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Consistent Force Field Studies of Intermolecular Forces in Hydrogen-Bonded Crystals. 1. Carboxylic Acids, Amides, and the C=O···H– Hydrogen Bonds

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Abstract: Energy functions for intermolecular atom–atom interactions in carboxylic acids are derived. The energy parameters are determined by the consistent force field method of least-squares fitting of calculated to experimental properties. Crystal structure parameters, sublimation energies, and dipole moments are used, taken from a data base of 14 mono- and dicarboxylic acids. Two force fields are examined, denoted 9-6-1 and 12-6-1, having for each type of atoms a repulsive term, proportional to either 9th or 12th inverse power of interatomic distance, respectively, a dispersion attractive term, and a partial atomic charge. The transferability of energy parameters from a similar force field for amides derived previously is examined in detail. It is found that the 110 observables may be fit, with only a single adjustable parameter, the charge on the hydroxyl hydrogen. Optimizing additional force constants rather than transferring them does not lead to a significant improvement in fit. The hydrogen bond of carboxylic acids is found to resemble that in amides in (1) requiring no special function, thus being well represented as a balance between van der Waals and Coulomb interactions between two polar bonds; (2) having negligibly small van der Waals parameters for the hydrogen. The difference between NH···O and OH···O hydrogen bond lengths and energies falls out naturally as a result of the different van der Waals radii of N and O. The concept of the hydrogen bond derived from our analysis is found to be in qualitative agreement with recent quantum-mechanical calculations of the hydrogen bond energy and its partitioning.

Introduction

This paper is part of a series whose purpose is to obtain a general force field for organic and biological molecules. By a general force field we mean a set of potential energy functions of interatomic distances and of molecular internal coordinates, which represents the energy of molecules and of assemblies of molecules in the electronic ground state. From the knowledge of the force field one can calculate all molecular properties which are determined by the energy of the system. Conversely, the consistent force field (CFF) method[1] uses all relevant and available experimental data of whole families of molecules in order to select the best potential energy functions and to determine their constant parameters by a least-squares procedure, such as to obtain a best fit to the experimental data.

The first steps in the series involved the derivation and the application of a consistent force field for intramolecular and intermolecular interactions in alkanes.[2,3] This was extended to intramolecular interactions in alkenes[4] and then to the study of intermolecular interactions in amide crystals and the amide hydrogen bond,[5,6] as a source of energy functions for peptides and proteins.

The need for a general consistent force field is continuously increasing, especially in studies of biological systems.[7] A reliable force field is needed for such studies as the energy-based refinement of the protein coordinates obtained by X-ray crystallography,[8] and the investigation of the formation[7,9] and dynamics[10] of protein tertiary structure. Application of such force fields to pharmacological compounds[11] may help in studies of the relation between conformation and biological activity. Interatomic potential functions are also needed in crystal-packing analysis, to compare quantitatively the equilibrium energy of different packing modes of related molecules.[12] They may also be used to study the effect of crystal forces on molecular conformation[13a] and the relative stability of polymorphic crystal forms in which the molecular conformation varies (conformational polymorphism),[13b,c] a phenomenon closely related to the existence of two different conformations accommodated randomly in the unit cells of a single crystal. The latter was discovered some time ago with the help of energy calculations.[14]

As a result of the ever-increasing interest in, and application of, intermolecular energy functions, as described above, there have been numerous studies in which such functions were developed. It has become apparent that the precise structural information available for the crystal state provides a rich source of information for deriving energy parameters. For this reason these energy functions have been derived from crystal data, in various ways, and using widely varying observables, both with respect to the number and type of crystals treated. The first organic molecules studied with this approach by Williams,[15] Kitaigorodskii,[16] and Warshel and Lifson[3] were the hydrocarbons. This is still a field of current research.[15c,17] An extensive study of polar molecules was carried out by Ferro and Hermans.[18] The most widely studied crystals are those containing hydrogen bonds,[19] because of the importance of this interaction. Potential functions for hydrogen-bonding systems have been suggested by Giglio et al.,[20] Ramachandran et al.,[21]

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Caillet and Claverie,[11b,c] Lifson et al.,[5,6,19] Scheraga et al.,[22] and Derissen and Smit.[23] The latter two are of special relevance to the present study as carboxylic acid crystals are treated (as well as amides and hydrocarbons in ref 22). More recently Scheraga and co-workers[24] have reconsidered the functional form used in their previous work, and developed a new potential form for saturated molecules.

In the following three papers our force field is further extended to include the O-H···O= hydrogen bond and carboxylic acids. In the first paper we present the derivation of the carboxylic acid force field. The nature of the O-H···O= hydrogen bond and the intermolecular forces in these acid crystals are discussed in light of these results. The conclusions drawn from this study are discussed in relation to those drawn from our previous study on amide crystals[5,6,19] and those drawn on the basis of various recent molecular orbital calculations.

In the second paper[25] we argue for the need of a benchmark by which to measure the validity of the analytical functions being derived in the literature to represent intermolecular forces. An initial data base for such a benchmark, consisting of the energetic and structural properties of 26 amide and carboxylic acid crystals, and several gas-phase dimers, is presented. This data base is used to compare several alternative representations of carboxylic acid and amide force fields.

Finally, in the third paper[26] we discuss problems related to the crystal packing of the carboxylic acids. The energetics of the various secondary structures (hydrogen-bonding modes), and the ways in which these structures are arranged to form a three-dimensional lattice (tertiary structure), are investigated. The detailed results of the lattice energy minimization of 14 carboxylic acid crystals studied in this work are presented, and the deviations discussed at the molecular level.

Analytical Representation of the Force Field. Because of the wide range of subjects for which interatomic functions are being employed, and because of limitations of computer time when dealing with large molecular systems, it is extremely important to establish a force field which will be general yet as simple as possible. In order to achieve generality we consider a large set of observables (crystal structures, sublimation energies, molecular dipole moments, dimerization energies, and dimer structures), measured for a large number of molecules. In order to achieve simplicity we retain the Lennard-Jones-Coulomb type potential used in previous CFF studies. Alternative repulsive terms of 9 or 12 inverse powers are investigated, while the electrostatic term involves partial atomic charges q_i. The expression for the interaction energy may then be given by

$$\begin{aligned} v_{12\text{-}6\text{-}1} &= \epsilon\{(r^*/r)^{12} - 2(r^*/r)^6\} \\ &\quad + q_iq_j/r = A/r^{12} - C/r^6 + q_iq_j/r \\ v_{9\text{-}6\text{-}1} &= \epsilon\{2(r^*/r)^9 - 3(r^*/r)^6\} \\ &\quad + q_iq_j/r = A/r^9 - C/r^6 + q_iq_j/r \end{aligned} \tag{1}$$

where in the first of the two equivalent expressions, ϵ is the depth of the potential at the minimum r^*. (The former expression is more physically interpretable while the latter is more convenient to use computationally[5,27]). The combination rule used for interactions between two different types of atoms i and j is

$$A_{ij} = (A_{ii}A_{jj})^{1/2};\ C_{ij} = (C_{ii}C_{jj})^{1/2} \tag{2}$$

This model accounts for the properties of the hydrogen bond in carboxylic acids, as it does in amides,[5,6] and no special, explicit functions are needed to represent this interaction.

The final point to be made with regard to this simple form, which we shall return to in part 2, is that it provides a basis for further improvement of the analytical form. Furthermore, it serves as a basis for comparison; additional terms and/or additional parameters should be required to improve the fit to experiment significantly over that obtained with this simple form.

Generality of the Potential Function. One of the most important properties of a force field when considering its application is transferability. In order to maintain the generality of the potential we initially transferred as many parameters as possible from the previous force fields,[3,5] and concentrated our efforts on the carboxyl functional group.

In addition to the alkyl (CH_3, CH_2) and carbonyl (C=O) groups found in amides the acids also contain the hydroxyl group. The strategy followed then was to add to the existing force field the minimum number of parameters for the hydroxyl group needed for reproducing the properties of acid crystals. Of course there is no a priori guarantee that the same parameters used to describe the carbonyl group in amides are suitable for acids, and this and other possible assumptions in deriving parameters were checked, both by the least-squares procedure discussed here and later by full lattice energy minimization. In exploring the various possibilities of choosing energy parameters and examining their transferability extensive use was made of ab initio electron density distributions.[28] This is discussed in more detail below.

As shown below, and in the following papers, the addition of only *one* independent parameter, namely, the charge on the hydroxyl hydrogen, was sufficient to obtain a reasonable fit to the extensive set of experimental data on carboxylic acids.

Method

Experimental Data and Their Application in the Optimization of Energy Parameters. The total data base used in the present studies[25,26] is comprised of the crystal structure parameters of 14 carboxylic acids, the sublimation energies of 12 of these crystals, the dimerization energies in the gas phase of 2 acids, and the dipole moments of 4 acids in the gas phase and in nonpolar solvents. The acids belong to either the homologous series of monocarboxylic acids, of the general formula $H(CH_2)_nCOOH$ with $n = 0, 1, \ldots, 4$, or to the dicarboxylic acids $COOH(CH_2)_nCOOH$, with $n = 0, 1, \ldots, 4, 6, 8$. Both the α and β crystal forms of oxalic acid[34] are considered, and methylmalonic acid[36] is also included. They represent a wide variety of hydrogen bond geometries as seen in Table I, in which the references to the experimental structures are also given. The H···O distances range between 1.6 and 1.8 Å; H···O=C angles vary between 114 and 130°, and O-H···O angles deviate from linearity by up to 33°. (A subset of these data comprising 110 observables is used in the least squares as described below.)

The acids chosen crystallize in a wide variety of packing modes[42] as seen in Figure 1. They are "linked" by hydrogen bonds into dimers (propionic,[31] butyric,[32] and valeric[33] acids), catamers, namely, linear chains of molecules connected by a single hydrogen bond (acetic[30] and formic[29] acids), chains consisting of hydrogen-bonded cyclic dimers (β-oxalic,[34] adipic,[39] suberic,[40] and sebacic[41] acids), twisted chains (malonic,[35] methylmalonic,[36] and glutaric[38] acids), and corrugated sheets (α-oxalic acid[34]).

The experimental sublimation enthalpy ΔH_s was related to the calculated lattice energy V_L, as in ref 5, by

$$V_L = -\Delta H_s - 2RT \tag{3}$$

where the last term represents an approximate correction for the difference between the gas-phase enthalpy $pV + 3RT$ and the estimated vibrational contribution to the crystal enthalpy $\sim 6RT$. In going from the solid to the gas phase both geometrical[42,43] and vibrational[44-46] changes occur. The energy contribution associated with these changes goes in opposite directions. An average geometrical contribution has been estimated by Derissen to be 1.8 kcal/mol by a valence force field

Table I. Experimental Hydrogen Bond Geometry[a] and Packing Modes of Carboxylic Acid Crystals

	acid	ref	O···H	∠C=O···H	180° − ∠O-H···O	space group	packing mode
formic	$HCOOH$	29	1.58[b]	122.5	6.8	$Pna2_1$	linear chains (catamers)
acetic	CH_3COOH	30[c]	1.65	130.2	16.7	$Pna2_1$	linear chains (catamers)
propionic	CH_3CH_2COOH	31	1.63	124.0	2.4	$P2_1/c$	dimer rings
butyric	$CH_3(CH_2)_2COOH$	32	1.62	125.2	0.3	$C2/m$	dimer rings
valeric	$CH_3(CH_2)_3COOH$	33	1.65	125.7	12.4	$P2_1/c$	dimer rings
α-oxalic	$(COOH)_2$	34	1.80	122.7	32.5	$Pcab$	corrugated sheets
β-oxalic	$(COOH)_2$	34	1.67	120.3	5.2	$P2_1/c$	linear chains of cyclic dimers
malonic	$(HOOC)CH_2COOH$	35	1.71	114.5	8.4	$P\bar{1}$	twisted chains of cyclic dimers
			1.67	127.5	10.8		
methylmalonic	$(HOOC)CH(CH_3)COOH$	36	1.74	123.5	10.5	$P\bar{1}$	twisted chains of cyclic dimers
			1.60	121.1	3.8		
succinic	$HOOC(CH_2)_2COOH$	37	1.61	125.0	0.0	$P2_1/a$	linear chains of cyclic dimers
glutaric	$HOOC(CH_2)_3COOH$	38	1.68	118.4	12.1	$I2/a$	twisted chains of cyclic dimers
adipic	$HOOC(CH_2)_4COOH$	39	1.62	120.2	6.1	$P2_1/c$	linear chains of cyclic dimers
suberic	$HOOC(CH_2)_6COOH$	40	1.65	119.4	10.2	$P2_1/c$	linear chains of cyclic dimers
sebacic	$HOOC(CH_2)_8COOH$	41	1.64	117.8	10.1	$P2_1/c$	linear chains of cyclic dimers

[a] The hydrogen atom positions are refined by minimization of intramolecular energy of these molecules with respect to hydrogen positions. Lengths in ångstroms, angles in degrees. [b] This value is approximate; it was obtained by a best fit of the molecular structure from electron diffraction of the dimer to the asymmetric unit of the crystal. [c] Data obtained by neutron diffraction.

while in the case of acetic acid we have obtained a value of ~2 kcal/mol from ab initio calculations.[47] Smit[23] has estimated the total change in energy due to both these contributions to be 0.5 kcal/mol in acetic acid. Since this contribution is small and neither good conformational energies nor extensive vibrational frequencies are available we have ignored this effect in the present work, but it is a subject to be treated in future applications.

The values of the sublimation enthalpy of the monocarboxylic acids were obtained by adding the heats of melting ΔH_m and vaporization ΔH_v (at 25 °C):

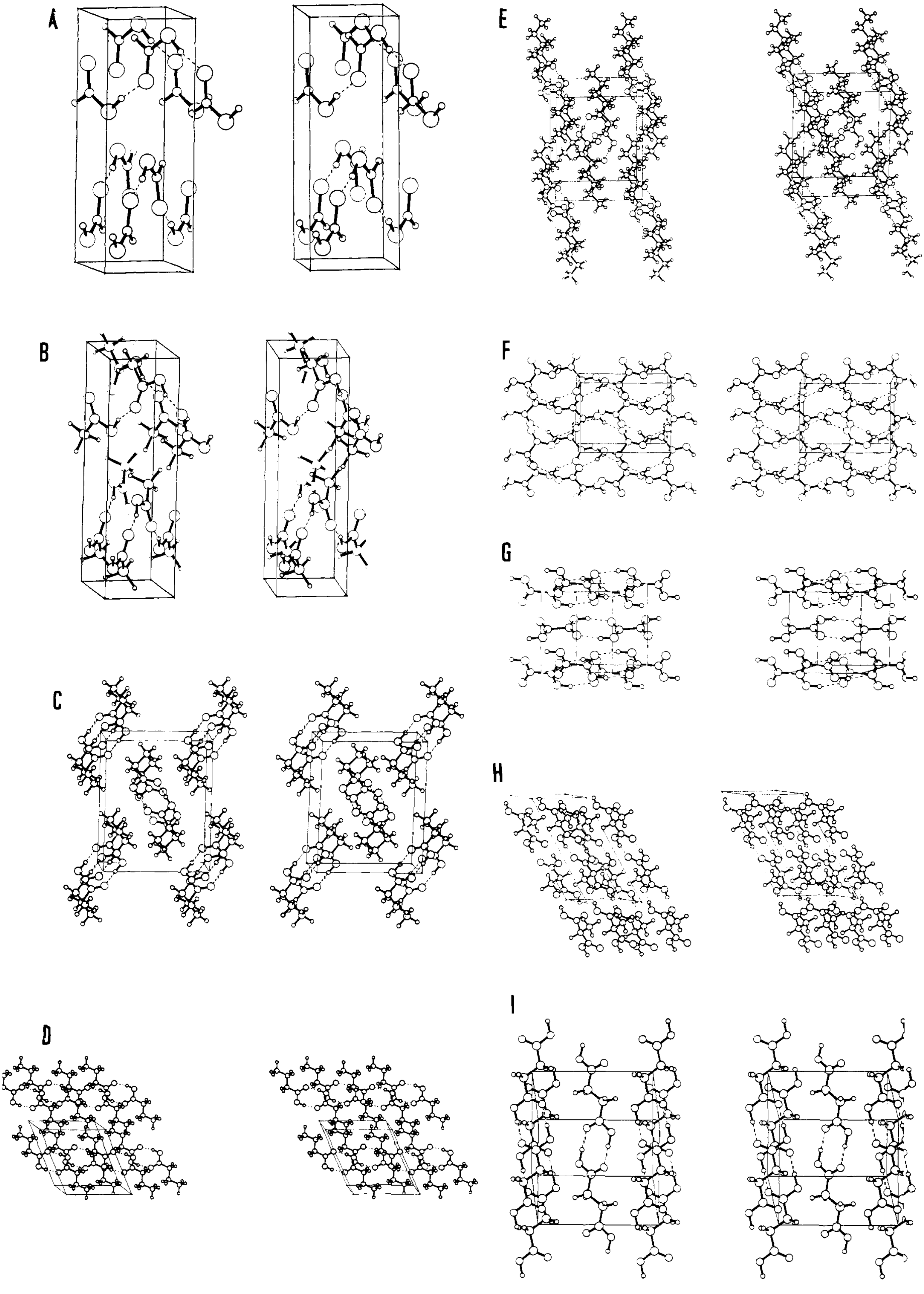
$$\Delta H_s = \Delta H_m + \Delta H_v \tag{4}$$

The ΔH_v were taken from Cox and Pilcher;[48] ΔH_m was available for formic acid[49] (3.0 kcal/mol), acetic acid[49] (2.8 kcal/mol), and valeric acid[50] (3.4 kcal/mol). Values of ΔH_m for propionic and butyric acids were estimated to be 3.0 kcal/mol. The sublimation enthalpies ΔH_s of α- and β-oxalic acid crystals were taken from Bradley and Cotson.[51] The values of ΔH_s for succinic and adipic acids were derived from the difference between their heats of formation in the gas and solid phases,[48] $\Delta H_f(g) - \Delta H_f(s)$. $\Delta H_f(g)$ of glutaric acid was calculated from the $\Delta H_f(g)$ of other acids, by the use of group contributions to the enthalpy of formation.[48] The experimental heats of sublimations are, for the most part, accurate to within 1 kcal/mol or less, but together with uncertainties in the term $2RT$ in eq 3 and the structural and vibrational changes the accuracy of ΔH_s is estimated to be 2 kcal/mol.

The least-squares procedure followed is the same as in our previous study of amides.[5,27] Here we shall summarize briefly the main points, and the reader is referred to ref 5 for more details. The internal coordinates of the molecules were fixed at their experimentally determined values. The positions of the hydrogens, essential for the calculation of intermolecular interactions, were refined by minimizing the intramolecular energy with respect to the hydrogen coordinates while all other coordinates were fixed at their experimental values. Only the nine components of the three unit cell vectors were varied in the least-squares optimization. However, when we applied the resulting force field to calculate the equilibrium structure of the crystal and its equilibrium energy, we minimized the energy with respect to all independent degrees of freedom, including the unit cell parameters as well as the position and orientation of all molecules in the unit cell (i.e., no symmetry constraints were imposed[6,25,26]).

We included 11 crystal structures, 7 sublimation energies, and 4 dipole moments, all taken from the total data base described above, in the least squares (see below, Tables IV and V). This results in 110 observables, or 29 more than in the derivation of the original amide force field, in which nine parameters were optimized. Here, at most, we study the optimization of four parameters, and ultimately require only one. The additional observables were included in the minimization step[25,26] to further test the applicability of the force field to properties not included in the optimization.

Transferability of Parameters and Ab Initio Considerations. As noted above, the question of transferability of potential parameters for atoms derived from model compounds to other model compounds and ultimately to the biological system of interest is of crucial importance. For the most part the decision as to whether two atoms may be assigned the same parameters has been made on the basis of chemical intuition in the derivation of previous force fields. More recently two alternative proposals for a more objective investigation of transferability have been put forward. Hagler and Lapiccirella[28] suggested that population analysis from several different wave functions, and consideration of the shape of the spatial electron densities either from molecular orbital calculations or experiment,[28,52] may be used as a guide for estimating the transferability of parameters of different functional groups. The final choice is to be determined, as always, by the fit to experiment. Clementi et al.[53] have suggested two criteria which they have recently applied in their derivation of analytical potentials from ab initio computations. They propose the use of the computed molecular orbital valency state energy (MOVS), as well as the net charges (from population analysis).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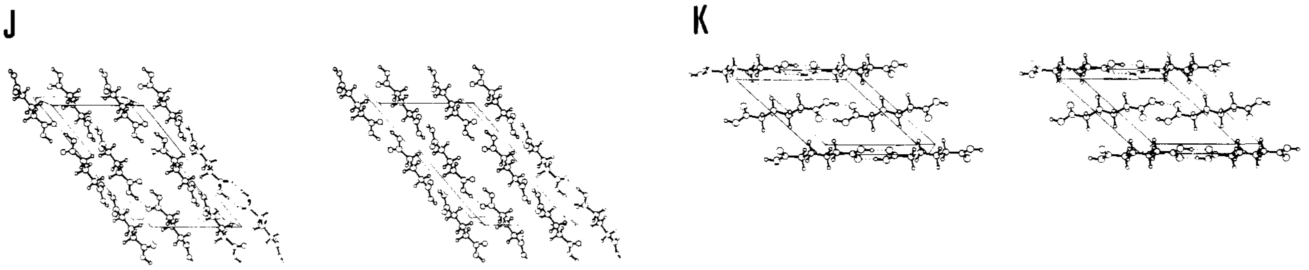

Figure 1. Stereoscopic views of the crystal structures of the carboxylic acids. Solid and dashed lines represent covalent and hydrogen bonds, respectively. The atoms H, C, and O are represented by circles of increasing size. In each figure the unit cell boundaries are indicated. (A) Formic acid (HCOOH, $Pna2_1$), viewed down the *c* axis; the *b* axis is horizontal. The molecules form hydrogen-bonded chains; the molecules in the chain are related by the *n* glide. The chains are related to each other by translations along *b* and *c* and by a twofold screw axis along *a*. (B) Acetic acid (CH_3COOH, $Pna2_1$), view and packing as in formic acid (A). (C) Propionic acid (C_2H_5COOH, $P2_1/c$), viewed down a^*; the *b* axis is horizontal. The molecules form hydrogen-bonded cyclic dimers via an inversion. The dimers are related by the twofold screw axis and by translations along *a*. (D) Butyric acid (C_3H_7COOH, $C2/m$), viewed down the b^* axis; the *a* axis is horizontal. The molecules are in the mirror plane and form hydrogen-bonded cyclic dimers related by an inversion. The dimers are translationally related. (E) Valeric acid (C_4H_9COOH, $P2_1/c$), view and packing as in propionic acid (C). (F) Oxalic acid [$(COOH)_2$, α modification *Pcab*], viewed down the *a* axis; the *b* axis is horizontal. Each molecule is hydrogen bonded to four other molecules by a *b* glide, creating corrugated sheets. The layers are related by the *a* glide. (G) Oxalic acid [$(COOH)_2$, β modification, $P2_1/c$], viewed down the c^* axis; the *a* axis is horizontal. Hydrogen-bonded cyclic dimers are formed on each side of the molecules via an inversion, resulting in ribbons along the *a* axis. The ribbons are related to each other by the twofold screw axis and by translations along *c*. (H) Methylmalonic acid [$HOOCCH(CH_3)COOH$, $P\bar{1}$], viewed down the a^* axis; the *b* axis is horizontal. Hydrogen-bonded cyclic dimers are formed on each side of the molecules via an inversion, resulting in ribbons along the *c* axis. Since the two carboxylic groups are not coplanar, the ribbons are twisted. The ribbons are related by translation along *b* and *a*. (I) Succinic acid [$HOOC(CH_2)_2COOH$] ($P2_1/a$)], viewed down the a^* axis; the *b* axis is horizontal. Hydrogen-bonded cyclic dimers are formed on each side of the molecules via an inversion, resulting in ribbons along the *c* axis. The ribbons are related to each other by the twofold screw axis and by translation along *a*. (J) Glutaric acid [$HOOC(CH_2)_3COOH$] ($I2/a$)], viewed down the *b* axis; the *a* axis is horizontal. The two carboxylic groups are related by a twofold axis. Twisted ribbons of hydrogen-bonded cyclic dimers are formed by the glide. (K) Adipic acid [$HOOC(CH_2)_4COOH$] ($P2_1/c$)], viewed down the *b* axis; the *a* axis is horizontal. For details of packing see G.

The population analyses of sets of primary amides, secondary amides, and carboxylic acids using CNDO/2, minimal, and split valence ab initio wave functions were reported in ref 28. These are given in Figures 2 and 3 along with several additional results using the split valence 6-31G basis.[54] In deciding on the various alternatives to test we have basically followed the criteria put forward by Hagler and Lapiccirella,[28] and the reader is referred to this reference for a more detailed discussion.

The parameters *A*, *C*, and *q* for the alkyl and the carbonyl group were transferred from the amide force field to the acids. The similarity of the carbonyl oxygen in acids and amides was discussed extensively in ref 28. It was shown there that not only are the net atomic populations of the oxygen atoms similar in the two families, as seen in Figures 2 and 3, but also the shapes of the total and deformation densities surrounding the carbonyl groups are very similar as judged by a comparison of the distance of a contour of constant electron density from the oxygen nuclei in acetic acid and *N*-methylacetamide (NMA). Integration of the lone pair deformation density still further supported the similarity, yielding 0.25 electron in NMA and 0.23 electron in acetic acid. Thus this atom is similar at all levels, population analysis, total electron density, deformation density, and integrated charge, and there seems little doubt that the parameters describing the carbonyl oxygen in an analytical representation should be the same. Similar considerations apply to the carbonyl carbon, although this atom is somewhat more difficult to characterize in terms of spatial distribution and electron density since it lies in the interior of the molecule and not the periphery. However, the carbon atom is not as crucial in determining the shape or excluded volume of the molecule for this reason, and, as noted previously, is not as important in determining crystal structures[5,6] and presumably biopolymer conformation.

The hydroxyl oxygen presents a particularly interesting case. Simple considerations based on chemical intuition or hybridization arguments would lead to the conclusion that this atom should have different potential constants from the carbonyl oxygen.[22,53] However, the total electron density is not perturbed very much by the small electron migration accompanying molecular formation.[28,55] Comparing the contours of constant *total* electron density of the carbonyl and hydroxyl oxygen in acetic acid[28] shows that the "shape" and excluded volume of these atoms are almost identical (deviating significantly only in the region of the hydroxyl hydrogen atom). Since this is basically the feature which the Lennard-Jones part of the potential represents, it is not unreasonable that these atoms be described by the same Lennard-Jones parameters. On the other hand, the polarizability, which is related to the C_6 coefficients, of these atoms is reported to differ.[56] Thus, as noted below, we tested the possibility of transferring the carbonyl oxygen parameters to the hydroxylic oxygen (see also discussion in part 2).

The partial atomic charges obtained from population analysis were used above as criteria for transferability. In addition the patterns of charge distribution which emerged from the population analysis were used as guides for assigning constraints on the partial atomic charges as well, to be tested by optimization. For example, one of the assumptions made in the amide work,[5,6] that the carbonyl group and NH and NH_2 groups maintain electroneutrality, was not supported in any of the three basis sets[28] (Figure 2). Electroneutrality of the COOH group as a whole seems to be a better approximation than electroneutrality of the OH and CO groups separately. Furthermore, if we remain within the simplified approximation of partial atomic charges, rather than a more realistic spatial distribution of the electrons (see, e.g., deformation density maps and discussion in ref 28), it seems reasonable to test the possibility of assigning the same charges to the carbonyl and hydroxyl oxygens. The population analysis is somewhat ambivalent on this point, with equivalence being suggested by the minimal STO-3G basis set and by CNDO/2, while in the split valence basis the charges on the oxygens differ by ~20–30%.

The final area in which the electron distribution may be used as a guide is with respect to the van der Waals parameters for the hydroxyl hydrogen. In the optimization of the amide force field it was found that these parameters offered no useful contribution and could equally well be set equal to zero.[5] This was rationalized in terms of the electron density about the N–H groups from which it was seen that the proton was essentially embedded in an approximately spherical distribution sur-

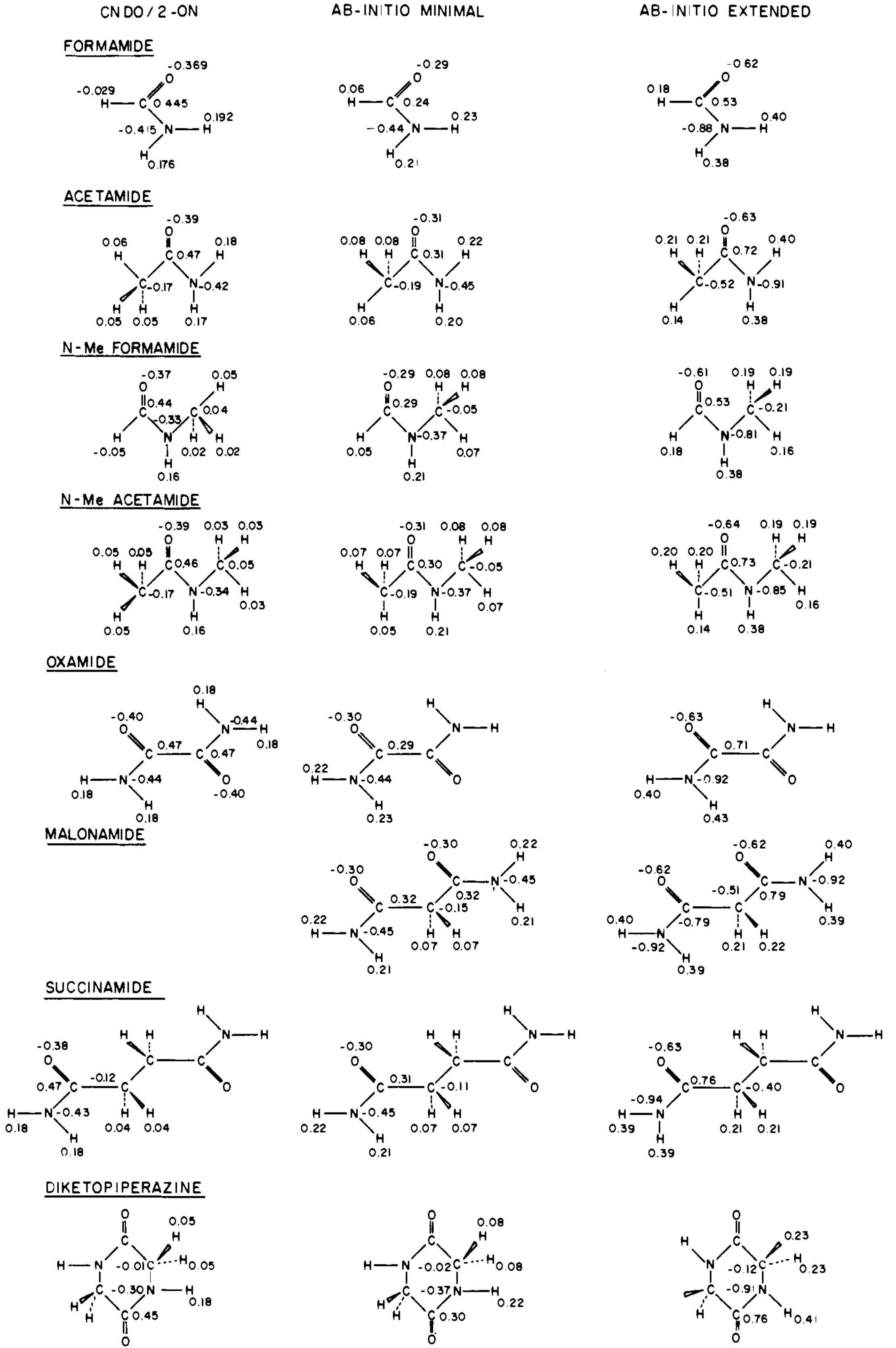

Figure 2. Net atomic charges in primary and secondary amides as obtained from population analysis of CNDO/2-ON,[22] minimal and extended ab initio wave functions (see ref 28).

rounding the nitrogen.[5,28] However, in the case of the acids, the electron density around the hydroxyl group extends significantly further in the direction of the hydroxyl proton than at an angle of ~120° from the O-H and C-O bonds (~0.3 Å for the 0.0268 electron/Å^3 contour). It was therefore questionable whether the same approximation would apply to the hydroxylic hydrogen. Nevertheless, on optimizing these parameters (r^* and ϵ of H_O), it was again found that they had exceedingly large standard deviations and could just as well be set equal to zero.

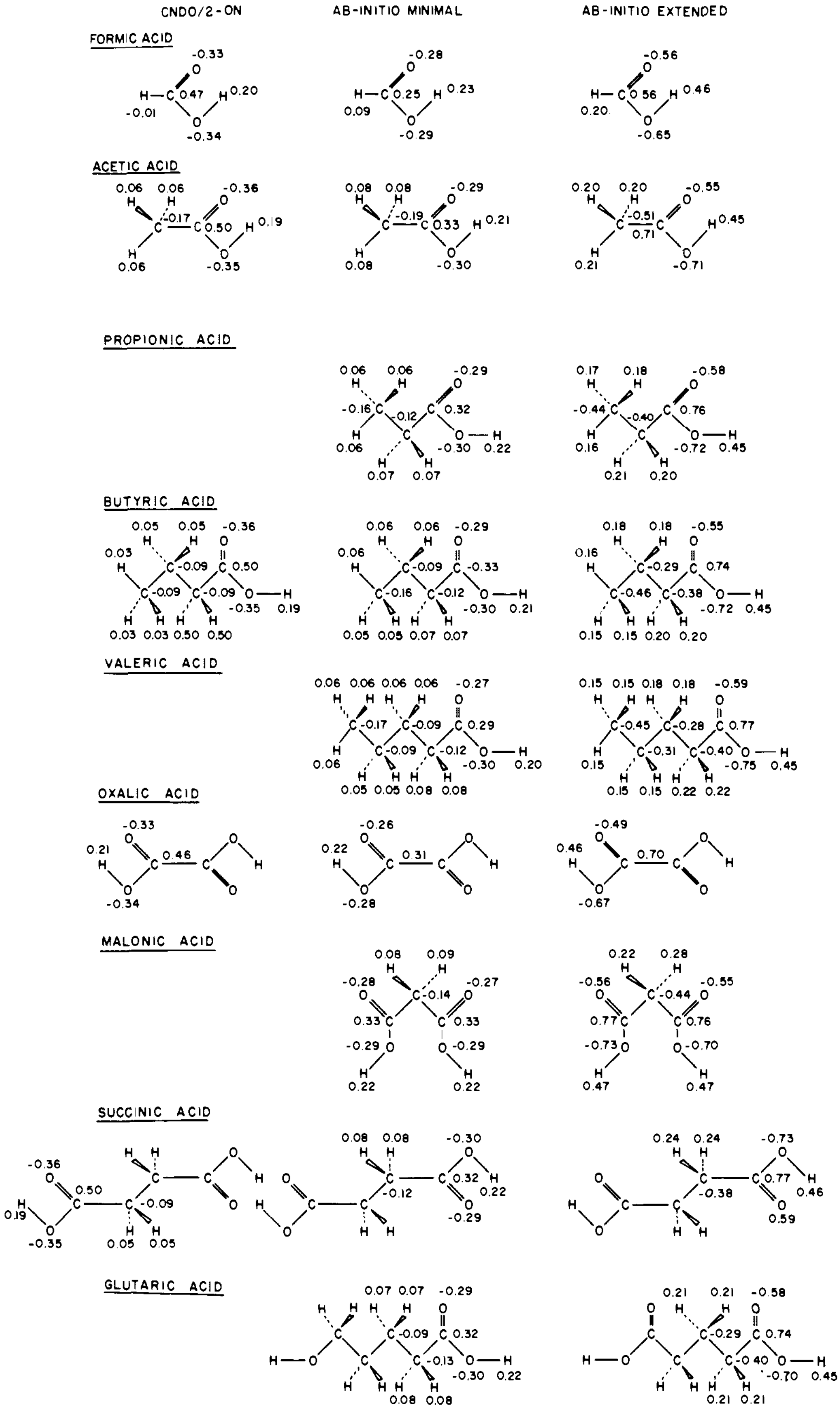

Figure 3. Net atomic charges in carboxylic acids as obtained from population analysis of CNDO/2-ON,[22] minimal and extended ab initio wave functions (see ref 28).

If we assume the maximum degree of transferability suggested by the above considerations we are left with only a single parameter to vary in the least-squares optimization, the charge on the hydroxylic hydrogen, $q(\mathrm{H_O})$, to fit the 110 observables outlined in the section on experimental data. In fact we chose to examine the transferability of the carbonyl oxygen parameters to the hydroxyl oxygen in some detail and, after some exploratory trials, focused our study on the following three alternative models: (I) transfer of all three parameters, A, C, and q of $\mathrm{O_C}$ to $\mathrm{O_H}$ (in this force field the only parameter left

Table II. Potential Energy Parameters of the Amide-Acid Force Field[a]

poten-tial	atom	9-6-1 potential					12-6-1 potential				
		$A \times 10^{-3}$	C	r^*	ϵ	q^b	$A \times 10^{-3}$	C	r^*	ϵ	q^b
		A. Parameters Derived from the Previous Study on Amides and Transferred to Carboxylic Acid									
	H_C	0.445	15	3.54	0.0025	0.11	7.15	32.9	2.75	0.038	0.10
	C	38.9	1230	3.62	0.184		1811	532	4.35	0.039	
	C_O	12.5	355	3.75	0.042		3022	1340	4.06	0.148	
	O_C	45.8	1410	3.65	0.198	−0.46	275	502	3.21	0.228	−0.38
	N(prim)	86.9	2020	4.01	0.161	−0.82	2271	1230	3.93	0.167	−0.83
	N(sec)	86.9	2020	4.01	0.161	−0.26	2271	1230	3.93	0.167	−0.28
	H_N	0.0	0	0.0	0.0		0	0	0.0	0.0	
		B. Parameters Optimized in the Present Study[c]									
I	H_O	0.0	0	0.0	0.0	0.41 (0.004)	0	0	0.0	0.0	0.35 (0.04)
II	O_H	45.8	1410	3.65	0.198	−0.48 (0.03)	275	502	3.21	0.228	−0.39 (0.02)
	H_O	0.0	0	0.0	0.0	0.42 (0.01)	0	0	0.0	0.0	0.35 (0.01)
III	O_H	42.2 (7)	1290 (194)	3.67	0.176	−0.46	384 (47)	539 (52)	3.35	0.190	−0.38
	H_O	0.0	0	0.0	0.0	0.42 (0.01)	0	0	0.0	0.0	0.38 (0.01)

[a] See Tables IV and VII of ref 5. [b] The charges on C, C_O, and H_N are determined by assuming electroneutrality of the groups CH_3, CH_2, CH, amide CO, NH, NH_2,[5] and COOH. [c] The values in parentheses are the standard deviations.

Table III. Root Mean Square Deviation Obtained in the Least-Squares Optimization

potential	optimized parameters	iteration	cell vectors $\sqrt{\Sigma(W\Delta a)^2}$	lattice energies $\sqrt{\Sigma(W\Delta V)^2}$	dipole moment $\sqrt{\Sigma(W\Delta \mu)^2}$	Total $\sqrt{\Sigma(W\Delta Y)^2}$
			9-6-1 Potentials			
I	$q(H_O)$	10	11.1	13.8	2.9	17.9
II	$q(H_O)$, $q(O_H)$	20	11.1	13.9	2.2	17.9
III	$q(H_O)$, $r^*(O_H)$, $\epsilon(O_H)$	20	11.1	13.4	3.1	17.7
			12-6-1 Potentials			
I	$q(H_O)$	10	13.2	10.1	1.3	16.7
II	$q(H_O)$, $q(O_H)$	30	13.2	10.1	1.5	16.7
III	$q(H_O)$, $r^*(O_H)$, $\epsilon(O_H)$	30	11.3	10.8	1.6	15.7

for optimization was $q(H_O)$); (II) transfer of the van der Waals parameters A and C of O_C (here the optimized parameters were $q(O_H)$ and $q(H_O)$); (III) transfer of the charge parameters $q(O_C)$ only (here we optimized $A(O_H)$, $C(O_H)$, and $q(H_O)$).

In all three models, the charge on the carbonyl oxygen was transferred from amides, as explained above, while the charge on the carbonyl carbon was determined by the assumed electroneutrality of the carboxyl group COOH as a whole.

It should be emphasized that these considerations are preliminary and not final, leading to models that are to be tested in detail at several levels. The first is the least-squares optimization reported below. The next two involve the results of lattice energy minimization. The second involves the evaluation of the results obtained with the various force fields against themselves and others in the literature using a variety of properties of crystals and gas-phase dimers.[25] The last involves a detailed evaluation of deviations from experiment of individual crystals which present particular problems.[26]

Results

The parameters of the 9-6-1 and 12-6-1 force fields based on the alternative models, I, II, and III, for the atoms O_H and H_O, are given in Table II. The complete carboxylic acids force fields may be obtained by including these values with the energy parameters of all other atoms as transferred from amides,[5] also given in this table.

The resultant root mean squares of the optimized deviations (calculated minus experimental values) of the various properties included in the optimization algorithm are given in Table III. These results, as similar results for other tentative trial models, served us as a first indication of the acceptability of the model. The second column of the table indicates the parameters varied while the third column gives the number of iterations in the optimization algorithm, after which it was terminated (there being no further change of parameters to within 0.1%). The roots of sum of squares for the predicted shifts[27] of unit cell vectors from their observed equilibrium values, as derived by the Newton-Raphson approximation,[5,27] the sum of squares of the deviations in lattice energies, the sum of squares of the dipole moments, and the total sum of squares are given in the last four columns, respectively.

A more detailed comparison of the potentials is obtained by examining the fits of the observables for each of the individual molecules. These results are given for the lattice energies and dipole moments in Table IV and for the predicted shifts in unit cell vectors, Δa, in Table V.

Discussion

The most striking conclusion from the results, as given in Tables III-V, is the almost total transferability of the energy functions of intermolecular interactions from the amides to the carboxylic acids. Thus, the intermolecular force field of amides and carboxylic acids as derived by the consistent force field analysis tends to confirm the picture of the hydrogen bond suggested in our study of amides.[5] The hydrogen bond appears as an essentially nonbonded interaction between two polar groups, in our case C═O and H—O (or H—N). The negli-

Table IV. Calculated[a] and Observed Lattice Energies and Dipole Moments of Carboxylic Acids

	obsd[b]	W	9-6-1 potentials			12-6-1 potentials		
			I	II	III	I	II	III
			Lattice Energies					
formic acid	−15.2	3.0	−11.7	−11.7	−11.8	−13.8	−13.8	−13.5
acetic acid	−16.3	3.0	−14.2	−14.2	−14.2	−15.0	−15.0	−15.0
propionic acid[c]	−17.7	0.0	−16.6	−16.6	−16.6	−16.7	−16.7	−16.9
butyric acid[c]	−19.2	0.0	−17.6	−17.5	−17.6	−17.6	−17.5	−17.7
valeric acid	−20.2	3.0	−20.0	−20.0	−20.0	−19.6	−19.6	−19.6
α-oxalic acid	−24.8	3.0	−24.8	−24.9	−24.7	−23.3	−23.4	−23.5
β-oxalic acid	−23.5	3.0	−24.6	−24.7	−24.7	−24.4	−24.4	−24.2
malonic acid		0.0	−26.1	−26.1	−26.2	−27.3	−27.3	−27.5
methylmalonic acid		0.0	−27.1	−27.0	−27.1	−27.1	−27.0	−27.2
succinic acid	−29.3	3.0	−30.8	−30.8	−30.8	−31.3	−31.2	−31.6
glutaric acid[c]	−29.0	0.0	−29.0	−28.9	−29.5	−29.5	−29.5	−29.5
adipic acid	−32.1	3.0	−31.8	−31.8	−31.8	−31.4	−31.3	−32.3
			Dipole Moments					
formic acid	1.41	5.0	1.89	1.81	1.91	1.58	1.54	1.72
acetic acid	1.70	5.0	1.85	1.77	1.87	1.56	1.52	1.68
propionic acid	1.76	5.0	1.94	1.86	1.96	1.64	1.59	1.76
butyric acid	1.68	5.0	1.90	1.82	1.93	1.61	1.56	1.74

[a] The energies correspond to the experimental crystal structures, and the dipole moments to the observed molecular geometries in the crystal. Energies are in kcal/mol, dipole moments in Debye units. [b] For references to the observed properties, see text. [c] These lattice energies were not included in optimization ($W = 0$), since they were estimated, as opposed to being taken directly from experiment (see text).

Table V. Root Mean Square Predicted Shifts of the Unit Cell Vectors [$\sqrt{\Sigma(\Delta X)^2/9}$] (Å)

acid	9-6-1 potentials			12-6-1 potentials			W
	I	II	III	I	II	III	
formic	0.092	0.096	0.088	0.096	0.099	0.079	10.0
acetic	0.135	0.142	0.129	0.137	0.140	0.126	10.0
propionic	0.076	0.078	0.076	0.067	0.068	0.061	10.0
butyric	0.125	0.124	0.117	0.186	0.184	0.150	10.0
valeric	0.051	0.053	0.053	0.039	0.040	0.034	10.0
α-oxalic	0.072	0.070	0.073	0.137	0.135	0.105	10.0
β-oxalic	0.137	0.139	0.137	0.500	0.500	0.576	3.0[a]
methylmalonic	0.204	0.206	0.208	0.204	0.206	0.151	10.0
succinic	0.059	0.054	0.062	0.171	0.169	0.134	10.0
glutaric	0.259	0.261	0.262	0.320	0.323	0.275	3.0[a]
adipic	0.162	0.157	0.166	0.048	0.048	0.057	10.0

[a] Reduced weights were used for these compounds since their predicted shift was large and the Newton–Raphson approximation breaks down for such large shifts.

gibly small van der Waals radius of the hydrogen atoms as well as the polarity of the bonds both originate from the electronegativity of O (or N), and together determine the main characteristic properties of the hydrogen bond, a short H···O distance and a strong electrostatic interaction.

Consideration of Tables III–V shows that at this level there is no clear preference for either the 12-6-1 or 9-6-1 potential, although the former has a slightly lower sum of squares deviation. The 9-6-1 seems to do better in predicting the structural properties while the 12-6-1 more than compensates for this by predicting lattice energies in better agreement with experiment. Analysis of Table V, however, shows that over half of the total deviation in lattice energies in the 9-6-1 potentials arises from formic acid. This is due in part to the fact that the experimental molecular geometry in the crystal is not precise,[29a] and instead we originally used the electron diffraction data from the gas-phase dimer.[57] Calculations using a more recent, low-temperature X-ray structure resulted in a calculated lattice energy of −12.8 kcal/mol using the 9-6-1 potential which results in a significant lowering of the sum of squares. Furthermore, it should be noted that these lattice energies are calculated at the experimentally observed crystal structure, rather than at the minimized (or calculated) structure. This may give rise to "bad contacts", which might be relieved by relatively small changes in structural parameters (although in general it is found that the lattice energy does not change by more than 1–2 kcal on minimization[5,26]). The minimized lattice energy is compared with the observed in the following paper, where a more extensive comparison indicates the 9-6-1 to be superior overall.[25]

The results also indicate that both the partial charge and van der Waals parameters of the carbonyl oxygen may be transferred to the hydroxyl oxygen. This holds true for both the 9-6-1 and the 12-6-1 force fields. Neither the charge nor the van der Waals parameters changed significantly when they were allowed to vary, and all remained, within their standard deviation, essentially equal to the carbonyl oxygen parameters, with the one exception of the parameter A in the 6-12 potential (Table II). Here the larger value of A, correlated with a slightly larger value of C, led to a slightly larger value of the van der Waals radius r^*, which is offset by a slight decrease in ϵ. Typically, these values are highly correlated and have large associated standard deviations.[5] Furthermore, and more importantly, the sum of squared deviations is not improved significantly by the addition of the extra parameters in any case, as seen in Table III.

Partial Atomic Charges. As discussed above, in the final force field the only parameter optimized was the charge on the

Table VI. Partitioning of Hydrogen Bond Energy from ab Initio Calculations (kcal/mol)

author(s)	substance	total	repulsion	coulomb	charge transfer	polarization
Dreyfus and Pullman[63]	$(HCOOH)_2$	−8	7	−10	−5	
Morokuma[64]	$(H_2O)_2$	−7.0	9.9	−8.0	−8.2	−0.7
Umeyama and Morokuma[59]	$(H_2O)_2$	−5.6	4.3	−7.5	−1.8	−0.5
Beyer, Lischka, and Schuster[66]	$(H_2O)_2$	−4.7	4.6	−7.3	−1.2	−0.7

hydroxylic hydrogen. The use of partial atomic charges to represent the deformation density in a molecule, although an almost universal practice at this stage of the development of force fields, is clearly a rather approximate representation and probably the point at which further improvement in force fields should be expected.[28,52] Nevertheless there are several satisfying features which emerge from the charge distributions obtained here. The calculated dipole moments are in reasonable agreement with the observed quantities, though a low weight was assigned to them in the optimization. In fact, as shown previously,[5] the sublimation energies are the dominant observables in determining the charges, while the structural observables are also significantly affected by these parameters. It is satisfying that the charge distribution which yields reasonable sublimation energies also gives results in agreement with the dipole moments. This would seem to indicate that, at least to within the degree of fit, the optimized charges and the electrostatic energy contribution represent a physical property, *not* an artifact or a substitute for another significant energy term. Furthermore, as in both the ab initio and CNDO/2 calculations, the optimization yielded a larger (absolute) charge on the carbonyl carbon than on the hydroxyl hydrogen. (This feature was not imposed in the optimization procedure, although the COOH group was constrained to be neutral.)

Validity of Representation. The results reported here and in the following papers[25,26] seem to indicate that the representation of the amide and acid hydrogen bonds simply by van der Waals and electrostatic interactions, as derived here, gives a *basically* correct account of the intermolecular interactions. This conclusion follows from several observations. First of all the carboxylic acid hydrogen bond length of ~2.65 Å, which is determined to a major extent by the "size", or van der Waals parameters of the oxygen atoms, is reproduced well (within 0.05 Å[25,26]) by the parameters *derived to account for amide* crystal properties.[5,6] In the latter systems the N–H···O= hydrogen bond distance, which is dependent in the same way on the oxygen and nitrogen "sizes", is significantly larger, ~2.95 Å. Furthermore, since the dimerization energies are accounted for (within ~1 kcal/mol[26]), as well as the sublimation energies, it indicates that the balance between the short- and long-range interactions is approximately correct. The agreement with the dipole moments has already been commented on above. These comments are intended to indicate that the major effects seem to be represented. It is clear that this is a simplified model embodying rather crude approximations in some respects, as for example the representation of the continuous electron distribution by discrete partial charges, and the neglect of polarization and charge-transfer effects as discussed below. These are presumably the reasons for the remaining deviations between experiment and calculated results some of which are still quite large.[26] An analysis of their importance and inclusion in the force field constitutes the direction to be taken in further improving the representation.

Comparison with ab Initio Studies of the Hydrogen Bond. In the context of the above discussion, it is worthwhile to compare the results obtained here with the extensive quantum-mechanical studies of the hydrogen bond,[58–62] which are approaching the nature of this interaction from another direction. The question most relevant to our discussion is: What part of the hydrogen bond energy may be attributed to nonbonded interactions, and how large is the additional contribution due to effects such as charge transfer and polarization?

A few years ago, there was a wide disagreement between the answers given to this question by the quantum mechanical method and by the CFF method.[61] Dreyfus and Pullman[63] carried out one of the first ab initio studies of the hydrogen bond using a minimal basis set. Partitioning the energy of formation of formamide dimers, they found a significant part of the energy to be due to charge transfer. Morokuma[64] performed similar calculations for the hydrogen bond energy of water dimers. Their results are given in the first two rows of Table VI. These results were later found to be sensitive to basis set.[65] Nevertheless, they were commonly accepted as evidence for the hydrogen bond having a significant charge-transfer contribution.

Recent progress in ab initio calculations has drastically revised the results obtained from partitioning,[59,66] as is seen in Table VI. Charge-transfer energy in water dimers was reduced from −8.2[64] to −1.7[59] or −1.2 kcal/mol.[66] These recent results bring the quantum-mechanical and the empirical descriptions of the nature of the hydrogen bond much closer, and both further support the models which have emphasized the importance of electrostatic potentials.[60,67]

The above discussion should not be taken to say that charge-transfer effects are nonexistent, but simply that their importance would seem to have been commonly overestimated. In regard to the absence of a term representing this contribution in the carboxylic force field derived here (and also in the amide force field), we note that we have *not* obtained a perfect fit to the crystal or dimer properties.[25] The residual deviation in structure and energy may in fact be due in part to the omission of the charge transfer and polarization interactions in the potential, as well as to other reasons such as the omission of anisotropy and, last but not least, to the approximate nature of the basic assumptions of additivity and transferability of atom–atom interaction potentials.

These considerations of the nature of the hydrogen bond are amenable to and should be put to further tests by the empirical analysis of various other molecular systems, as well as by the use of more precise molecular orbital calculations. In this latter regard it is of interest to see if the model used here is capable of accounting for the relative insensitivity of the donor–acceptor distance on the acceptor atom found from the molecular orbital calculations on small molecules.[59,62] It should be noted in this regard that there are some exceptions to this rule. For example, the experimental N–H···O distance in primary amide crystals is typically ~2.9–3.0 Å[5,6] while the N–H···N distance in hexamethylenediamine ($H_2N(CH_2)_6NH_2$) is 3.21 Å,[68] in 2-amino-4,6-dichloropyrimidine the N–H···N distances are 3.21 and 3.37 Å,[69] and in methylamine[70] 3.18 and 3.27 Å. It is such considerations by which the two methods may complement each other. Thus the detailed considerations available from partitioning of ab initio results about the nature of the intermolecular potential can be used in order to improve CFF models of analytical representations and help to understand the deviations from experiment. The wide applicability of the empirical representation may help to ensure that the conclusions drawn are general and applicable to a wide range of molecular and crystal properties and not to the small set to which the more accurate molecular orbital treatments are restricted.

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References and Notes

(1) S. Lifson, 23e Reunion Annuele, Orleans, 1972. See also: *J. Chim. Phys. Phys.-Chim. Biol.*, **65**, 40 (1968), and ref 2.
(2) S. Lifson and A. Warshel, *J. Chem. Phys.*, **49**, 5116 (1968).
(3) A. Warshel and S. Lifson, *J. Chem. Phys.*, **53**, 582 (1970).
(4) O. Ermer and S. Lifson, *J. Am. Chem. Soc.*, **95**, 4121 (1973).
(5) A. T. Hagler, E. Huler, and S. Lifson, *J. Am. Chem. Soc.*, **96**, 5319 (1974).
(6) A. T. Hagler and S. Lifson, *J. Am. Chem. Soc.*, **96**, 5327 (1974).
(7) (a) C. B. Anfinsen and H. A. Scheraga, *Adv. Protein Chem.*, **30**, 205 (1976); (b) A. T. Hagler, *Isr. J. Chem.*, **16**, 202 (1977); (c) G. Nemethy and H. A. Scheraga, *Q. Rev. Biophys.*, **10**, 239 (1977).
(8) (a) M. Levitt, *J. Mol. Biol.*, **82**, 393 (1974); (b) P. K. Warme and H. A. Scheraga, *Biochemistry*, **13**, 757 (1974).
(9) (a) A. T. Hagler and B. Honig, *Proc. Natl. Acad. Sci. U.S.A.*, in press; (b) S. Tanaka and H. A. Scheraga, *ibid.*, **72**, 1221 (1975); (c) M. Levitt and A. Warshel, *Nature (London)*, **253**, 694 (1974); (d) I. D. Kuntz, G. M. Crippen, P. A. Kollman, and D. Kimelman, *J. Mol. Biol.*, **106**, 483 (1976).
(10) M. Karplus and D. Weaver, *Nature (London)*, **260**, 404 (1976).
(11) (a) B. Pullman, *Adv. Quantum Chem.*, **10**, 251 (1977); (b) J. Caillet and P. Claveire, *Biopolymers*, **13**, 601 (1974); (c) *Acta Crystallogr., Sect. A*, **31**, 448 (1975).
(12) A. T. Hagler and L. Leiserowitz, *J. Am. Chem. Soc.*, **100**, 5879 (1978).
(13) (a) A. T. Hagler, L. Leiserowitz, and M. Tuval, *J. Am. Chem. Soc.*, **98**, 4600 (1976); (b) J. Bernstein and A. T. Hagler, *ibid.*, **100**, 673 (1978); (c) A. T. Hagler and J. Bernstein, *ibid.*, **100**, 6349 (1978).
(14) J. D. Dunitz, H. Eser, M. Bixon, and S. Lifson, *Helv. Chim. Acta*, **50**, 1572 (1967).
(15) (a) D. E. Williams, *J. Chem. Phys.*, **45**, 3770 (1967); (b) *Acta Crystallogr., Sect. A*, **30**, 71 (1974); (c) D. E. Williams and T. L. Starr, *Comput. Chem.*, **1**, 173 (1977).
(16) A. I. Kitaigorodskii, "Molecular Crystals and Molecules", Elsevier, Amsterdam, 1973, and references cited therein.
(17) K. Mirsky, *Acta Crystallogr., Sect. A*, **32**, 199 (1976).
(18) D. R. Ferro and J. Hermans "Liquid Crystals and Ordered Fluids", J. F. Johnson and R. Porter, Eds., Plenum Press, New York, 1970.
(19) See discussion in A. T. Hagler, S. Lifson, and E. Huler, "Peptides, Polypeptides and Proteins", Wiley-Interscience, New York, 1974, p 35.
(20) (a) E. Giglio, *Nature (London)*, **222**, 339 (1970); (b) V. M. Coiro, P. Giacomello, and E. Giglio, *Acta Crystallogr., Sect. B*, **27**, 2112 (1971); (c) E. Gavazzo, F. Mazza, and E. Giglio, *ibid.*, **30**, 1351 (1974).
(21) (a) R. Chidambaram, R. Balasubramanian, and G. N. Ramachandran, *Biochim. Biophys. Acta*, **221**, 182 (1970); (b) C. N. Ramachandran, K. P. Sarathy, and A. S. Kolaskar, *Z. Naturforsch. A*, **28**, 643 (1973).
(22) (a) F. A. Momany, L. M. Carruthers, R. F. McGuire, and H. A. Scheraga, *J. Phys. Chem.*, **78**, 1595 (1974); (b) G. Nemethy and H. A. Scheraga, *ibid.*, **81**, 928 (1977).
(23) (a) J. L. Derissen and P. H. Smit, *Acta Crystallogr.*, submitted; (b) P. H. Smit, Ph.D. Dissertation, Department of Structural Chemistry, Rijksuniversiteit, The Netherlands, 1978.
(24) (a) L. L. Shipman, A. W. Burgess, and H. A. Scheraga, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 543 (1975); (b) L. L. Shipman, A. W. Burgess, and H. A. Scheraga, *J. Phys. Chem.*, **80**, 52 (1976).
(25) Part 2: A. T. Hagler, S. Lifson, and P. Dauber, *J. Am. Chem. Soc.*, following paper in this issue.
(26) Part 3: A. T. Hagler, P. Dauber, and S. Lifson, *J. Am. Chem. Soc.*, accompanying paper in this issue.
(27) A. T. Hagler and S. Lifson, *Acta Crystallogr., Sect. B*, **30**, 619 (1974).
(28) A. T. Hagler and A. Lapiccirella, *Biopolymers*, **15**, 1167 (1976).
(29) (a) F. P. Holzberg and I. Fanbuchen, *Acta Crystallogr.*, **6**, 127 (1953); (b) I. Nahringbauer, *Acta Crystallogr., Sect. B*, **34**, 315 (1978).
(30) P. Jonson, *Acta Crystallogr., Sect. B*, **27**, 893 (1971).
(31) F. J. Strieter, D. H. Templeton, R. F. Scheuerman, and R. L. Sass, *Acta Crystallogr.*, **15**, 1233 (1962).
(32) F. J. Strieter and D. H. Templeton, *Acta Crystallogr.*, **15**, 1240 (1962).
(33) R. F. Schenerman and R. L. Sass, *Acta Crystallogr.*, **15**, 1244 (1962).
(34) J. L. Derissen and P. H. Smit, *Acta Crystallogr., Sect. B*, **30**, 2240 (1974).
(35) J. A. Coedkoop and C. H. MacGillavry, *Acta Crystallogr.*, **10**, 125 (1957).
(36) J. L. Derissen, *Acta Crystallogr., Sect. B*, **26**, 901 (1970).
(37) J. S. Broadley, D. W. T. Cruickshank, J. D. Morrison, J. M. Robertson, and H. M. R. Shearer, *Proc. R. Soc. London, Ser. A*, **251**, 441 (1959).
(38) J. D. Morrison and J. M. Robertson, *J. Chem. Soc.*, 1001 (1949).
(39) P. J. Housty and M. Hospital, *Acta Crystallogr.*, **18**, 693 (1965).
(40) P. J. Housty and M. Hospital, *Acta Crystallogr.*, **18**, 753 (1965).
(41) P. J. Housty and M. Hospital, *Acta Crystallogr.*, **20**, 325 (1966).
(42) An extensive review characterizing the packing modes and hydrogen bonding in carboxylic acids has recently been presented: L. Leiserowitz, *Acta Crystallogr., Sect. B*, **32**, 775 (1976).
(43) J. L. Derissen, *J. Mol. Struct.*, **38**, 177 (1977).
(44) S. J. Cyvin, I. Alfheim, and G. Hagen, *Acta Chem. Scand.*, 3038 (1970).
(45) I. Alfheim, G. Hagen, and S. J. Cyvin, *J. Mol. Struct.*, **8**, 159 (1971).
(46) K. Fukushima and B. J. Zwolinkski, *J. Chem. Phys.*, **50**, 737 (1969).
(47) M. Engel, unpublished results.
(48) J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds", Academic Press, New York, 1970.
(49) D. R. Stull, E. F. Westrum, and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds", Wiley, New York, 1969.
(50) L. A. Dougall and J. E. Kilpatrick, *J. Chem. Phys.*, **42**, 2311 (1965).
(51) R. S. Bradley and S. Cotson, *J. Chem. Soc.*, 1684 (1953).
(52) See *Isr. J. Chem.*, **16**, No.'s 2–3 (1977), and references cited therein; this volume is devoted to Electron Density Mapping in Molecules and Crystals.
(53) (a) E. Clementi, F. Cavallone, and R. Scordamaglia, *J. Am. Chem. Soc.*, **99**, 5531 (1977); (b) R. Scordamaglia, F. Cavallone, and E. Clementi, *ibid.*, **99**, 5545 (1977); (c) G. Boles and E. Clementi, *ibid.*, **99**, 5550 (1977).
(54) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
(55) C. A. Coulson, "The Shape and Structure of Molecules", Oxford Chemistry Series, Clarendon Press, Oxford, 1973.
(56) J. Ketelaar, "Chemical Constitution", American Elsevier, New York, 1958, p 91.
(57) A. Almenningen, O. Bostiansen, and T. Motzfeldt, *Acta Chem. Scand.*, **23**, 2848 (1969).
(58) The reader is referred to the representative and more recent publications (ref 59–62) and references cited therein.
(59) H. Umeyama and K. Morokuma, *J. Am. Chem. Soc.*, **99**, 1316 (1977).
(60) P. A. Kollman, *J. Am. Chem. Soc.*, **99**, 4874 (1977).
(61) P. Schuster in "The Hydrogen Bond", Vol. 1, P. Schuster, G. Zundel, and G. Sandorfy, Eds., North-Holland Publishing Co., Amsterdam, 1976.
(62) (a) L. C. Allen, *J. Am. Chem. Soc.*, **97**, 6921 (1975); (b) J. D. Dill, L. C. Allen, W. C. Topp, and J. A. Pople, *ibid.*, **97**, 7220 (1975).
(63) M. Dreyfus and A. Pullman, *Theor. Chim. Acta*, **19**, 20 (1970).
(64) K. Morokuma, *J. Chem. Phys.*, **55**, 1236 (1971).
(65) See ref 61 and references cited therein.
(66) Reference 61, note added in proof (p 154), referring to A. Beyer, H. Lischka, and P. Scuster, to be published.
(67) R. Bonacorrsi, A. Pullman, E. Screcco, and J. Tomasi, *Chem. Phys. Lett.*, **12**, 622 (1972).
(68) W. P. Binne and J. M. Robertson, *Acta Crystallogr.*, **3**, 424 (1950).
(69) Reference 16, p 81.
(70) A. Atoji and W. N. Lipsomb, *Acta Crystallogr.*, **6**, 770 (1953).