene (8)	a	1.395	1.398	–0.003
	b	1.406	1.405	0.001
	c	1.438	1.440	–0.002
	d	1.367	1.367	0.000
	e	1.425	1.418	0.007
	f	1.430	1.428	0.002

TABLE 7 (continued)

Molecule	Bond ^a	Bond length (Å)		Expt.–Calc.
		Expt. ^b	Calc.	
Chrysene (9)	a	1.394	1.410	–0.016
	b	1.381	1.383	–0.002
	c	1.409	1.422	–0.013
	d	1.407	1.414	–0.007
	e	1.468	1.447	0.021
	f	1.369	1.369	0.000
	g	1.421	1.427	–0.006
	h	1.428	1.417	0.011
	i	1.363	1.381	–0.018
	j	1.428	1.434	–0.006
	k	1.401	1.411	–0.010
Triphenylene (10)	a	1.397	1.399	–0.002
	b	1.381	1.387	–0.006
	c	1.410	1.415	–0.005
	d	1.413	1.416	–0.003
	e	1.458	1.460	–0.002
Perylene (11)	a	1.370	1.378	–0.008
	b	1.418	1.411	0.007
	c	1.397	1.395	0.002
	d	1.425	1.431	–0.006
	e	1.424	1.419	0.005
	f	1.400	1.419	–0.019
	g	1.471	1.464	0.007

^a See Fig. 2.^b Summarised in Ref. 4a.^c Two-atom pi-system treated using standard force field; Hückel algorithm is not invoked.

Rotational barriers

Rotational profiles around C_{sp²}–C_{sp²} single bonds in four simple conjugated hydrocarbons were determined using the SPIN01 option in COSMIC. A ‘soft’ spin was performed using a step size of 10°, with 50 cycles of conjugate gradient minimisation at each point. Biphenyl, styrene, trans-stilbene and butadiene were selected for study. In these conjugated systems, the minimum energy conformation is determined by the delicate balance between conjugation energy, favouring a planar form, and steric interactions (mainly H–H) forcing the molecule out of the plane, thus providing a good test for both the Hückel algorithm and the modifications to the non-bonded potential. Calculated and experimental energy barriers are listed in Table 9 and the rotational profiles for biphenyl and butadiene, obtained using both COSMIC and MM2 [2b], are compared in Figs. 4 and 5.

Biphenyl

Both COSMIC and MM2 agree with the observed gas-phase dihedral angle between the phenyl

TABLE 8
CALCULATED AND EXPERIMENTAL BOND LENGTHS IN CONJUGATED AND AROMATIC NITROGEN
HETEROCYCLES

Molecule	Bond ^a	Bond length (Å)		Expt.–Calc.
		Expt. ^b	Calc.	
Methyleneimine (12) ^c	a	1.273	1.273	0.000
Pyridine (13)	a	1.338	1.339	–0.001
	b	1.394	1.395	–0.001
	c	1.392	1.395	–0.003
Pyrazine (14)	a	1.339	1.338	0.001
	b	1.393	1.398	–0.005
Pyrimidine (15)	a	1.340	1.338	0.002
	b	1.339	1.337	0.002
	c	1.392	1.393	–0.001
Pyrrole (16)	a	1.371	1.372	–0.001
	b	1.382	1.360	0.022
	c	1.417	1.421	–0.004
Imidazole (17)	a	1.380	1.383	–0.003
	b	1.357	1.349	0.008
	c	1.374	1.376	–0.002
	d	1.386	1.355	0.031
	e	1.333	1.298	0.035
Purine (18)	a	1.333	1.343	–0.010
	b	1.389	1.390	–0.001
	c	1.349	1.354	–0.005
	d	1.332	1.339	–0.007
	e	1.337	1.345	–0.008
	f	1.403	1.391	0.012
	g	1.374	1.362	–0.012
	h	1.374	1.377	–0.003
	i	1.332	1.361	–0.029
	j	1.312	1.314	–0.002

^a See Fig. 3.

^b Summarised in Ref. 30.

^c Two-atom pi-system treated using standard force field; Hückel algorithm is not invoked.

rings of 42–50° [32,33]. In addition, the relative energies of both the planar ($\omega=0^\circ$) and perpendicular ($\omega=90^\circ$) forms are correctly calculated. Before the amendments to the H–H potential were made, the calculated planar barrier was much lower using COSMIC ($<0.8 \text{ kcal mol}^{-1}$) because of the smaller hydrogen vdW radius.

TABLE 9
ROTATIONAL BARRIERS^a OF C_{sp}²-C_{sp}² 'SINGLE' BONDS IN CONJUGATED HYDROCARBONS

Molecule		COSMIC ^b	Expt.	MM2 ^c
Biphenyl	ω_{\min}	43°	50° ^d , 42° ^e	41°
	E_0-E_{90}	2.31	2.0 ^d	2.17
	$E_{90}-E_0$	1.23	1.0 ^d	1.27
Styrene	$E_{90}-E_0$	2.85	1.78 ^f , 2.8–3.6 ^g	3.36
<i>trans</i> -Stilbene	$E_{90}-E_0$	3.66	—	3.0
1,3-Butadiene	$E_{\text{cis}}-E_{\text{trans}}$	1.78	2.5–3.1 ^h	2.33
	$E_{90}-E_{\text{trans}}$	5.32	4.0–5.0 ^h , 7.16 ⁱ	7.20

^a Barrier heights in kcal mol⁻¹.

^b This work.

^c Ref. 4b.

^d Ref. 32.

^e Ref. 33.

^f Ref. 34.

^g Ref. 35.

^h Summarised in Ref. 36.

ⁱ Ref. 37.

Styrene, trans-stilbene and butadiene

All three molecules are calculated to be planar using both force fields. The MM2 barrier for styrene is slightly higher than obtained using COSMIC, but both are within the range of the experimental values. In *trans*-stilbene the situation is reversed, with the COSMIC rotational barrier being slightly higher. The phenyl groups have been reported to be $30 \pm 15^\circ$ out of the plane in the

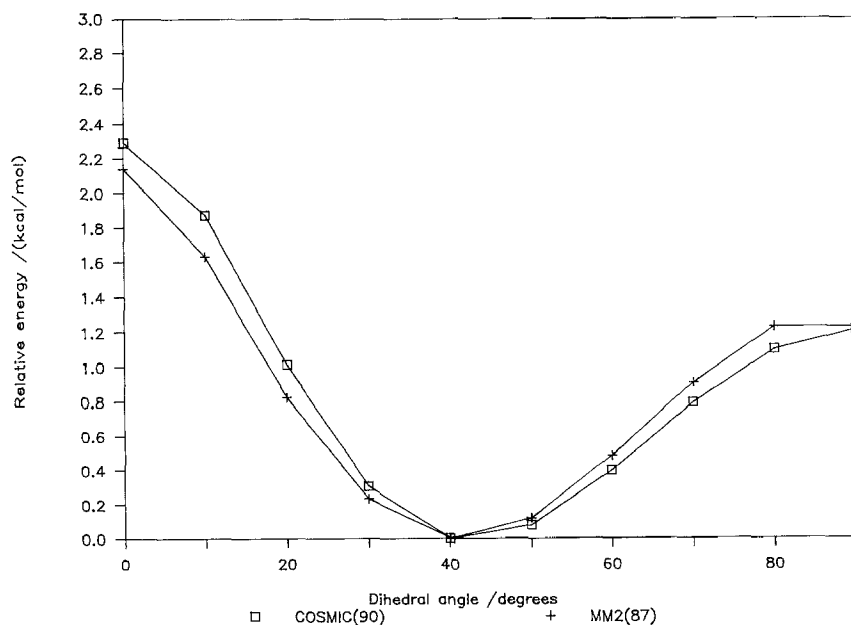


Fig. 4. Energy profiles for rotation around the central bond in biphenyl calculated using COSMIC(90) and MM2(87).

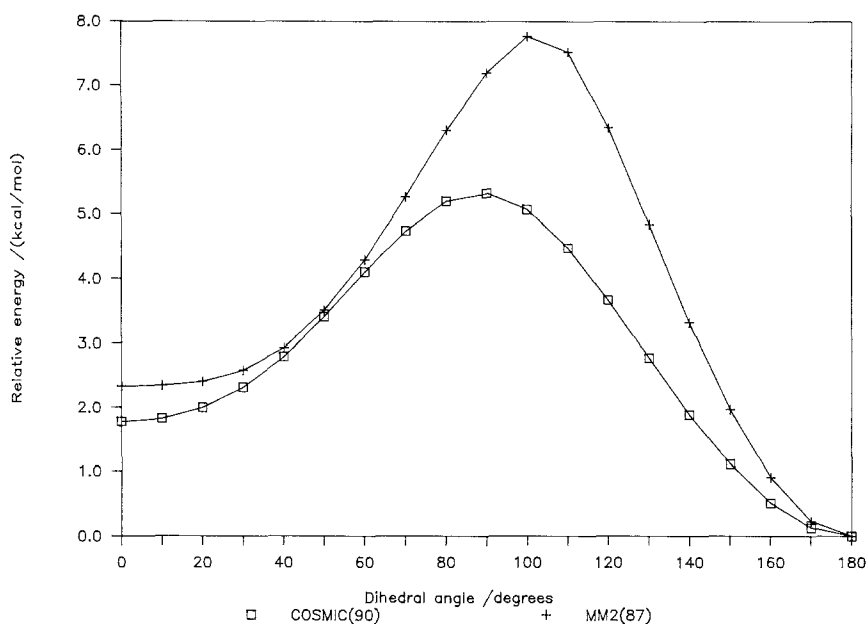


Fig. 5. Energy profiles for rotation around the central bond in butadiene calculated using COSMIC(90) and MM2(87).

gas phase [38], but the calculated potential curves are sufficiently shallow to allow significant torsional deviation from the planar form.

In butadiene, there is some variation in the experimental barrier height, which ranges from 4 to 7 kcal mol⁻¹ [36,37]. The COSMIC value (5.32 kcal mol⁻¹) falls towards the bottom end of the range, whilst MM2 has been parameterised to fit the higher value (7.20 kcal mol⁻¹) [4a]. The calculated *cis-trans* energy difference in COSMIC is less than observed (1.8 vs. 2.5–3.1 kcal mol⁻¹). To obtain a better fit with experiment, it would be necessary to include contributions from one-fold and three-fold terms in the torsional potential, as is done in MM2.

Anti-aromatics

With the iterative improvements to the standard Hückel method, COSMIC is also capable of handling anti-aromatic systems such as cyclooctatetraene. The 'tub' form is calculated to be 8.39 kcal mol⁻¹ more stable than the planar conformation. Calculated bond lengths for the alternating single and double bonds are (observed values in brackets [39]): 1.459 Å (1.475 Å) and 1.347 Å (1.340 Å), respectively.

3. CHARGED ATOM TYPES

Although COSMIC contains a fairly extensive set of atom types to cover the majority of neutral molecules, the only charged atom type at present is N_{sp³}⁺ which is used in ammonium ion. We have added two more charged atom types, namely N_{sp²}⁺ and O_{sp³}⁻, which are commonly needed for modelling ionised amino-acid side chains such as Asp⁻ and His⁺, but which can also be used more

generally in charged conjugated systems such as carboxylate, phenoxide and pyridinium ions.

$N_{sp^2}^+$ has the same connectivity and approximate geometry as the N_{tri} atom type used in pyrrole and amide groups, but has one less pi-electron. Similarly, $O_{sp^3}^-$ shares the same connectivity as O_{sp^2} but with one extra pi-electron. We have therefore taken valence force-field parameters (bond lengths, angles and dihedral terms) for these charged atoms directly from their respective neutral parents, the only difference being the number of pi-electrons donated to the conjugated system (read from the Hückel parameter file). Changes in any bond lengths and rotational barriers due to the charged atoms are then catered for automatically by the Hückel algorithm and the defined bond-order relationships. The COSMIC interface to the CHARGE2 [43] program, for calculating partial atomic charges, has been modified to accept these new atom types and set the excess charge on the pi-system accordingly.

One consequence of the new types is that the nitro group (O–N–O), which was previously defined as $O_{sp^{2/3}}-N_{tri}-O_{sp^{2/3}}$ (atom types 22–9–22), can now be defined as the formal resonance form $O_{sp^3}^- - N_{sp^2}^+ - O_{sp^2}$ (atom types 26–25–11). The Hückel algorithms in COSMIC and CHARGE2 ensure that equal bond lengths and atomic charges are calculated for each N–O bond and oxygen atom. A crude bond-order relationship has been derived for N–O bonds from a consideration of bond lengths in both nitro and oxime units. Force constants were taken from the carbon–carbon bond parameters. This relationship is used for $N_{sp^2}^+ - O_{sp^3}^-$, $N_{sp^2}^+ - O_{sp^2}$, and $N_{sp^2} - O_{sp^3}$ (see Appendix). The calculated parameters for the N–O bond in the nitro group are $l_0 = 1.266 \text{ \AA}$, $\frac{1}{2}k = 558.9 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$, compared with the existing parameters for bond type 9–22 of 1.240 \AA and $560.0 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$.

A striking example of the versatility of the combination of the charged atom types, the Hückel algorithm and CHARGE2 is provided by nitrophenoxide (Fig. 6). Significant variations in bond lengths and atomic charges are observed depending on the relative position of the nitro group. In the *ortho*- and *para*- positions, the negative charge on the phenoxide oxygen is delocalised around the ring and onto the nitro group, resulting in a shortening of the C–O (from 1.26 \AA to 1.24 \AA) and C–N (from 1.37 \AA to 1.34 \AA) bond lengths, relative to *meta*-nitrophenoxide. With the nitro group in the *meta*-position, delocalisation is not possible, and the charge on the oxygen is virtually identical to that in the parent phenoxide ion.

4. HYDROGEN BONDING

Hydrogen bonds are formed by the largely electrostatic interaction of a protonic hydrogen (i.e., a hydrogen bonded to an electronegative atom) and an electronegative H-bond acceptor atom. The quantitative modelling of hydrogen bond energies and geometries is not usually possible in molecular mechanics, without in some way modifying the non-bonded potentials to allow much closer contact between the protonic hydrogen and the H-bond acceptor atom. There are two extreme approaches to the problem:

a) The standard vdW non-bonded potential between a protonic hydrogen and a possible H-bond acceptor is replaced by an explicit hydrogen bond potential. This typically has a much reduced vdW radius for the hydrogen ($< 0.5 \text{ \AA}$) and a deep energy well ($> 0.5 \text{ kcal mol}^{-1}$). The hydrogen bonding energy then comes from a combination of this explicit potential and the existing electrostatic attraction.

b) The vdW radius of the protonic hydrogen is reduced to zero, leaving a purely electrostatic at-

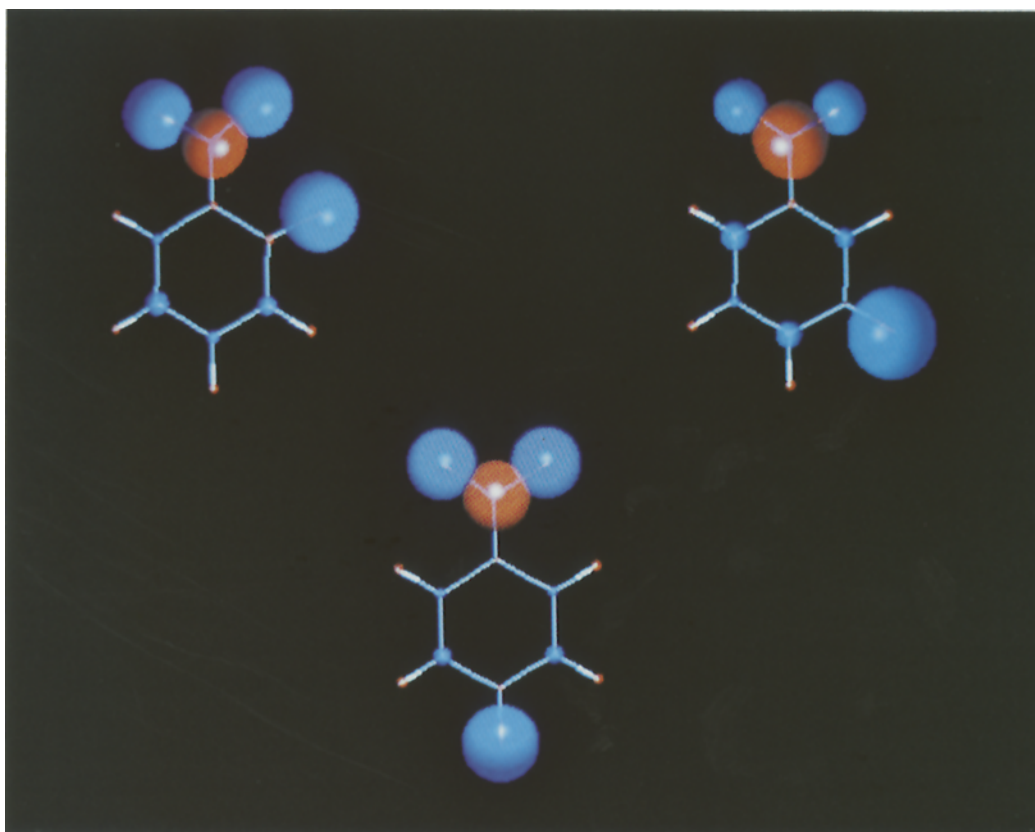


Fig. 6. Partial atomic charges in (clockwise from top left) *ortho*-, *meta*- and *para*-nitrophenoxide calculated using CHARGE2. Sphere radii are proportional to the magnitude of the charge (blue = negative, red = positive).

traction between the acceptor and donor atoms. Using this method one needs to be careful that the vdW radii of the acceptor atom and the electronegative atom to which the hydrogen is bound are large enough to provide a repulsive barrier to prevent the hydrogen and H-bond acceptor atoms from approaching too closely, or even fusing.

Method b) is used by the Discover CVFF force field [5b], and is perhaps simpler and more elegant but is extremely difficult to parameterise, as the hydrogen bond length and stabilisation energy are very sensitive to the partial atomic charges on the participating atoms. The first method, which is used by both MM2 [2b] and AMBER [6], is easier to 'fine tune' to give reasonably quantitative energies and geometries by optimising the additional H-bonding parameters.

COSMIC originally set the vdW radius of protonic hydrogens to zero [1], as in method b) above. However, we have found that the introduction of 'softer' atoms with the Morse vdW potential has allowed therefore developed new hydrogen bonding potentials along the lines fusion of the acceptor and donor hydrogen bonding atoms, and we have described in method a).

We considered a number of simple hydrogen-bonded dimers (water dimer, N-methylacetamide dimer and formic acid dimer) in our parameterisation procedure, and found that a vdW radius for

TABLE 10
HYDROGEN BOND ENERGIES AND LENGTHS FOR SIMPLE DIMERS

Dimer	Stabilisation energy (kcal mol ⁻¹)		O...H/Å	
	Calc. ^a	Expt.	Calc. ^a	Expt.
Water	5.5	5.4 ^b	1.85	2.03 ^c
Formic acid	10.8	14.1 ^d	1.86	—
NMA	7.7	(7.0) ^e	1.86	(1.82) ^e

^a This work.

^d Ref. 42.

^b Ref. 40.

^e Calculated values using the AMBER force field, See Ref. 6a.

^c Ref. 41.

protonic hydrogens of 0.5 Å and a well depth of 1.0 kcal mol⁻¹ gives at least semi-quantitative energies and hydrogen bond lengths (Table 10). These values are only used for H(protonic)–H-bond acceptor interactions (H–N, H–O, H–F, H–Cl, H–Br); for other H(protonic) interactions, the standard vdW terms are still used (i.e. vdW radius = 1.2 Å, $-E_{\min} = 0.051$ kcal mol⁻¹).

CONCLUSIONS

In this paper, four modifications to the COSMIC force field have been described which substantially improve its accuracy and applicability. These changes have been implemented with a minimum of disruption to the existing force field functions and parameter sets, and are in keeping with the COSMIC philosophy of using as few general atom types as possible. The Hückel scheme alleviates the need to add specific pi-atom types for conjugated systems, and indeed renders the C_{ar} atom type almost redundant. The new charged atom types, N_{sp²}⁺ and O_{sp³}⁻, are also general in their usage and, in combination with the Hückel algorithm and the CHARGE2 program for calculating empirical partial atomic charges, provide a powerful framework for molecular mechanics calculations on charged conjugated systems.

We recognise that the reparameterisation of the non-bonded potentials is incomplete, and that the use of two values for the hydrogen van der Waals radius is by no means ideal, but we feel that the improvement in conformational energies is great enough to justify this step. A complete reparameterisation is currently under way at a number of sites.

Several referees have commented on the limited set of compounds used to evaluate the new force field. We acknowledge this fact, although it was only ever our intention to provide enough experimental evidence to demonstrate the success of the force field enhancements. We would welcome reports of more extensive testing on larger experimental datasets from other research groups, and would consider any further suggested improvements for incorporation in later versions of COSMIC.

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