structures of the hydrated TlX_n^{3-n} species in solution by means of neutron diffraction. Recently, such measurements have been started. It is our hope that, if successful, they will widen our knowledge of the dynamic behavior of thallium(III) complexes in solution and, in the best case, provide a contribution for better understanding of dynamic processes involving complexed metal ions in general.

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Registry No. $Tl(H_2O)_6^{3+}$, 79060-89-2; $TlBr^{2+}$, 97867-16-8; $TlBr_2^+$, 97867-17-9; $TlBr_3$, 13701-90-1; $TlBr_4^-$, 15905-99-4; $TlBr_5^{2-}$, 44246-40-4; Br^-, 24959-67-9; ^{205}Tl, 14280-49-0.

Maximally Diagonal Force Constants in Dependent Angle-Bending Coordinates. 2. Implications for the Design of Empirical Force Fields

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Abstract: The vast amount of information compiled in experimentally determined and quantum-mechanically calculated force fields for small molecules could be used to assist in the further development of empirical potentials used in molecular-mechanics and molecular-dynamics simulations of organic and biological systems. Unfortunately, most such force fields are defined in well-determined sets of internal coordinates, whereas empirical potentials use larger sets of dependent coordinates. This paper illustrates a unique "localized" representation of the angle-deformation potential in dependent coordinates which is exactly diagonal for in-plane bending at trigonal-planar centers and is nearly diagonal for angle bending at tetracoordinate centers. The transformation to this representation is accomplished by introducing "virtual force constants" which couple to the vanishing null-coordinate displacement. Four applications show how this transformation can be used to aid the development of improved empirical potentials. The first extracts localized force constants for angle bending at carbonyl groups in aldehydes, ketones, amides, acids, and esters from published force fields, and then demonstrates that these values are reasonably transferable and are well described by the empirical relationship

$$k_\theta = 1.75 Z_a C_b Z_c (R_{ab} + R_{bc})^{-1} \theta_{abc}^{-2} \exp(-2D)$$

where Z and C are atomic parameters and $D = (R_{ab} - R_{bc})^2/(R_{ab} + R_{bc})^2$ and shows that the corresponding force constants used in MM2, AMBER, VFF, and CHARMM do not exhibit the systematic trends found in the experimental data. The second compares "canonical" and localized force constants for angle bending at methylene groups in alkanes for three published force fields. The third application extends the approach to stretch–bend and bend–bend′ interactions and transforms a calculated in-plane force field for ethylene to dependent coordinates to show how one can test model assumptions concerning the importance of and functional form required for specific interactions. The fourth application shows how the transformation to localized force constants can be carried out at a variety of geometries to probe the anharmonicity of the molecular energy surface.

Computational simulations of bioactive macromolecules, and of the substrates, inhibitors, agonists, and antagonists which interact with them, are coming to play an ever larger role in the study of biochemical processes and in the design of pharmaceutical agents.[1] For reasons of computational efficiency, these simulations have generally employed molecular-mechanics or molecular-dynamics calculations based on empirical potentials (force fields). Most simulations have been qualitative in nature and have focussed on the prediction of geometries rather than energies or of gas-phase energies rather than energies in solution. Encouragingly, recent reports have shown that results approaching quantitative accuracy can be achieved for relative free energies of enzyme-inhibitor binding in systems of real chemical interest.[2] Nevertheless, it seems clear that current models for empirical force fields are too simple in form, in that they fail to account for important physical effects which affect the phenomena being modeled. Electrostatic effects in particular are poorly understood, but even "valence interactions" which depend on deformations in bond lengths, bond angles, and dihedral angles are not always modeled accurately. More realistic functional forms need to be developed, and soundly-based parameters need to be determined for a much wider range of chemical functionality. Fortunately, these needs are well understood, and considerable effort to develop improved empirical potentials is being carried out to address them.[3]

This development effort potentially could make use of the many experimental spectroscopic and quantum-mechanical force fields which have been determined for small molecules, but several factors have made it difficult to do so. One potential difficulty arises from the fact that spectroscopic and quantum-mechanical force fields (for the sake of brevity, we shall call these *spectroscopic* force fields) locally expand the potential energy in internal-coordinate displacements about the equilibrium geometry. Such force fields mathematically "fold" all the physical interactions—including those arising from electrostatic and nonbonded interactions—onto the manifold of internal-coordinate displacements. In contrast, *empirical* force fields need to provide ex-

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[3] (a) For one current effort see, for example: Palca, J. *Nature* **1986**, *322*, 586. (a) A second effort is reflected in the following: Dasgupta, S.; Goddard, W. A. III *J. Chem. Phys.* **1989**, *90*, 7207–7215.

0002-7863/90/1512-4710$02.50/0

pressions for the potential energy that are applicable to all energetically accessible conformations. Such force fields usually address this broader goal by representing torsional contributions via a Fourier series and by incorporating explicit van der Waals and electrostatic contributions based on nonbonded distances. This aspect makes empirical force fields *nonlocal* in character. As a result, while both spectroscopic and empirical force fields employ similar valence-coordinate terms for describing bond stretching and angle bending, these terms play somewhat different roles in the two cases. Fortunately, however, numerical comparisons (see below) indicate that spectroscopic force constants for these valence-coordinate terms are not materially affected by the implicit presence of van der Waals and electrostatic interactions. Consequently, spectroscopic values for such force constants can be expected to provide good guidance for the parameterization of valence-coordinate terms in empirical models.

For spectroscopic force fields to be employed for this purpose, however, one particular difficulty must first be overcome. This difficulty arises from the fact that empirical force fields employ dependent sets of internal bond lengths, bond angles, and dihedral angles, whereas spectroscopic force fields usually employ smaller sets of linearly independent internal coordinates. The problem arises because force constants in dependent coordinates cannot be unambiguously defined, as it is always possible to form an infinite number of related sets which describe the same harmonic deformation potential.[4] Thus, even when a spectroscopic force field is developed directly in dependent coordinates,[5] the derived force constants may not be appropriate for use in a given empirical force field.

The relationship between spectroscopic and empirical force constants is even less direct when spectroscopic force fields employ "well-determined" independent internal coordinates for angle bending. For in-plane bending at a trigonal-planar center, for example, just two angular coordinates (say, μ and ν) arise in the "well-determined" set, and it may not be obvious how to relate the "real" force constants defined in terms of μ and ν to force constants defined in terms of the three "primitive" angles (say, α, β, and γ) which form the dependent set. (The dependency arises, of course, from the constraint $\alpha + \beta + \gamma = 360°$ for in-plane deformations.) An analogous dependency arises at tetracoordinate centers, where only five of the six "primitive" angles are independent.

Nevertheless, it *is* possible to resolve the underlying ambiguity and to extract a particular set of force constants which is likely to be useful in developing an empirical potential. We showed in paper 1[6] that such force constants can be obtained by imposing an auxiliary condition on the determination of the force constants—namely, the condition that the force-constant matrix in dependent coordinates be maximally diagonal. Indeed, the resultant matrix of "*localized*" force constants is fully diagonal for in-plane bending at a trigonal-planar center and typically is nearly diagonal for angle-bending at a tetracoordinate center. We showed that the derived localized force constants are unique, in the sense that the same localized force constants are obtained from any physically equivalent set of supplied force constants, whether the latter are defined in terms of well-determined or of dependent angular coordinates.[6] It seems plausible that the condition of maximum diagonality should yield the most nearly "independent" and transferable set of angle-bending force constants. As support for this conjecture, we reported on work underway[7] in which the transformation to localized force constants has been applied to a large number of experimentally determined and quantum-mechanically calculated spectroscopic force fields covering a wide range of organic and inorganic molecules. Though still incomplete, that work has yielded localized force constants for more than 120 discrete valence angles and has revealed a strong underlying systematics which implies not only transferability but also a degree of predictability similar to that provided by Badger's rule for bond stretching.[8] With few exceptions, the localized force constants for angles θ_{abc} are fit with an rms relative deviation of ca. 12% by the simple expression

$$k_\theta = 1.75 Z_a C_b Z_c (R_{ab} + R_{bc})^{-1} \theta_{abc}{}^{-2} \exp(-2D) \qquad (1)$$

where $D = (R_{ab} - R_{bc})^2/(R_{ab} + R_{bc})^2$. This expression, which was developed from a more limited but illustrative form described by Chang,[9] incorporates four plausible physical effects: (1) a dependence on the chemical composition through the atomic Z and C parameters in the first factor; (2) a dependence on scale through the second factor (shorter bond lengths produce larger force constants); (3) a dependence on shape through the third factor (smaller equilibrium bond angles are associated with larger force constants); and (4) a (weak) dependence on asymmetry through the fourth factor (markedly dissimilar bond lengths yield smaller force constants).[10] Tentative values for the atomic Z and C parameters are listed in Table I. By using these values, the estimated force constants are obtained in mdyn-Å/rad² when bond lengths and bond angles are in Å and in radians, respectively.

Table I. Atomic Constants Z and C in the Correlation of Angle-Bending Force Constants[a]

atom	Z	C	atom	Z	C
H	1.44		Si		0.95
B		0.77	P	2.53	1.23
tetra-C	2.49	0.97[b]	S	3.01	1.22
C	2.49	1.05	Cl	2.84	1.03
N	2.67	1.06	Br	2.88	
O	3.12	1.24	As		0.94
F	2.67		I	2.97	

[a] Tentative values of atomic parameters for use in eq 1. The calculated force constants are given in mdyn-Å/rad² when bond lengths and angles are in Å and radians, respectively. [b] Special value for tetracoordinate carbon.

In this paper we will illustrate four ways in which the transformation to localized force constants can be employed to aid the development of a model empirical force field. First, we shall explore transferability and will test the empirical correlation cited in eq 1 by extracting localized force constants from a number of published spectroscopic force fields which describe angle bending at carbonyl groups. In this connection, we will also compare the derived "consensus" force constants for aldehydes, ketones, amides, carboxylic acids, and esters with those employed in MM2,[11] AMBER,[12] VFF,[13] and CHARMM[14] and will show that none of the latter force fields accurately models the local interactions involved in angle bending at carbonyl groups. Secondly, we will compare three spectroscopic force fields for angle bending at methylene groups in alkanes by applying the localization procedures defined in paper 1[6] to them. Thirdly, we shall extend the current approach to accommodate the related indeterminacies which arise for stretch–bend and bend–bend′ interactions and will illustrate the extension by transforming a quantum-mechanically calculated force field for in-plane bending in ethylene to dependent coordinates. This exercise will also allow us to examine certain model-building assumptions which can be made in developing an empirical force field. Finally, again using ethylene as an example, we shall show how a comparison of localized force constants as a function of geometric distortion can be used to characterize and to aid in parameterizing important effects arising from anharmonic contributions to the force field. A force-field model will probably have to account for significant anharmonicities if it is to describe

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thermally accessible geometric fluctuations to satisfactory accuracy.

Procedures for Calculating Localized Force Constants

To provide an appropriate context for these applications, we shall begin by describing the conceptual basis for the transformation to localized force constants and by summarizing the main results from paper 1. For a more detailed discussion, the reader is referred to that paper.[6]

In paper 1,[6] we discussed the special but significant cases of in-plane bending at trigonal-planar centers ($N = 3$) and of angle bending at tetracoordinate centers ($N = 6$). For these cases we showed that one can calculate a unique set of "localized" force constants in N dependent angular coordinates—i.e., a localized $N \times N$ "force matrix", $\mathbf{F}^{\mathrm{loc}}$—by starting either (i) from an $n \times n$ input force matrix $\mathbf{F}^{\mathrm{int}}$ defined in terms of the smaller set of n well-determined angular coordinates, where $N = n + 1$ or (ii) from a supplied $N \times N$ force matrix $\mathbf{F}^{\delta}$ defined, like $\mathbf{F}^{\mathrm{loc}}$ itself, in the basis of N dependent coordinates. The fundamental idea is easily stated: in the framework of the n well-determined coordinates, the displacement of the *null coordinate* itself, whose addition formally extends the dimension of the coordinate space from n to N, is not physically realizeable. Therefore, we can supplement the "real" force constants by adding a set of "*virtual force constants*", λ, which couple to the null-coordinate displacement. These virtual force constants have no effect on the physical quadratic deformation potential and hence can be chosen to make $\mathbf{F}^{\mathrm{loc}}$ maximally diagonal. When the supplied force matrix is defined in well-determined coordinates, the transformation to the N-dimensional basis of the dependent angles can be carried out as shown in eq 2. Here, $\mathbf{F}^{\sigma}$ is the matrix of dimension $N \times N$ obtained by supplementing (or "bordering") the real force constants from $\mathbf{F}^{\mathrm{int}}$ with an Nth row and column of zeros, and $\mathbf{F}^{\lambda}$ is a symmetric $N \times N$ matrix whose elements vanish except for the "virtual force constants" λ which occupy its Nth row and column. As we showed in paper 1, the values for the virtual force constants can be readily determined by means of a least-squares procedure which requires that the off-diagonal elements of $\mathbf{F}^{\mathrm{loc}}$ be made as small as possible.[6] For trigonal-planar centers, the resultant $\mathbf{F}^{\mathrm{loc}}$ is exactly diagonal. For tetracoordinate centers, in contrast, the off-diagonal elements of $\mathbf{F}^{\mathrm{loc}}$ tend to be small (i.e., a few percent of the diagonal elements) but do not all vanish. However, designated off-diagonal elements can be made to vanish by employing a related constrained least-squares procedure;[6] as we illustrate below, this capability is useful for exploring and implementing specific model-building hypotheses which serve to reduce the complexity of the derived force field. The transformation matrix $\mathbf{T}$, also of dimension $N \times N$, consists of n rows which express the displacements of the n well-determined angular coordinates in terms of those of the N dependent angles, followed by an Nth row which similarly expands the displacement of the null coordinate. We showed that eq 2 yields a result for $\mathbf{F}^{\mathrm{loc}}$ which is unique and is physically equivalent to $\mathbf{F}^{\mathrm{int}}$, in that both sets of force constants describe the same quadratic deformation potential.[6]

$$\mathbf{F}^{\mathrm{loc}} = \mathbf{T}^{\mathrm{T}}(\mathbf{F}^{\sigma} + \mathbf{F}^{\lambda})\mathbf{T} \qquad (2)$$

Alternatively, when the supplied force matrix is already defined in the dependent basis (i.e., is $\mathbf{F}^{\delta}$), $\mathbf{F}^{\mathrm{loc}}$ is obtained via the relationship

$$\mathbf{F}^{\mathrm{loc}} = \mathbf{F}^{\delta} + \mathbf{T}^{\mathrm{T}}\mathbf{F}^{\lambda}\mathbf{T} \qquad (3)$$

Here, the second term on the right-hand side transforms the virtual force constants into the dependent basis, and the least-squares procedure determines the λ values that yield transformed off-diagonal elements which annihilate the off-diagonal elements of $\mathbf{F}^{\delta}$ in so far as possible. The transformation matrix $\mathbf{T}$ must be nonsingular and (by convention) must contain the expansion of the null-coordinate displacement in its Nth row. Otherwise, however, $\mathbf{T}$ is arbitrary; while different choices yield different virtual force constants, the same localized force constants are obtained. As a special case, $\mathbf{F}^{\delta}$ can be the canonical force matrix $\mathbf{F}^{\mathrm{can}}$. The canonical representation, like the localized one, also is uniquely defined.[15] However, this representation is intrinsically nondiagonal, and as a result may be less likely to be useful in developing transferable empirical potentials (see Application II below).

The relationship between the two cases described by eq 2 and 3 can be clarified by replacing the term in eq 2 which arises from $\mathbf{F}^{\sigma}$ by

$$\mathbf{F}^{\delta} = \mathbf{T}^{\mathrm{T}}\mathbf{F}^{\sigma}\mathbf{T} = \mathbf{S}^{\mathrm{T}}\mathbf{F}^{\mathrm{int}}\mathbf{S} \qquad (4)$$

Here, the $n \times N$ transformation matrix $\mathbf{S}$ expands the displacements of the n well-determined angular coordinates in terms of those of the N dependent angles. Thus, eq 2 can be rewritten as

$$\begin{aligned}\mathbf{F}^{\mathrm{loc}} &= \mathbf{S}^{\mathrm{T}}\mathbf{F}^{\mathrm{int}}\mathbf{S} + \mathbf{T}^{\mathrm{T}}\mathbf{F}^{\lambda}\mathbf{T} \qquad (5)\\ &= \mathbf{F}^{\delta} + \mathbf{T}^{\mathrm{T}}\mathbf{F}^{\lambda}\mathbf{T}\end{aligned}$$

where $\mathbf{S}$ is well defined, but where, as in eq 3, $\mathbf{T}$ is essentially arbitrary. Hence, in both cases in effect we add to an initial representation in dependent coordinates, $\mathbf{F}^{\delta}$, contributions which are not physically realizeable but which mathematically serve to minimize (or remove completely) the off-diagonal terms.

For trigonal-planar centers, the transformation from well-determined to dependent coordinates is straightforward and can be expressed in closed form. For five representations commonly employed in published force fields,[16-20] Table II relates the force constants defined in a well-determined basis of angular displacements $\Delta\mu$ and $\Delta\nu$ to the localized force constants defined in terms of the dependent-angle displacements $\Delta\alpha$, $\Delta\beta$, and $\Delta\gamma$. For completeness, the values obtained for the virtual force constants are also listed.

For tetracoordinate centers, closed-form expressions appear not to exist, and the (constrained or unconstrained) least-squares procedure must be used.[6]

Application I: Force Constants for Angle Bending at Carbonyl Carbons

We shall begin by addressing the question of the degree to which force constants for angle bending at carbonyl carbon are transferable between different molecules of a given structural class as well as between different classes of molecules containing carbonyl groups. Our approach will be to examine a diverse set of experimentally determined and quantum-mechanically calculated spectroscopic force fields for angle bending at carbonyl groups after we have expressed the associated force constants in a common framework—that provided by the transformation to localized force constants.

These comparisons will enable us to test the conjecture that localized angle-bending force constants will prove sufficiently "independent" and transferable as to allow the (harmonic) angle-bending deformation potential for an arbitrary carbonyl center to be reconstructed, to useful accuracy, from the three localized force constants for the angular interactions which comprise that center. Should this "mix and match" hypothesis fail, we would need to determine the whole angular deformation potential separately and independently for each class of carbonyl compounds—i.e., for each distinguishable triplet of attached atoms (or, more properly, of atom types) for which we might wish to carry out an empirical force-field calculation. As force-field development proceeds and as computational power advances, we can probably expect to see this more complex approach come into general use. However, this approach requires the determination of a far larger number of force-field parameters and offers little prospect for carrying out "reasonable" calculations on novel

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systems for which the requisite detailed parameterization studies have not yet been performed. It seems judicious, then, to employ the simpler strategy at this stage in force-field development—if it can be shown to be sufficiently accurate. We shall show here that this strategy indeed appears to be a reasonable one for angle bending at carbonyl carbon.

A second objective will be to explore the degree to which the empirical correlation expressed in eq 1 holds for the set of force constants considered here. While the full study on which eq 1 is based is not yet complete,[10] the comparisons presented here will allow us to illustrate how well, or poorly, it works in one important instance.

A third objective will be to critically examine the potentials for angle bending at carbonyl carbon employed in several widely used empirical force fields. Two points of philosophy are of interest in this connection. The first holds that inaccuracies in angle-bending (and bond-stretching) potentials may not be important, because conformational and intermolecular-interaction energies usually are determined largely by relatively "soft" torsional and nonbonded interactions. Errors in the description of "hard" bond-stretching and angle-bending deformations may therefore largely cancel in the energy differences which determine experimentally relevant comparisons of energies and free energies. Thus, numerically accurate comparisons may be obtained even in the presence of inaccuracies in the empirical physical model. This expectation probably is valid to some degree. However, it is important to note that the careful numerical studies needed to determine what errors (e.g., in angle-bending potentials) can be tolerated seem not to have been carried out. Thus, no assurance can be given that the relatively large errors in current force fields addressed below will be acceptable. The second point is the inverse of the first—namely, that some tolerance for error in angle-bending potentials probably does exist. Hence, while a simple "mix and match" strategy based on localized force constants is only approximately valid, it may be good enough to allow accurate calculations of energy differences.

Transferability of Angle-Bending Force Constants. To provide some data for use in our comparisons, we list in Table III a selection of experimentally determined and quantum-mechanically calculated "spectroscopic" force constants for angle-bending at carbonyl carbon in a number of aldehydes, ketones, amides, carboxylic acids, and esters.[20-29] The IVFF (internal valence force field) values for formaldehyde, acetaldehyde, and acetone[21] were determined from spectroscopic data in a basis of dependent angular coordinates under the constraint that off-diagonal angle–angle force constants vanish. These IVFF values therefore are directly comparable to the localized force constants employed in this paper. The remaining force constants were obtained from the published symmetry-coordinate force constants with the aid of Table II, as described in the footnotes to Table III. The entries marked SVFF are based on experimental determinations, while the QM values are based on good quality (split-valence ab initio) calculations, scaled either by the original authors (SQM) or by us (QM × 0.8) to offset the consistent overestimation of force constants calculated by the closed-shell SCF procedure; while approximate, the scale factor of 0.8 is representative[23,25,26] and can be expected to place the calculated force constants reasonably on scale with the experimental values. For the amides, it appears that well-determined experimental force fields have not been reported.[27] Consequently, quantum-mechanically calculated force constants have been used.

Examining Table III, we see, first, that like force constants do tend to be roughly transferable, though some systematic differences can be observed. For example, the H—C═O force constants, despite some scatter, are consistently higher in aldehydes than in derivatives for formic acid. Among other series, the seven N—C═O values, all determined from comparable ab initio calculations, are relatively consistent. This observation suggests that the "mix and match" approach discussed above is accurate enough (at least in this case) to be serviceable in constructing an empirical force field—particularly if small errors do tend to cancel when experimentally relevant energy differences are taken, as discussed above.

It is important to note that the degree of transferability might be greater (or less) than this comparison suggests. The reason, as noted earlier, is that (presumably nontransferable) electrostatic and van der Waals nonbonded contributions are included in the spectroscopic (experimental or quantum-mechanical) angle-bending force constants, whereas these contributions are provided for separately in an empirical force field. Consequently, the spectroscopic values for angle-bending (and other valence-coordinate) force constants *might* differ significantly from the values needed in an empirical force field. If this were true, of course, spectroscopic studies could not aid in the development of empirical force fields.

To determine whether large differences in force constants are likely to result from the difference in the way spectroscopic and empirical force fields treat nonbonded interactions, we have carried out a computational simulation which has allowed us to extract and compare "spectroscopic" and "empirical" force constants for *trans-N*-methylacetamide (NMA), a specific but presumably representative system. We determined the "spectroscopic" force constants by fitting a model potential function to the cartesian first and second derivatives of the energy, calculated with GAUSSIAN 82[30] by using a 6-31G* basis set for a representative (force-field optimized) geometry for NMA.[31] The model potential employed quadratic valence-coordinate deformations which included stretch–stretch, stretch–bend, and θ–θ–ϕ[32] bend–bend′ cross terms in addition to standard diagonal terms for bond stretching, in- and out-of-plane bending, and torsional motion. To determine the "empirical" force constants, we also computed the cartesian first and second derivatives produced by the AMBER[12] "12-6-1" and VFF[13] "9-6-1" and "12-6-1" nonbonded potentials. These potentials sum Lennard-Jones and coulombic interactions over atom pairs

$$E_{\mathrm{nb(12\text{-}6\text{-}1)}} = \Sigma(\epsilon^*_{ij}((R^*_{ij}/R_{ij})^{-12} - 2(R^*_{ij}/R_{ij})^{-6})) + 322qiqj/R_{ij})$$

$$E_{\mathrm{nb(9\text{-}6\text{-}1)}} = \Sigma(\epsilon^*_{ij}(2(R^*_{ij}/R_{ij})^{-9} - 3(R^*_{ij}/R_{ij})^{-6})) + 322qiqj/R_{ij})$$

except that 1,2- and 1,3-pairs are omitted and 1,4-interactions are scaled by 0.5 in AMBER. The well depth ϵ^* and van der Waals diameter R^* obey the combining rules $\epsilon^*_{ij} = (\epsilon^*_i\epsilon^*_j)^{1/2}$ and R^*_{ij}

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(31) The force-field geometry for *trans-N*-methylacetamide used in the quantum calculations was determined by using OPTIMOL, a modeling program developed at the Merck Sharp and Dohme Research Laboratories by the author and colleagues. OPTIMOL uses a "MM2-X" (MM2 extended) force field, developed internally at Merck, which shares many parameters with MM2 (ref 11). MM2-X differs principally from MM2 in that lone pairs on heteroatoms are not used and in that electrostatic interactions take place between atom-centered charges, thus allowing proper treatment of charged systems. MM2-X has been parameterized for a wide range of chemical functionality. For *trans-N*-methylacetamide, the OPTIMOL/MM2-X calculation yields a planar structure having C—C, C═O, C_{sp2}—N, N—H, and C_{sp3}–N bond lengths of 1.530, 1.228, 1.339, 1.006, and 1.455 A, respectively, and C—C═O, C—C—N, O═C—N, C—N—C, C_{sp2}—N—H, and C_{sp3}—N—H bond angles of 121.1, 116.2, 122.7, 121.7, 119.5 and 118.9°, respectively.

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Table II. Expressions for Localized Force Constants, k, and Virtual Force Constants, λ, for In-Plane Bending at Trigonal-Planar Centers[a]

	Representation				
	1[b]	2[c]	3[d]	4[e]	5[f]
$k_{\alpha\alpha}$	$(3k_{\mu\mu} - k_{\nu\nu})/2$	$k_{\mu\mu} - {}^1/_2k_{\nu\nu}$	$(k_{\mu\mu} - k_{\nu\nu})/2$	$k_{\mu\nu}$	$k_{\mu\mu} - k_{\nu\nu}/4$
$k_{\beta\beta}$	$k_{\nu\nu} - \sqrt{3}k_{\mu\nu}$	$k_{\nu\nu} - \sqrt{2}k_{\mu\nu}$	$k_{\nu\nu} + k_{\mu\nu}$	$k_{\mu\mu} - k_{\mu\nu}$	$k_{\nu\nu}/2 - k_{\mu\nu}$
$k_{\gamma\gamma}$	$k_{\nu\nu} + \sqrt{3}k_{\mu\nu}$	$k_{\nu\nu} + \sqrt{2}k_{\mu\nu}$	$k_{\nu\nu} - k_{\mu\nu}$	$k_{\nu\nu} - k_{\mu\nu}$	$k_{\nu\nu}/2 + k_{\mu\nu}$
$\lambda_{\mu\omega}$	$(k_{\mu\mu} - k_{\nu\nu})/\sqrt{2}$	$-\sqrt{3}k_{\nu\nu}/2$	$-\sqrt{3/2}(k_{\mu\mu} - k_{\nu\nu})$	$-\sqrt{3}k_{\mu\nu}$	$-\sqrt{3}k_{\nu\nu}/4$
$\lambda_{\nu\omega}$	$-\sqrt{2}k_{\mu\nu}$	$-\sqrt{3}k_{\mu\nu}$	0	$-\sqrt{3}k_{\mu\nu}$	$-\sqrt{3}k_{\mu\nu}$
$\lambda_{\omega\omega}$	$(k_{\mu\mu} + k_{\nu\nu})/2$	${}^3/_2k_{\nu\nu}$	${}^3/_2(k_{\mu\mu} - k_{\nu\nu})$	$3k_{\mu\nu}$	$3k_{\nu\nu}/4$

[a] The force constants k are those which make diagonal the representation of the quadratic angle-bending potential. In each representation, the virtual force constants λ couple displacements in the physical angles $\Delta\mu$ and $\Delta\nu$ to the null-coordinate displacement $\Delta\omega$, where $\Delta\omega = (\Delta\alpha + \Delta\beta + \Delta\gamma)/3^{1/2}$. [b] $\Delta\mu = (2\Delta\alpha - \Delta\beta - \Delta\gamma)/6^{1/2}$; $\Delta\nu = (\Delta\beta - \Delta\gamma)/2^{1/2}$. Cf. ref 16. [c] $\Delta\mu = \Delta\alpha$; $\Delta\nu = (\Delta\beta - \Delta\gamma)/2^{1/2}$. Cf. ref 17. [d] $\Delta\mu = (\Delta\beta + \Delta\gamma)/2^{1/2}$; $\Delta\nu = (\Delta\beta - \Delta\gamma)/2^{1/2}$. Cf. ref 18. [e] $\Delta\mu = \Delta\beta$; $\Delta\nu = \Delta\gamma$. Cf. ref 19. [f] $\Delta\mu = \Delta\alpha$; $\Delta\nu = (\Delta\beta - \Delta\gamma)/2$ (unnormalized). Cf. ref 20.

Table III. Localized Force Constants (mdyn-Å/rad^2) for Angle Bending at Carbonyl Carbons

		k(X—C═O)				k(X—C—Y)						
molecule	source	H—C═O	C—C═O	N—C═O	O—C═O	H—C—H	H—C—C	H—C—N	H—C—O	C—C—C	C—C—N	C—C—O
						Aldehydes and Ketones						
$H_2C{=}O$	IVFF[a]	0.83				0.46						
	SVFF[b]	0.83				0.44						
	SQM[c]	0.79				0.42						
CH_3CHO	IVFF[a]	0.83	1.00				0.46					
	SVFF[d]	0.92	0.88				0.39					
CH_3CH_2CHO	SVFF[e]	0.59	1.02				0.57					
CH_3COCH_3	IVFF[a]		1.00							1.65		
	SVFF[d]		1.08							1.05		
	SVFF[f]		1.12							1.11		
						Amides						
$HCONH_2$	SQMg	0.63		1.30				0.64				
	QM × 0.8[h]	0.64		1.20				0.63				
$HCONHCH_3$	SQM[g,i]	0.64		1.35				0.62				
	QM × 0.8[h,i]	0.69		1.35				0.63				
CH_3CONH_2	SQM[g]		0.93	1.26							0.99	
	QM × 0.8[h]		0.89	1.25							0.95	
$CH_3CONHCH_3$	QM × 0.8[h,i]		0.92	1.42							0.96	
						Acids and Esters						
HCOOH	SVFF[f,i]	0.61			1.55				0.63			
	SVFF[i,k]	0.63			1.63				0.61			
HCO_2CH_3	SVFF[l,i]	0.64			1.58				0.57			
CH_3CO_2H	SVFF[f,i]		1.23		1.33							1.07
$CH_3CO_2CH_3$	SVFF[f,i]		1.05		1.15							1.10
consensus value:		0.71	1.01	1.30	1.45	0.44	0.47	0.63	0.60	1.08[n]	0.97	1.08
determinations used:		13	11	7	5	3	3	4	3	2	3	2

[a] From force field VF.3 in ref 20. [b] From ref 22 using representation 1 in Table II. [c] From ref 23 using rep. 1. [d] From ref 24 using rep. 1. [e] From ref 25 for the syn conformer, using rep. 1. [f] From ref 20 using rep. 5. [g] From ref 26 using rep. 2. [h] From force constants in ref 27 after scaling by 0.8, using rep. 1. [i] Trans conformation. [j] Cis conformation. [k] From F-matrix B in ref 28, using rep. 1. [l] From ref 20 using rep. 5 or equivalently from ref 29 using rep. 1. [m] Average of the individual determinations except where noted. [n] Excluding the IVFF value (see text).

Table IV. Nonbonded Parameters for AMBER and VFF Calculations on *trans-N*-Methylacetamide

parameter	AMBER[a]	VFF "9-6"[b]	VFF "12-6"[b]
	vdW Radius, R^* (Å)		
C_{sp2}	1.85	1.875	2.03
O	1.60	1.825	1.605
N	1.75	2.005	1.965
H(N)	1.00		
C_{sp3}	1.80	1.81	2.175
H(C)	1.54	1.77	1.375
	Well Depth, ϵ^* (kcal/mol)		
C_{sp2}	0.12	0.042	0.148
O	0.20	0.198	0.228
N	0.16	0.161	0.167
H(N)	0.02	0.00	0.00
C_{sp3}	0.06	0.184	0.039
H(C)	0.01	0.0025	0.038
	Atomic Charges, q		
C_{sp2}	0.616	0.38	0.46
O	−0.504	−0.38	−0.46
N	−0.463	−0.28	−0.26
H(N)	0.252	0.28	0.26
C_{sp3}(C)	−0.142	−0.30	−0.33
H(C–C)	0.010	0.10	0.11
C_{sp3}(N)	0.067	−0.30	−0.33
H(C–N)	0.048	0.10	0.11

[a] Reference 12. The partial atomic charges are those given in the AMBER 3.1 database for the ACE (C-terminal acetyl) and NME (N-terminal *N*-methyl) residues; for the atoms C_{sp2}, O, N, and H(N), they agree with the amide backbone charges published in ref 12. [b] Reference 13.

Table V. Comparison of Spectroscopic and Simulated Empirical Force Constants for *trans-N*-Methylacetamide

		simulated empirical[b]		
quantity	spectroscopic[a]	AMBER	VFF "9-6"	VFF "12-6"
	Diagonal Force Constants for Bond Stretching[c]			
C═O	12.47	12.42	12.37	12.30
C_{sp2}—N	8.84	8.76	8.74	8.67
C_{sp3}—C	4.44	4.40	4.41	4.29
C_{sp3}—N	5.87	5.84	5.82	5.73
H—C_{sp3}	4.97	4.96	4.96	4.95
H—H	7.82	7.81	7.81	7.82
	Angle Bending[d]			
C—C═O	1.13	1.04	1.03	0.98
N—C═O	1.55	1.43	1.38	1.25
C—C—N	0.84	0.86	0.83	0.79
C—N—C	1.10	1.05	0.97	0.98
C_{sp2}—N—H	0.63	0.63	0.61	0.58
C_{sp3}—N—H	0.58	0.57	0.60	0.62
N—C—H	0.97	0.97	0.97	0.96
C—C—H	0.72	0.71	0.70	0.68
H—C—H	0.66	0.66	0.66	0.66
	Out-of-Plane Bending[c,e]			
C:C_{sp3},O,N	3.39	3.29	2.96	2.79
N:C,C_{sp3},H(N)	−0.34	−0.60	−1.21	−1.62
	rms Averages (Differences) by Interaction Type			
bond stretching[c]	7.89	(0.04)	(0.06)	(0.13)
angle bending[d]	0.96	(0.05)	(0.08)	(0.12)
out-of-plane[c,e]	2.40	(0.20)	(0.69)	(1.00)
torsion[f]	15.6	(0.46)	(2.52)	(3.61)
stretch–stretch[c]	0.57	(0.01)	(0.02)	(0.04)
stretch–bend[g]	0.40	(0.04)	(0.05)	(0.07)
θ–θ–ϕ[d]	0.10	(0.03)	(0.04)	(0.05)

[a] Based on fits to ab initio 6-31G* energy first and second derivatives (see text). [b] Based on fits to the 6-31G* first and second derivatives after removal of AMBER and VFF nonbonded contributions (Table IV). See text. [c] mdyn/Å. [d] mdyn-Å/rad^2. [e] Based on a quadratic deformation from a reference value of 0 Å in the height of the central atom (the first listed atom) above the plane defined by the three attached atoms. [f] Based on $V_1(1 - \cos\theta)$ potentials about the C_{sp3}—C, C—N, and C_{sp3}—N bonds, where the V_1 parameters are in kcal/mol. [g] mdyn/rad.

$= 0.5(R^*_i + R^*_j)$. Values of the nonbonded parameters are listed in Table IV. We then subtracted the derivatives resulting from the AMBER or VFF nonbonded potential from the ab initio derivatives. Finally, we fit the residual derivatives by using the same model potential to obtain the "empirical" force constants which in combination with the AMBER or VFF nonbonded potentials describe the ab initio 6-31G* potential energy surface. The fits used the parameter-derivation software "PROBE" being developed by the Biosym Consortium project cited earlier.[3a,33]

The "spectroscopic" force constants and their "empirical" counterparts are compared in Table V. Least affected are the force constants for bond stretching where corrections associated with the explicit use of the empirical nonbonded potentials average only 1–2%. Clearly, nonbonded contributions to spectroscopic force constants for bond stretching are insignificant, at least in NMA. The force constants for angle bending vary more widely (by 10% on average), but even the maximum variation, in the O═C—N force constant, does not exceed 20%. Except for the relatively small "θ-θ-ϕ" bend-bend′ terms, the force constants for the cross terms also vary only modestly. It may be significant that the nonbonded contributions from the well-regarded AMBER potential induce the smallest changes in the spectroscopic force constants. AMBER's nonbonded parameters obey clear and intuitively reasonable systematic trends. In contrast, the VFF radii and well depths show large variations between the "9-6-1" and "12-6-1" sets, indicating that not all of these parameters can be soundly based physically. But even the force constants obtained in connection with the VFF "12-6-1" nonbonded potential remain qualitatively similar to the spectroscopic values, suggesting that no great harm would be done in an empirical force field by employing spectroscopic values for the valence-coordinate force constants.

Returning now to Table III, we see that the individual values for the five O—C═O determinations fluctuate much more widely than do the H—C═O and N—C═O values. Here, too, nontransferable nonbonded contributions presumably airse, but experimental error undoubtedly contributes to the observed variation as well. These variations, though, are small in comparison to the more extreme differences between independently determined spectroscopic force fields which can be found in the literature. More typical of the latter is the variation of ca. 50% between the higher IVFF and the two lower SVFF values for the C–C–C force constant in acetone.

Unfortunately, experiment is not the firm anchor here that one might wish it to be. To appreciate why, it might be helpful to note that "experimental" force constants can be rigorously "measured" only for diatomic molecules. In polyatomic systems, a model for the form of the potential-energy surface must be invoked to relate the experimental observables (e.g., vibrational frequencies, centrifugal distortion constants) to the derived force constants. Even then the process is not straightforward, as quite different sets of force constants can give comparable overall fits to the available experimental data. Consequently, experimentally determined force fields can be seriously in error, even for as simple a molecule as ethylene,[34] though reliable results usually can be obtained when quantum-mechanical calculations are employed to calibrate or constrain the fitting procedure.[35] The fact that inaccurately determined spectroscopic force constants have been reported makes it difficult to discern systematic trends and to develop empirical correlations like that presented in eq 1. One must select which experimental force constants to accept and which to reject—and, except where calculated values provide useful

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(33) Maple, J. R.; Dinur, U.; Hagler, A. T. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5350–5354.

(34) Pulay, P.; Meyer, W. *J. Mol. Spectrosc.* **1971**, *40*, 59–70.

(35) See, for example: Sugawara, Y.; Hirakawa, A. Y.; Tsuboi, M. *J. Mol. Spectrosc.* **1984**, *108*, 206–214.

guidance, such decisions inevitably will be colored by the very considerations of regularity being addressed. A satisfactory balance must therefore be struck between rejecting data too readily and accepting it too uncritically. We can illustrate our approach in the current instance by calling attention to the set of "consensus values" presented in Tables III and VI; except for the C–C–C force constant, where we have rejected the high IVFF value, we have chosen simply to average the individual determinations, in the hope that especially large errors can be avoided in this way.

Illustration of the Empirical Correlation in Eq 1. As Table VI shows, eq 1 reproduces the consensus force constants fairly well. Most of the systematic trends expected from it are in fact observed. For example, the force constants X—C═O and H–C–X tend to increase in the intuitively reasonable order H < C < N < O. Overall, the empirical relationship reproduces the consensus force constants with an average absolute error of 0.09 mdyn-Å/radian^2 and a rms relative error of 16%. These errors are comparable to those obtained in the broader correlation cited in the Introduction.

Assessment of Angle-Bending Potentials in Four Empirical Force Fields. A further indication of how well eq 1 performs is given by the comparisons in Table VI to force constants employed by the widely used MM2,[11] AMBER,[12] VFF,[13,36] and CHARMM[13] molecular-mechanics force fields.[37] Of these, only AMBER does comparably well—for those interactions for which parameters have been reported (see note added in proof). But even AMBER cannot be said to be completely satisfactory, as it replaces the significant variation along the series C—C═O, N—C═O, O—C═O by a single, more or less average, value. Indeed, this parsimony is a characteristic element, as AMBER shares only ca. 20 distinct values among approximately 400 distinguishable angle-bending force constants.[12] Table VI also confirms the widely known fact that MM2 significantly—though intentionally[38]—underestimates angle-bending force constants, making it unlikely to be reliable for computing vibrational frequencies or for calculating properties which depend on their accuracy. VFF is not much more accurate then MM2 (by the present measure) and fares little better than the null-hypothesis choice of assigning a constant value of 0.89 (the average of the consensus values) to each interaction. Finally, the published CHARMM parameters show even less correlation with the consensus values, and for this series of interactions do not appear clearly superior to the null-hypothesis values.

It appears, then, that the potentials for angle bending at carbonyl groups are inaccurately modeled in MM2, VFF, and CHARMM and that the AMBER potential, while correct in scale, nevertheless fails to incorporate significant trends. Each of these force fields can therefore be expected to encounter some degree of difficulty

Table VI. Comparison of Force Constants for Angle Bending at Carbonyl Carbons (mdyn-Å/rad^2)

		k(X—C═O)				k(X—C—Y)							av abs. diff or % rms
source		H—C═O	C—C═O	N—C═O	O—C═O	H—C—H	H—C—C	H—C—N	H—C—O	C—C—C	C—C—N	C—C—O	
consensus value[a]		0.71	1.01	1.30	1.45	0.44	0.47	0.63	0.60	1.08	0.97	1.08	
eq 1	value[b]	0.70[c]	1.02[d]	1.16[e]	1.37[f]	0.39[g]	0.55[h]	0.67[i]	0.83[j]	0.85[k]	0.96[l]	1.22[m]	
	diff	−0.01	0.01	−0.14	−0.08	−0.05	0.08	0.04	0.23	−0.23	−0.01	0.14	0.09
	% diff	−1	1	−11	6	−11	17	6	38	−21	−1	13	16%
MM2	value[n]	0.37	0.46	0.67	0.80		0.37	0.30	0.65	0.40	0.66	0.65	
	diff	−0.34	−0.55	−0.63	−0.65		−0.10	−0.33	0.05	−0.68	−0.31	−0.43	0.41
	% diff	−49	−54	−48	−45		−32	−52	8	−64	−32	−40	45%
AMBER	value[n]		1.21	1.11	1.11[o]						0.97	0.97[o]	
	diff		0.10	−0.19	−0.34						0.00	−0.11	0.15
	% diff		10	−15	−23						0	−10	14%
VFF	value[n]	0.76	0.94	0.94	2.01			0.63	0.76	0.72	0.74	1.71	
	diff	0.05	−0.07	−0.36	0.56			0.00	0.16	0.36	−0.23	0.63	0.27
	% diff	7	−7	−28	39			0	27	33	−24	57	30%
CHARMM	value[n]	1.18	1.18	0.90	1.18			0.56			0.28	1.18	
	diff	0.47	0.17	−0.40	−0.27			−0.07			−0.69	0.10	0.31
	% diff	66	15	−31	−19			−11			−71	9	40%
null hypothesis	value[p]	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	
	diff	0.18	−0.12	−0.41	−0.56	0.45	0.42	0.26	0.29	−0.19	−0.08	−0.19	0.29
	% diff	25	−12	−32	−39	102	89	41	48	−18	−8	−19	49%

[a] From Table III. [b] Calculated using $Z_H = 1.44$, $Z_C = 2.49$, $Z_N = 2.67$, $Z_O = 3.12$, $C_C = 0.97$ (see Table I). [c] Calculated using r(CH) = 1.11 Å, r(C═O) = 1.21 Å, θ(H—C═O) = 124°, averages of values appropriate for aldehydes and formates. [d] Using 1.49 Å, 1.21 Å, and 124°, averages appropriate for the contributing functional groups. [e] Using 1.34 Å, 1.21 Å, and 125°. [f] Using 1.35 Å, 1.21 Å, and 124°. [g] Using 1.11 Å and 116°. [h] Using 1.11 Å, 1.52 Å, and 115°. [i] Using 1.11 Å, 1.35 Å, and 113°. [j] Using 1.10 Å, 1.34 Å, and 110°. [k] Using 1.51 Å and 116°. [l] Using 1.50 Å, 1.34 Å, and 116°. [m] Using 1.52 Å, 1.35 Å, and 111°. [n] Cf. ref 37. [o] Bash, P. Ph.D Thesis, University of California, San Francisco, CA, 1986. [p] Average of the consensus values in the first row.

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(36) The force constants cited are those employed in the VFF force field used by program DISCOVER from Biosym Technologies, Inc., as specified by Dauber-Osguthorpe, P.; Hagler, A. T. Private communication. Except for the C–C–C interaction, these angle-bending force constants are also cited in the following: Dauber-Osguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. J. *Proteins* **1988**, *4*, 31–47.

(37) The listed MM2 force constants are those employed in the MM2 program (ref 11); those involving amide nitrogen are from the 1987 parameter set (Allinger, L. Private communication). MM2 atoms types used are 1, 3, 5, 6, 7, and 9. For AMBER, VFF, and CHARMM, the published force constants are given in kcal/(mol-rad^2) and are converted to mdyn-Å/rad^2 by dividing by 143.942. In addition, AMBER, VFF, and CHARMM all employ the form $k_\theta(\theta - \theta_0)^2$, whereas MM2 and this work employ the form $0.5{*}k_\theta(\theta - \theta_0)^2$. To allow for this difference in form, therefore, the AMBER, VFF, and CHARMM force constants (refs 12, 13, 14, 36) have been divided by 71.97 to give the values listed in Table VI. For the N—C═O force constants, for example, the AMBER N—C—O force constant of 80 kcal/(mol-rad^2) becomes 1.11 mdyn-Å/rad^2, the CHARMM NH1—C—O force constant of 65 kcal/(mol-rad^2) becomes 0.90 mdyn-Å/rad^2, and the VFF n–c′–o′ force constant of 68 kcal/(mol-rad^2) becomes 0.94 mdyn-Å/rad^2. Other atom types used in referencing angle-bending force constants are HA (CHARMM) for aliphatic hydrogen, CT (AMBER, CHARMM) and c (VFF) for all-atom aliphatic carbon, and OS (AMBER), OC (CHARMM), and o (VFF) for singly-bonded carboxyl oxygen. Note that one of the AMBER force constants, that for the C—C═O (CT—C—O) interaction, is incorrectly cited twice in ref 12, as 80 and as 87 kcal/(mol-rad^2); the correct value is 80 kcal/(mol-rad) (Kollman, P. Private communication). Also, as noted in Table VI two of the remaining AMBER force constants are not cited in ref 12 but are given in the Ph.D. Thesis of P. Bash.

(38) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907–1918.

Table VII. Force Constants and Symmetry Coordinates for the C—CH_2—C Group and Structural Parameters Used in the Force Constant Determinations[a]

coordinate	symmetry	force constant	description	GCFF[b]	IVFF-1[c]	IVFF-2[d]
s-2	a1	$f(C)CH_2(C)-2$	CH2 scis.	0.575	0.569	
s-4	b2	−4	CH2 rock	0.766	0.705	0.689
s-5	b1	−5	CH2 wag	0.622	0.627	0.623
s-6	a2	−6	CH2 twist	0.639	0.659	0.665
s-D	a1	−D	CCC def.	0.941	1.024	1.088
	a1	−2D	scis./def.	0.047	0.121	0.041
			r(CH)[e]	1.110	1.093	1.093
			r(CC)[e]	1.539	1.540	1.540
			θ(HCC)[f]	110.4	tet	tet
			θ(CCC)[f]	112.2	tet	tet

[a] Force constants are in mdyn-Å/rad². [b] Reference 42. [c] From ref 5, as quoted in ref 42. [d] From ref 39, as quoted in ref 42. [e] In Å. [f] In deg; "tet" indicates the tetrahedral angle.

in describing the vibrational behavior of carbonyl-containing molecules. We recognize that it may seem appropriate to support this conclusion by comparing empirically calculated to spectroscopically observed vibrational frequencies, and the reader may wonder why we have not offered such comparisons here. A brief discussion of the approach we have taken is therefore in order. A key point is that a comparison of vibrational frequencies alone would not be sufficient. We would also need to demonstrate that the corresponding normal-mode displacements are also predicted accurately, for otherwise the empirical procedure might be getting the "right answer for the wrong reason". Unfortunately, the requistie "experimental" normal modes, like force constants, are derived, rather than observed, quantites and are subject to significant experimental uncertainties. Moreover, comparisons of normal-mode displacements are difficult to make. This information is not ordinarily presented in the literature (other than at a purely qualitative or schematic level), though of course it can be reconstructed from published geometries and force constants. Nevertheless, detailed comparisons of both vibrational frequencies and normal-mode displacements would be of great interest. Such comparisons are beyond the scope of this paper but indeed *would* be required to establish that a given empirical force field *is* accurate.

The much simpler approach we have taken here, in contrast, cannot prove that an empirical force field *is* accurate but *can* demonstrate that one is *not*. This more limited objective is attainable because the forms of the potential used in spectroscopic and in empirical force fields correspond very closely. Because the correspondence is close, results obtained from two such methods will agree *uniformly* only if the methods agree in all relevant particulars (just as two vector quantities expanded in the same coordinate system will agree closely only if each of their components do). In this regard, we have noted that empirical and spectroscopic force fields differ in how they handle nonbonded interactions, but have shown in one particular but presumably representative case (see also Application IV below) that the implicit incorporation of nonbonded contributions has relatively little influence on the spectroscopic values for angle-bending force constants. Hence, if the empirical and spectroscopic values for these force constants differ substantially (as we have shown to be the case), *some* of the predictions made by the empirical force field must differ substantially from those made on the basis of the spectroscopic force field.

In summary, then, we find that force constants for angle bending at carbonyl carbon are substantially transferable both within and between different classes of molecules. Moreover, these force constants obey clear systematic trends which relate to their atomic constitution and geometry. In contrast, the force constants employed in widely used empirical force fields do not exhibit comparable trends and appear to be inaccurately modeled (though minimally so for AMBER).

Application II: Comparison of Force Fields for Angle-Bending at Methylene Groups

Force fields for alkanes have been among the earliest and most intensively explored. Beginning nearly 25 years ago, a detailed IVFF (internal valence force field) in dependent valence coordinates was developed by Schachtsneider and Snyder for *n*-alkanes,[5] extended to branched alkanes,[39] and further revised.[40] In subsequent applications, IVFF force fields have been determined for many other classes of compounds.[41] More recently, an alternative approach based on the use of well-determined "local symmetry" coordinates has been applied to alkanes and to other classes of saturated molecules.[42,43] This GCFF (group coordinate force field) employs redundancy-free linear combinations of the dependent angle-bending coordinates. In contrast, the IVFF approach encounters indeterminacies but addresses them by requiring that a sufficient number of the distinguishable force constants for off-diagonal interactions vanish. Both approaches seek to define a transferable force field and largely succeed. They differ in that the IVFF approach transfers individual diagonal and nonvanishing off-diagonal force constants, while the GCFF approach takes whole functional groups (methyls, methylenes, etc.) as its transferable entities. In this respect, the IVFF approach is closer in spirit to the approach taken in empirical molecular-mechanics force fields.

IVFF and GCFF force fields have recently been compared for alkanes and other classes of saturated compounds by transforming the IVFF force constants to the GCFF symmetry-coordinate basis.[44] For one case—that of angle bending at methylene carbons in C–CH_2–C fragments—we shall make a similar comparison in dependent coordinates. This approach will allow us to contrast the canonical[15] and localized representations and to explore the consequences of imposing specific constraints within the latter representation.

Table VII lists the $f_{(C)CH_2(C)-n}$ force constants in the symmetry-coordinate basis[44] for the GCFF set,[42] the IVFF-1 set taken from Calculation V in the original paper,[5] and the IVFF-2 set.[39] Assuming tetrahedral bond angles, the symmetry coordinates −2, −4, −5, −6, −*D* and the null (redundancy) coordinate −*R* are given by[44]

$$\sigma_{-2} = 20^{-1/2}(4\Delta\delta - \Delta_{\gamma 1A} - \Delta_{\gamma 1B} - \Delta_{\gamma 2A} - \Delta_{\gamma 2B})$$

$$\sigma_{-4} = 0.5(\Delta_{\gamma 1A} - \Delta_{\gamma 1B} + \Delta_{\gamma 2A} - \Delta_{\gamma 2B})$$

$$\sigma_{-5} = 0.5(\Delta_{\gamma 1A} + \Delta_{\gamma 1B} - \Delta_{\gamma 2A} - \Delta_{\gamma 2B})$$

$$\sigma_{-6} = 0.5(\Delta_{\gamma 1A} - \Delta_{\gamma 1B} - \Delta_{\gamma 2A} + \Delta_{\gamma 2B})$$

$$\sigma_{-D} = 30^{-1/2}(5\Delta\omega - \Delta\delta - \Delta_{\gamma 1A} - \Delta_{\gamma 1B} - \Delta_{\gamma 2A} - \Delta_{\gamma 2B})$$

$$\omega_{-R} = 6^{-1/2}(\Delta\omega + \Delta\delta + \Delta_{\gamma 1A} + \Delta_{\gamma 1B} + \Delta_{\gamma 2A} + \Delta_{\gamma 2B})$$

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(39) Snyder, R. G.; Schachtsneider, J. H. *Spectrochim. Acta* **1965**, *21*, 169–195.

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(44) Matsuura, H.; Tasumi, M. In *Vibrational Spectra and Structure*; Durig, J. R., Ed.; Elsevier: Amsterdam, 1983; Vol. 12, Chapter 2, pp 69–143.

Table VIII. Force Constants (×1000) in Dependent Coordinates for Angle Bending at Methylene Groups in Alkanes (mdyn-Å/rad^2)[a]

		F^{can}			F^{loc}			$F^{loc'}$			$F^{loc''}$		
interaction	symbol	GCFF	IVFF-1	IVFF-2	GCFF	IVFF-1	IVFF-2	GCFF	IVFF-1	IVFF-2	GCFF	IVFF-1	IVFF-2
						Diagonal							
H—C—H	H_δ	487	455	478	553	502	535	531	427	519	549	551	550
C—C—C	H_ω	784	853	907	998	1100	1178	977	1025	1162	959	901	1131
H—C—C	H_γ	571	571	562	679	676	662	694	666	656	694	666	656
						Off-Diagonal							
C—C—C′ C—C—H	$F_{\gamma\omega}$	−166	−195	−190	−5	−19	−4	−9	−62	−15	−18	−124	−31
C—C—H C—C—H′	F_γ	−131	−111	−115	−23	−6	−15	−8	−16	−21	−8	−16	−21
C—C—H C′—C—H	F'_γ	−59	−72	−82	49	33	18	64	23	12	64	23	12
C—C—H H′—C—H	$F_{\delta\gamma}$	−92	−96	−83	−5	−19	−4	−9	−62	−15	(0)	(0)	(0)
H—C—H′ C—C—C′	$F''_{\delta\omega}$	−118	−72	−148	22	76	16	(0)	(0)	(0)	(0)	(0)	(0)
C—C—H C′—C—H′	F''_γ	−122	−95	−94	−15	10	6	(0)	(0)	(0)	(0)	(0)	(0)
rms off-diagonal		124	132	130	22	27	10	24	46	14	25	65	18

[a] Based on data in Table VII. The interaction symbols relate to deformation modes shown in Figure 1.

where δ denotes the H–C–H angle, ω, the C–C–C angle, and γ, the C–C–H angles associated with carbons A, B and hydrogens 1, 2 (see Figure 1). The symmetries and qualitative characters of the σ coordinates are also indicated in Table VII.

As Matsuura and Tasumi discuss,[44] five diagonal force constants and one nonvanishing off-diagonal force constant arise in the GCFF approach (assuming C_{2v} symmetry). Correspondingly, at most six nonvanishing force constants can be determined in the IVFF approach from among the full set H_γ, H_δ, H_ω, $F_{\gamma\omega}$, F_γ, F'_γ, $F_{\delta\gamma}$, $F''_{\delta\omega}$, and F''_γ defined in Figure 1. As Matsuura and Tasumi point out, the IVFF force fields were determined by setting the last three interaction constants to zero. To determine the effect of this and other possible choices for resolving the indeterminancy which occurs in dependent coordinates, we report in Table VIII the values these force constants take in the canonical and in three localized representations. The canonical force constants were obtained as shown in eq 4, where $\mathbf{F}^{int}$ (or the expanded $\mathbf{F}^v$) contains the symmetry-coordinate force constants from Table VII, and S (or the expanded matrix T) employs the relationships for the σ coordinates given above; the resultant matrix $\mathbf{F}^\delta$ is $\mathbf{F}^{can}$ because T is unitary.[6] The first of the three sets of localized force constants represents an unconstrained localization, and the second and third reflect the constraints[6] indicated by the expressly zeroed force constants shown in parentheses.

Table VIII confirms that the canonical representations contain sizeable negative off-diagonal force constants, as necessitated by the requirement that any given row or column of $\mathbf{F}^{can}$ sum to zero.[15] (For trigonal-planar centers, the canonical off-diagonal elements would be even larger, as just two are paired with each diagonal force constant.) In constructing an empirical force field, many complications will probably be avoided if it is possible to neglect the off-diagonal angle-bending force constants without great cost in accuracy. Almost certainly, this neglect would not be justifiable in the canonical framework. In contrast, both the unconstrained and constrained localizations yield much smaller off-diagonal force constants in the present case (and yield identically zero values for trigonal-planar centers) and would seem to offer a more hopeful prospect. $\mathbf{F}^{loc'}$, the first of the constrained localizations, is obtained by requiring that three off-diagonal elements (one of type $F''_{\delta\omega}$ and two of type F''_γ, representing "opposite" angles having no sides in common) vanish; $\mathbf{F}^{loc''}$ suppresses an additional four interactions of type $F_{\delta\gamma}$.[45] Neglect of all the off-diagonal elements is most easily justified for the unconstrained localization for IVFF-2, where the rms value of these elements, 0.010, is less than one-tenth of that for the canonical representation and is just over 1% of the rms value for the diagonal elements. For this force field, the off-diagonal elements remain small even when constraints are imposed.

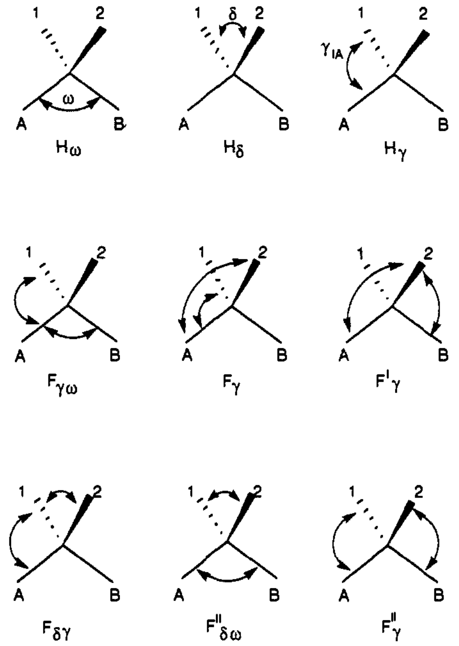

Figure 1. Internal coordinates and IVFF force-field interactions in C–CH2–C fragments. A and B represent carbon atoms; 1 and 2 represent hydrogens.

For IVFF-1, $\mathbf{F}^{loc''}$ enforces the assumptions employed in the original determination and therefore reproduces the reported values for the six nonzero force constants.[5] (Equivalently, each IVFF localization could have been performed by starting from these values and employing eq 3.) Here, the relatively large value of −0.124 for $F_{\gamma\omega}$ dominates the off-diagonal elements, and it may be asked whether this force field is physically as reasonable as the others. Interestingly, we note that the diagonal force constants themselves fluctuate widely as constraints are added or removed. In contrast, GCFF and IVFF-2 are far more stable and agree closely except that H_ω, the C–C–C force constant, is about 20% larger in the latter case. For use in constructing an empirical force field, a diagonal representation based on $\mathbf{F}^{loc}$ for one of these two force fields would seem appropriate. Alternatively, certain off-diagonal interactions (perhaps those in $\mathbf{F}^{loc''}$) could be retained if they could be shown to be suitably transferable to other compounds possessing analogous interactions.

Application III: The Harmonic In-Plane Force Field of Ethylene in Dependent Coordinates

In well-determined coordinates, the in-plane vibrations in ethylene can be described by one C=C stretching coordinate, four C–H stretching coordinates, and two nonredundant angle-bending coordinates at each carbon. In dependent coordinates of the type considered in this paper, in contrast, each carbon participates in

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(45) As only six virtual force constants are to be determined and three constraints are required for the $F''_{\delta\omega}$ and F''_γ elements, only three of the additional four off-diagonal elements of type $F_{\delta\gamma}$ can be constrained to zero. When three such elements are so constrained, however, the fourth $F_{\delta\gamma}$ element also is found to vanish.

Table IX. 4-21G Scaled QM In-Plane Force Field for Ethylene[a]

coordinate	description	rCC	rC1-H3	rC1-H4	rC2-H5	rC2-H6	μ_1	μ_2	ν_1	ν_2
1	rCC	8.952								
2	rC1-H3	0.075	5.177							
3	rC1-H4	0.075	0.027	5.177						
4	rC2-H5	0.075	0.015	−0.005	5.177					
5	rC2-H6	0.075	−0.005	0.015	0.027	5.177				
6	μ_1[c]	−0.212	0.062	0.062	−0.009	−0.009	0.455			
7	μ_2[d]	−0.212	−0.009	−0.009	0.062	0.062	0.017	0.455		
8	ν_1[e]	0.	0.107[g]	−0.107[g]	−0.036	0.036	0.	0.	0.529	
9	ν_2[f]	0.	−0.036	0.036	0.107	−0.107	0.	0.	−0.081	0.529

[a] From ref 23. Units are mdyn/Å for stretch–stretch terms, mdyn/rad for stretch–bend terms, and mdyn-Å/rad^2 for bend–bend terms. [b] See Figure 2. [c] $\Delta\mu_1 = 6^{-1/2}(2\Delta\alpha_1 - \Delta\beta_1 - \Delta\gamma_1)$. [d] $\Delta\mu_2 = 6^{-1/2}(2\Delta\alpha_2 - \Delta\beta_2 - \Delta\gamma_2)$. [e] $\Delta\nu_1 = 2^{-1/2}(\Delta\beta_1 - \Delta\gamma_1)$. [f] $\Delta\nu_2 = 2^{-1/2}(\Delta\beta_2 - \Delta\gamma_2)$. [g] The signs for these two terms are reversed in ref 23, apparently erroneously.

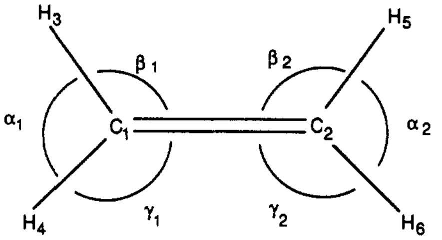

Figure 2. Internal in-plane coordinates for ethylene.

one redundancy (characterized as of type (1) in ref 4) which arises from the constraint that the three dependent angular coordinates (the two H—C═C angles plus the H-C-H angle) sum to 360°. When we describe angle bending in terms of three dependent angles at each carbon, the nine well-determined coordinates expand to 11, and we encounter the problem of how to express the force constants in a physically equivalent manner over dependent coordinates. For the 3 × 3 portions of the expanded 11 × 11 force constant matrix which describe angle bending at a given carbon, the transformations to localized force constants specified in Table II can be applied straightforwardly. Expansion from a lower to a higher dimension also comes into play for interactions which couple angle bending at one carbon with bond stretching at either carbon or with angle bending at the other carbon. We show here that virtual force constants also can be employed to perform this expansion in a controlled manner, subject to specific model-building assumptions whose validity can thereby be assessed.

We shall employ the scaled quantum mechanical (SQM) force field for ethylene reported by Pulay et al.,[23] because the internal consistency of a computed force field will best serve our objective of critically examining possible model-building assumptions. Pulay's force field is based on SCF 4-21G calculations and employs carefully calibrated scaling factors which allow it to reproduce the observed frequencies for ethylene and ethylene-d_4 quite well. The force constants are listed in Table IX, where they are given in terms of valence coordinates defined through Figure 2.

Angle Bending. Transformation to dependent coordinates of the force constant elements for angle bending at C_1 ($F_{6,6}$, $F_{6,8}$, and $F_{8,8}$) or at C_2 ($F_{7,7}$, $F_{7,9}$, and $F_{9,9}$) is easily made using representation 1 in Table II, giving

$$k_{\alpha_1} = k_{\alpha_2} = 0.418$$

$$k_{\beta_1} = k_{\beta_2} = k_{\gamma_1} = k_{\gamma_2} = 0.529$$

Stretch–Bend Interactions. One such set of interactions arises at C_1 between C═C, C_1—H_3, and C_1—H_4 stretching (coordinates 1, 2, and 3) and μ_1 and ν_1 bending (coordinates 6 and 8). Formally, the expansion from the representation as two nonredundant angles to the representation as three dependent angles at C_1 can be made as shown below, where $\mathbf{T}$ relates $\Delta\mu_1$, $\Delta\nu_1$, and $\Delta\omega_1$, the

$$\mathbf{F}^{\mathrm{loc}} = \mathbf{F}^{\sigma,\lambda}\mathbf{T}$$

null-coordinate displacement, to deformations in the dependent angles in the manner specified for representation 1 in Table II, and $\mathbf{F}^{\sigma,\lambda}$ is obtained by supplementing the 3 × 2 matrix of force constants defined in terms of the two nonredundant angles with a third column containing the virtual force constants $\lambda_{1,\omega}$, $\lambda_{2,\omega}$, and $\lambda_{3,\omega}$. The result explicitly obtained for $\mathbf{F}^{\mathrm{loc}}$ is

$$\mathbf{F}^{\mathrm{loc}} = \begin{bmatrix} -0.17310 + \lambda'_{1,\omega} & 0.08655 + \lambda'_{1,\omega} & 0.08655 + \lambda'_{1,\omega} \\ 0.05062 + \lambda'_{2,\omega} & 0.05035 + \lambda'_{2,\omega} & -0.10099 + \lambda'_{2,\omega} \\ 0.05062 + \lambda'_{3,\omega} & -0.10099 + \lambda'_{3,\omega} & 0.05035 + \lambda'_{3,\omega} \end{bmatrix} \quad (6)$$

where the order of the rows is ΔrC═C, ΔrC_1–H_3, and ΔrC_1–H_4 and that of the columns is $\Delta\alpha_1$, $\Delta\beta_1$, $\Delta\gamma_1$, and $\lambda'_{n,\omega} = 3^{-1/2}\lambda_{n,\omega}$. For clarity, we have intentionally retained additional decimal figures.

Because the quadratic in-plane potential does not depend on the λ, all sets of force constants covered by eq 6 are physically equivalent. To obtain a specific set, we must find the values needed to enforce a particular model-building assumption. For example, if we wished to make the stretch-bend force constants as small as possible in the least-squares sense, we would take $\lambda = 0$. Here however, we shall instead require that $k_{\mathrm{C{=}C},\alpha1}$, $k_{\mathrm{C1\text{-}H3},\gamma1}$, and $k_{\mathrm{C1\text{-}H4},\beta1}$ vanish, so that each angle interacts only with the two bonds which form its sides (cf. Figure 2). The required values are readily seen to be $\lambda'_{1,\omega} = 0.17310$ and $\lambda'_{2,\omega} = \lambda'_{3,\omega} = 0.10099$, giving

$$\mathbf{F}^{\mathrm{loc}} = \begin{bmatrix} (0) & 0.260 & 0.260 \\ 0.152 & 0.151 & (0) \\ 0.152 & (0) & 0.151 \end{bmatrix}$$

Thus, in dependent coordinates the stretch–bend interactions are characterized by the force constants

$$\begin{aligned} k_{\mathrm{C{=}C'.H{-}C{=}C'}} &= 0.260 \\ k_{\mathrm{H{-}C.H{-}C{-}H'}} &= 0.151 \\ k_{\mathrm{H{-}C,H{-}C{=}C'}} &= 0.152 \end{aligned} \quad (7)$$

when we require that the *distal* stretch–bend interactions (i.e., those which couple the bending of a given angle to the stretching of bonds at the same vertex other than those which form that angle) vanish.

In this case, the three available virtual force constants were sufficient to enforce the model assumption. For stretch–bend interaction at a tetracoordinate center, in contrast, each of the six primitive angles will have two proximal stretch bends involving the bonds which form its sides and, in addition, two distal stretch bends involving the two other bonds to the central atom. We might wish to neglect the force constants for these 12 distal stretch–bend interactions. However, there are only six disposable virtual force constants. Here, therefore, the distal stretch-bending force constants cannot be reduced to zero by the transformation but can be minimized (in the least-squares sense), and the accuracy of the model assumption can itself then be judged by how small the residual distal stretch–bend force constants have become. For the methyl groups in N-methylacetamide, for example, we find that the residual values for the distal stretch–bend interactions typically are at least 10 times smaller than are the force constants for the proximal stretch bends.[7] While not in itself definitive, this finding suggests that neglect of distal stretch–bend interactions is justified in constructing a model empirical potential.

Stretch–Bend′ Interactions. The interaction between angle bending at C_1 and bond stretching at C_2 (or *vice versa*) can be handled analogously. Again, we need a model assumption, which we shall take as being that the stretches at B will couple only to the angles at A which share a common atom (namely, B). Accordingly, we will require that the distal interactions between α_1 and the C_2–H_5 and C_2–H_6 stretches vanish. If λ_{4,ω_1} and λ_{5,ω_1} couple the null coordinate at C_1 with the stretching of the C_2–H_5 and C_2–H_6 bonds (coordinates 4 and 5), respectively, we find that a value of 0.01273 is required for each virtual force constant, and obtain

$$k_{\mathrm{H-C,C=C'-H'}}(\mathrm{cis}) = -0.014$$

$$k_{\mathrm{H-C.C=C'-H'}}(\mathrm{trans}) = 0.036$$

These force constants are substantially smaller than those for the more proximal interactions characterized by eq 7 and might well be ignored in constructing an empirical force field. If they were to be retained, however, the assigned force "constant" clearly would need to depend on the molecular conformation. By analogy to the bend–bend′ interactions discussed below, one might choose a representation of the form

$$k_{\mathrm{H-C,C=C'-H'}} = A \cos \phi_{\mathrm{H-C=C'-H'}} \tag{8}$$

But while eq 8 is qualitatively right, it is quantitatively wrong, because it requires equal magnitudes for the cis and trans couplings. A more elaborate relationship would probably be needed to express these force constants sufficiently accurately to justify their retention in an empirical force field—if indeed retention of such small terms can be justified in current generation force fields.

Bend–Bend′ Interactions. To complete the specification of the in-plane force constants, we now consider the interaction of angle bending at C_1 (coordinates 6 and 8) with angle bending at C_2 (coordinates 7 and 9). We carry out the expansion via

$$\mathbf{F}^{\mathrm{loc}} = \mathbf{T}_2^{\mathrm{T}}\mathbf{F}^{\sigma,\lambda}\mathbf{T}_1 \tag{9}$$

where $\mathbf{T}_1$ and $\mathbf{T}_2$ define the transformation of coordinates at C_1 and C_2, and $\mathbf{F}^{\sigma,\lambda}$ is obtained by supplementing the 2 × 2 matrix of "real" force constants with a third row and column of virtual force constants:

$$\mathbf{F}^{\sigma,\lambda} = \begin{bmatrix} 0.017 & 0 & \lambda_{7,\omega_1} \\ 0 & -0.081 & \lambda_{9,\omega_1} \\ \lambda_{\omega_2,6} & \lambda_{\omega_2,8} & \lambda_{\omega_2,\omega_1} \end{bmatrix}$$

In this case, we shall take the model assumption to be that angles at two bonded centers A and B couple only if they contain A–B as a common side, so that once again the more proximal interactions survive and the more distal ones vanish. We now work out the expressions for the elements of $\mathbf{F}^{\mathrm{loc}}$ in eq 9 and solve the simultaneous equations which result from equating to zero the expressions for elements which are to vanish. In this case, we find $\lambda_{9,\omega_1} = \lambda_{\omega_2,8} = 0$ (as might be expected from the fact that these elements couple deformations of different symmetry), $\lambda_{7,\omega_1} = \lambda_{\omega_2,6} = -0.02403$, and $\lambda_{\omega_2,\omega_1} = 0.03399$. The result is

$$\mathbf{F}^{\mathrm{loc}} = \begin{bmatrix} (0) & (0) & (0) \\ (0) & -0.015 & 0.066 \\ (0) & 0.066 & -0.015 \end{bmatrix}$$

Thus, the localized bend–bend′ force constants are

$$k_{\mathrm{H-C=C'.C=C'-H'}}(\mathrm{cis}) = -0.015$$

$$k_{\mathrm{H-C=C'.C=C'-H'}}(\mathrm{trans}) = 0.066$$

and again the force "constant" is found to depend on the molecular conformation. These bend–bend′ interactions are usually neglected in empirical force fields but are retained in one implementation of the consistent force field as "θ–θ–ϕ" interactions taken to be proportional to the product of the two angular deformations times the cosine of the four-atom torsion angle.[32] This functional dependence requires that the quadratic force constant itself be proportional to cos ϕ, such that

$$k_{\mathrm{H-C=C',C=C'-H'}} = A \cos \phi_{\mathrm{H-C=C'-H'}}$$

As in the previous discussion of stretch–bend′ interactions, we see that this particular form is not quantitatively accurate enough in the present case to make retaining these interactions clearly superior to neglecting them. Let us note, however, the caveat expressed repeatedly and examined earlier in the treatment of angle-bending at carbonyl carbons: the experimentally determined and quantum-mechanically calculated "spectroscopic" force fields considered in this paper fold all the physical interactions onto the valence-coordinate deformations, whereas empirical force fields provide separately for electrostatic and van der Waals interactions. Accordingly, the stretch–bend and bend–bend′ force constants needed for use in the latter might possibly conform more closely to a cos ϕ dependence than is evident here. To determine whether this is the case, we would need to remove the effects of electrostatic and van der Waals interactions from the valence-coordinate force constants before applying the transformations described in this section. Indeed, we have done so in connection with the study reported in Application IV below and have found that representative estimates for the nonbonded interactions in ethylene leave the assessment offered here unchanged.

The complete localized force field in dependent coordinates for the in-plane vibrations of ethylene is given in Table X.

Application IV: Anharmonicities in the In-Plane Force Field for Ethylene

So far, our discussion has focussed on ways in which the transformation of angle-bending force constants to the localized representation can assist in the development of model empirical force fields defined at the quadratic (harmonic) level. To be sure, molecular energy surfaces are significantly anharmonic. However, while spectroscopic force fields often employ cubic (and even quartic) terms, less appears to be known about the role such terms should play in an empirical force field. Again using the in-plane deformation of ethylene as the example system, we show here how the transformation to localized force constants can be employed to clarify the role and significance of such anharmonicities.

Our approach will be as follows. We shall begin by obtaining the localized force constants for the in-plane force field for ethylene from a quantum mechanical calculation in the manner described in Application III. Then, we shall compare these force constants to ones calculated for systematically distorted geometries by using distortions of the magnitude we wish to be able to accommodate in a force-field calculation. When the geometric distortions produce relatively large changes in the localized force constants, we shall infer that the harmonic representation is insufficient. We might then choose the following: (i) to add additional (e.g., cubic) terms or replace a harmonic function by an anharmonic one; (ii) to incorporate additional physical interactions (e.g., by adding polarization terms to the standard Coulombic description for electrostatic interactions); (iii) to retain the quadratic description even though the localized force constants vary to some extent; or (iv) to simplify the force field by neglecting terms whose associated force constants are small and are highly variable.

The localized force constants which result from this procedure are listed in Table XI. They were obtained from analytic second derivatives calculated with a 6-31G* basis set using GAUSSIAN 86.[46] To simplify the analysis, all structures have D_{2h} symmetry. Structure 0 is the 6-31G* equilibrium geometry, while structures 1 and 2 apply increments of ±0.03 Å in the C=C bond length, structures 3 and 4 apply increments of ±0.05 Å in the C—H bond lengths, and structures 5 and 6 vary the H—C=C angles by ±3°. In each case, all other internal coordinates have been kept at their equilibrium values. Each set of paired structures, when taken together with the equilibrium structure, therefore yields three points on a unidimensional distortion coordinate, thus allowing

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(46) GAUSSIAN 86; Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fluder, E. M.; Topiol, S.; Pople, J. A. Carnegie-Mellon Quantum Chemistry Publishing Unit: Pittsburgh, PA, 1984.

Table X. Localized In-Plane Force Field for Ethylene in Dependent Angle-Bending Coordinates[a]

coordinate	description[b]	*r*CC	*r*C1–H3	*r*C1–H4	*r*C2–H5	*r*C2–H6	α_1	β_1	γ_1	α_2	β_2	γ_2
1	*r*CC	8.952										
2	*r*C1–H3	0.075	5.177									
3	*r*C1–H4	0.075	0.027	5.177								
4	*r*C2–H5	0.075	0.015	−0.005	5.177							
5	*r*C2–H6	0.075	−0.005	0.015	0.027	5.177						
6	α_1	(0)	0.152	0.152	(0)	(0)	0.418					
7	β_1	0.260	0.151	(0)	−0.014	0.036	(0)	0.529				
8	γ_1	0.260	(0)	0.151	0.036	−0.014	(0)	(0)	0.529			
9	α_2	(0)	(0)	(0)	0.152	0.152	(0)	(0)	(0)	0.418		
10	β_2	0.260	−0.014	0.036	0.151	0.151	(0)	−0.015	0.066	(0)	0.529	
11	γ_2	0.260	0.036	−0.014	(0)	(0)	(0)	0.066	−0.015	(0)	(0)	0.529

[a] Units are mdyn/Å for stretch–stretch, mdyn/rad for stretch–bend, and mdyn-Å/rad^2 for bend–bend interactions. Explicit zeros identify interactions required to vanish in making the transformation to dependent coordinates. [b] See Figure 2.

Table XI. Localized In-Plane Force Constants for Ethylene for Systematically Distorted D_{2h} Geometries[a]

	structure						
	0	1	2	3	4	5	6
Geometry and Energy							
*r*C═C	1.317	1.287	1.347				
*r*C—H	1.076			1.026	1.126		
α(H—C—H)	116.4					122.4	110.4
β(H—C═C)	121.8					118.8	124.8
Δ*E*, kcal	(0.0)	0.80	0.72	4.98	4.14	1.36	1.38
Diagonal Force Constants							
*r*C═C	11.64	13.64	9.90	11.69	11.58	11.74	11.55
*r*C—H	6.24	6.22	6.25	8.24	4.68	6.24	6.22
α	0.515	0.515	0.515	0.535	0.494	0.454	0.578
β	0.636	0.651	0.620	0.645	0.625	0.691	0.587
Stretch–Stretch Cross Terms							
*r*C═C,*r*C—H	0.110	0.118	0.103	0.094	0.122	0.118	0.104
*r*C—H,*r*C—H (gem)	0.053	0.055	0.050	0.038	0.060	0.025	0.085
Stretch–Bend Cross Terms							
*r*C═C,β	0.284	0.298	0.272	0.291	0.278	0.316	0.261
*r*C—H,α	0.159	0.160	0.158	0.161	0.156	0.138	0.182
*r*C—H,β	0.141	0.147	0.135	0.158	0.123	0.191	0.139
Stretch–Stretch′ Cross Terms							
*r*C—H,*r*′C—H (cis)	0.017	0.018	0.016	0.016	0.018	0.019	0.015
*r*C—H,*r*′C—H (trans)	−0.004	−0.003	−0.004	−0.003	−0.004	−0.003	−0.004
Stretch–Bend′ Cross Terms							
*r*C—H,β′ (cis)	−0.020	−0.022	−0.017	−0.020	−0.020	−0.022	−0.018
*r*C—H,β′ (trans)	0.051	0.054	0.049	0.049	0.053	0.057	0.045
Bend–Bend′ (θ–θ–φ) Cross Terms							
β,β′ (cis)	−0.019	−0.015	−0.022	−0.026	−0.012	−0.009	−0.025
β,β′ (trans)	0.085	0.082	0.088	0.089	0.081	0.094	0.077

[a] Based on 6-31G* calculations. See Table X for units for force constants and notation for the internal variables. [b] 6-31G* equilibrium geometry. [c] Bond lengths are in Å, bond angles are in deg.

the dependence of the force constants on a particular internal coordinate to be readily assessed. Note that the distortion energies—ca. 1 kcal/mol per (dependent) internal coordinate—are quite modest and should easily be handled by a high-quality empirical force field.

Diagonal Force Constants. Table XI shows that the force constants for C═C and C—H bond stretching depend strongly on the respective C═C and C—H bond lengths. This variation is accurately described by a Morse function of form

$$E_{XY} = D_{XY} \cdot (1 - \exp(-\alpha(r - r_0))^2$$

where E_{XY} is the contribution to the total energy which arises from alterations in the X–Y bond length r from the reference value r_0. Thus, the parameters $\alpha_{CC} = 1.785$ Å^{-1}, $D_{CC} = 263$ kcal/mol (1.827×10^{-13} ergs), and $r_0 = 1.317$ Å yield force constants of 9.83, 11.64, and 13.63 mdyn/Å at the three C═C bond lengths. Similarly, $\alpha_{CH} = 1.902$ Å^{-1}, $D_{CH} = 124$ kcal/mol (0.862×10^{-13} ergs), and $r_0 = 1.076$ Å give force constants of 4.66, 6.24, and 8.22 mdyn/Å. The VFF force field employs such a Morse representation.[13] In contrast, MM2[11] employs the "cubic-stretch" form

$$E_{XY} = \tfrac{1}{2}k(r - r_0)^2(1 + \mathrm{CS}(r - r_0))$$

where the cubic coefficient, CS, can be shown to correspond to $-\alpha$. Thus the standard MM2 value for CS of −2 Å^{-1} is a good choice here. However, the Morse function better represents the actual nonlinear variation of the force constant with r and avoids the well-known "cubic-stretch catastrophy" in which abnormally large bond lengths drive the energy toward minus infinity. A quartic polynomial in $(r - r_0)$ can also accurately reproduce the dependence of the force constant on $(r - r_0)$ while remaining well-behaved.[47]

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(47) A function which corresponds closely to a fourth-order Taylor series expansion of the Morse potential would have properties suitable for use in an empirical force-field calculation. Such a function would unphysically diverge to plus infinity but only at bond lengths which would not be physically attainable anyway.

The diagonal force constants for angle bending also depend significantly on the molecular geometry and vary inversely with the associated bond angle. This observation suggests that a Morse or cubic representation could be employed. Alternatively, we might write

$$k_\theta = k^0_\theta(\theta_0/\theta)^n$$

where an exponent of $n = 2$ is suggested by comparison to the empirical correlation of angle-bending force constants with geometry presented in eq 1. For the H—C═C and H—C—H force constants reported in Table XI, the values $n = 3.31$ and $n = 2.34$ account well for the observed variations. Though usually neglected in current force fields, these variations represent the departure from harmonicity next most important after that associated with the variations in the force constants for bond stretching. Anharmonic potentials for angle bending should be employed in next-generation force fields.

In addition to these predominant "self anharmonicities", Table XI shows that what we may call "cross anharmonicities" also arise. For example, the force constant for C═C stretching varies by up to 0.10 mdyn/Å over the range of C—H bond lengths and H—C═C and H—C—H angles considered here, and the force constants for angle bending show a similar dependence on the C—H and C═C bond lengths. Such dependencies are not commonly included in current-generation force fields, as they would require the introduction of cubic terms (e.g., terms proportional to the square of the displacement from equilibrium in the C═C bond distance times that in the C—H bond length or the H—C═C angle, where the last factor in effect would allow the effective C═C force constant to vary with the C—H distance or H—C═C angle). While these cross anharmonicities are not large, any force field which fails to provide for them will thereby incur a certain irreducible level of error. If they are neglected, this fact will need to be borne in mind when considering whether the force constants for particular cross terms are large and constant enough to merit retention in a force field being developed to achieve a given level of accuracy.

Stretch–Stretch Cross Terms. Table XI also reports the force constants for the cross terms which couple the stretching of bonds originating at a common vertex. Agreeably, the force constant for C═C, C—H interaction is nearly independent of geometry. However, that for the geminal C—H, C—H′ interaction, while slightly smaller, depends strongly on the H—C—H bond angle. Thus, a variation from 122.4° to 110.4° in this angle decreases the force constant from 0.025 to 0.080 mdyn/Å or by roughly 3-fold. In view of its small size and high variability (another form of cross anharmonicity which also indicates the importance of cubic terms), it may be asked whether retaining this interaction with an averaged force constant (of ca. 0.05 mdyn/Å) is clearly superior to neglecting it.

Stretch–Bend Cross Terms. The force constants which couple the stretching of a given bond with bending at an angle formed from that bond also show a fair degree of variability. But as they are relatively large (0.1–0.3 mdyn/rad) it would seem appropriate to retain the associated interactions, perhaps using the mid-range force constants found at the equilibrium geometry.

Cross Terms for Stretch–Stretch′, Stretch–Bend′, and Bend–Bend′ Interactions. As we saw in Application III, cross terms involving the stretching or bending of more widely separated bonds and angles tend to be small. Neglect of the stretch–stretch′ interactions is particularly easy to justify, and the stretch–bend′ force constants are also quite small. The H—C═C′, C═C′—H′ (or "θ–θ–ϕ") interactions, however, have force constants which are roughly 10% as large as those for diagonal angle bending. These longer range interactions should probably be retained—though we again note that the "θ–θ–ϕ" form would incorrectly require that the force constants for the trans and cis interactions have equal magnitudes (cf. Application III above).

In summary, anharmonicities in the potential energy surface for ethylene lead to significant variations in the diagonal force constants for both bond stretching and angle bending. The predominant self anharmonicities can readily be accounted for in a force-field model, e.g., by employing a Morse function for bond stretching. However, the diagonal force constants also depend to some extent on the other internal coordinates. These "cross anharmonicities" could be described by adding cubic terms, but such a representation would introduce a much greater degree of complexity into the force-field model. In ethylene, at least, these cross anharmonicities are relatively large in comparison to the cross-term force constants for stretch–stretch interactions. As a result, retaining cross terms for bond stretching may not be justified in a model which neglects cross anharmonicities. Cross terms which couple bond stretching with angle bending at a given center are relatively large and should probably be retained. The "θ–θ–ϕ" interactions which couple angle bending at two connected vertices might also be retained, though the traditional "θ–θ–ϕ" functional form appears to be inadequate.

Contributions to Valence-Coordinate Force Constants from vdW and Electrostatic Interactions. The preceding analysis has been made within the context of a "spectroscopic" force field in which the physical contributions associated with van der Waals and electrostatic nonbonded interactions are embedded within the valence-coordinate (bond stretching and angle bending) terms. As these nonbonded interactions will be separately described in an empirical force field, the empirical valence-coordinate force constants might take on quite different values—in which case conclusions reached above might not be valid. To examine this possibility, we have converted the "spectroscopic" in-plane force constants for ethylene into "empirical" force constants in a manner analogous to that employed for *N*-methylacetamide in Application I. In particular, we have adjusted the 6-31G* analytical derivatives by subtracting the contributions obtained by using three representative models for the 1,4-nonbonded interactions between hydrogen atoms on adjacent carbons (these being the only nonbonded interactions usually considered for ethylene). Representation A used the MM2 "exp-6" potential and parameters[11] (i.e., $\epsilon^*_{\text{H-H}} = 0.047$ kcal/mol and $R^*_{\text{H-H}} = 3.0$ Å, but for computational convenience placed the vdW center at the hydrogen atom (rather than slightly displacing it inward toward the parent carbon). As usual in MM2, the hydrogen atoms were given no electrostatic charge. Representation B employed a Lennard-Jones "9-6" potential for each H-H interaction

$$E_{\text{H-H}} = \epsilon^*_{\text{H-H}}(2\rho^9 - 3\rho^6)$$

with a well depth $\epsilon^*_{\text{H-H}}$ of 0.04 kcal/mol and a vdW diameter $R^*_{\text{H-H}}$ of 2.8 Å, where $\rho = R^*_{\text{H-H}}/R_{\text{H-H}}$. Representation C employed the same Lennard-Jones potential but added a Coulombic term calculated by assigning charges of +0.1 to the H atoms and by using a dielectric constant of 1.0. The force-field parameters were derived by fitting the modified sets of first and second derivatives to the force-field model employed in Table XI. The PROBE software being developed by the Biosym Consortium effort[3a,33] was used for all the calculations, including that for representation 0 in Table XII, where the fit to the unmodified analytical derivatives yielded the same force constants as had previously been obtained for structure 0 in Table XI by the approach described in Application III.

The results, listed in Table XII, show clearly that nonbonded potentials within the range covered in representations A–C make contributions to the valence-coordinate force constants which are too small to affect the conclusions reached here and in Application III above.

Conclusions

This paper has presented four applications of a uniquely defined transformation from well-determined to dependent coordinates for in-plane bending at trigonal-planar centers and for angle-bending at tetracoordinate centers. These applications indicate that much that is relevant to the design of empirical force fields can be learned by transforming experimental and quantum-mechanical spectroscopic force fields for small acyclic molecules to the localized representation described above. We have seen, in

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(48) Knowles, J. R. *Science* **1987**, *236*, 1252–1258.

Table XII. Localized In-Plane Force Constants for Ethylene for Various Representations for Nonbonded Interactions[a]

	representation			
	O[b]	A[c]	B[d]	C[e]
Diagonal Force Constants				
*r*C═C	11.64	11.62	11.62	11.63
*r*C—H	6.24	6.22	6.22	6.23
α	0.515	0.517	0.516	0.515
β	0.636	0.616	0.627	0.625
Stretch–Stretch Cross Terms				
*r*C═C,*r*C—H	0.110	0.105	0.108	0.108
*r*C—H,*r*C—H (gem)	0.053	0.067	0.059	0.058
Stretch–Bend Cross Terms				
*r*C═C,β	0.284	0.275	0.280	0.281
*r*C—H,α	0.159	0.153	0.156	0.157
*r*C—H,β	0.141	0.130	0.134	0.138
Stretch–Stretch′ Cross Terms				
*r*C—H,*r*′C—H (cis)	0.017	0.029	0.022	0.022
*r*C—H,*r*′C—H (trans)	−0.004	−0.014	−0.008	−0.007
Stretch–Bend′ Cross Terms				
*r*C—H,β' (cis)	−0.020	−0.016	−0.018	−0.018
*r*C—H,β' (trans)	0.051	0.044	0.049	0.048
Bend–Bend′ (θ–θ–ϕ) Cross Terms				
β,β' (cis)	−0.019	−0.022	−0.021	−0.021
β,β' (trans)	0.085	0.085	0.085	0.086

[a] Based on 6-31G* calculations carried out at the equilibrium geometry. See Table X for units for force constants and notation for the internal variables. [b] These "spectroscopic" force constants reproduce the calculated 6-31G* second derivatives. [c] Obtained after removal of contributions from exp-6 nonbonded interactions ($\epsilon^*_{\mathrm{H\text{-}H}} = 0.047$ kcal/mol, $R^*_{\mathrm{H\text{-}H}} = 3.0$ Å), as described in the text. [d] Obtained after removal of Lennard-Jones 9-6 contributions ($\epsilon^*_{\mathrm{H\text{-}H}} = 0.04$ kcal/mol, $R^*_{\mathrm{H\text{-}H}} = 2.8$ Å). [e] Obtained after removal of 9-6-1 Lennard-Jones plus coulombic contributions ($\epsilon^*_{\mathrm{H\text{-}H}} = 0.04$ kcal/mol, $R^*_{\mathrm{H\text{-}H}} = 2.8$ Å, $q_{\mathrm{H}} = +0.10$).

particular, that a simple empirical expression nicely describes the diagonal localized force constants for angle bending at carbonyl groups. In contrast, the force constants employed in widely used empirical potentials fail to exhibit the trends observed in the experimental data. We have also found that published force fields for angle bending at a tetracoordinate center (i.e., at methylene groups in alkanes) are nearly diagonal in the localized representation, suggesting that neglect of cross terms in angle bending may be justified in developing an empirical potential. Thirdly, we have seen that virtual force constants can be employed to control the representation in dependent coordinates of stretch–bend and bend–bend′ cross terms, thereby providing a means for assessing model assumptions concerning the functional form and physical significance of such interactions. And finally, we have see that significant anharmonicity is present in the potential-energy surface for in-plane vibrations in ethylene and that such anharmonicities can be characterized by determining the dependence on molecular geometry of quadratic force constants obtained in the localized representation.

There are exciting times for those who work at the interface between biology and chemistry. For example, the new experiments made possible by the techniques of genetic engineering are yielding a wealth of new information on the relationship between protein structure and function.[48] But as Knowles notes,[48] the key to understanding this new information often lies not in experiment but in theory—in the ability to sort out through reliable calculations the factors which contribute to an experimental result. If theory is to serve in this role, better theoretical models will have to be developed. It would be most unfortunate if the vast amount of information on molecular properties compiled in "spectroscopic" force fields could not be utilized effectively in their development. The approach described in this paper suggests how it can be utilized.

Acknowledgment. I thank Drs. John Maple, Uri Dinur, and Arnold Hagler of Biosyn Technologies for making available the parameter-derivation software "PROBE"[33] used in the calculations on *N*-methylacetamide and on ethylene which were carried out to determine the magnitude of contributions to spectroscopic valence-coordinate force constants from nonbonded interactions. It also thank a referee for many clarifying suggestions and for identifying the need to justify the basis for comparing spectroscopic angle-bending force constants with those employed in empirical force fields.

Note Added in Proof. According to P. Kollman, additional AMBER force constants for angle bending at carbonyl carbon are cited in a forthcoming paper (Debolt, S.; Kollman, P. A. *J. Am. Chem. Soc.* In press); in the notation and units of Table VI, their values are H—C═O = 0.56, H—C—H = 0.49, and C—C—C = 0.98. Inclusion of these force constants would extend the generally good comparisons for the AMBER force field presented in Table VI and leave essentially unchanged the figures of merit cited there.

Energies and Isomerizations of $(CH)_{12}$ Hydrocarbons

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Abstract: Energy-optimized geometries of 15 isomeric $(CH)_{12}$ hydrocarbons are presented. Geometries were optimized with ab initio restricted Hartree–Fock calculations with the split-valence 3-21G basis set. Energies were calculated at those geometries with the polarized 6-31G* basis. Compound **8** is suggested as the most stable isomer of the $(CH)_{12}$ family. Previously calculated energetics for isomerizations of benzene dimers and molecules related to truncated tetrahedrane are reexamined. Other possible isomerizations and some new $(CH)_{12}$ isomers are considered.

Those compounds consisting entirely of carbons each bearing a single hydrogen, polymethine hydrocarbons, play an important role in organic chemistry. Among them are numbered the simple annulenes,[2] the prismanes,[3] dodecahedrane,[4] and the elusive

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