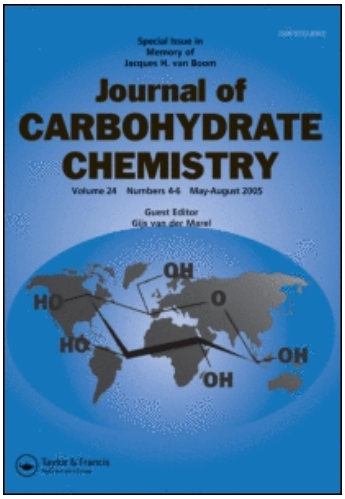

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CONSISTENT FORCE FIELDS FOR SACCHARIDES[1]

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ABSTRACT

Consistent force fields for carbohydrates were hitherto developed by extensive *optimization of potential energy function parameters* on experimental data and on *ab initio* results. A wide range of experimental data is used: internal structures obtained from gas phase electron diffraction and from x-ray and neutron diffraction, vibrational frequencies, dipole moments, unit cell dimensions and lattice energies. The range of model compounds covered so far includes alkanes, ethers, alcohols, ketones and mono- and disaccharides. Electrostatic interactions are handled by fractional charges assigned to individual atoms. Charges are modeled such that Mulliken population analyses are reproduced. Morse functions are used for all bonded interactions; experimentally derived dissociation energies are used as parameters. Van der Waals interactions are modeled with Lennard-Jones 12-6 functions. The anomeric and exo-anomeric effects are accounted for *without addition of specific terms.* The work is done in the framework of the Consistent Force Field which originated in Israel and was further developed in Denmark. The actual methods and strategies employed have been described previously. Extensive testing of the force field is reported, and ways and means of improvement are indicated. Principles of mapping of conformational space are discussed, and a discussion on which properties to preferentially reproduce in modeling is invited.

SHORT HISTORY OF THE CFF ATTEMPTS

We have worked on the Consistent Force Field[3] for thirty years,[4] and tried to apply the method to saccharides for twenty; the previous history has been published.[5] The full power of the CFF was not available in its updated form until 1985,[6] and then optimization

was undertaken. In 1991 we finished the first serious bid for an optimized force field for carbohydrates and their derivatives, **PEF91L**.[7]

Until then we had worked with hand-fitted force fields like most other researchers in modeling, and our main results were the demonstration that relaxation in all internal degrees of freedom is necessary for meaningful calculation of conformations of disaccharides and, by implication, of oligosaccharides; and the proof that quite good results can be provided even with rather primitive potential energy functions, if their parameters are judiciously chosen.

PEF91L was applied to a variety of problems, notably the charting of the conformational space of gentiobiose.[7]

Our work over the years had shown that it was of overriding importance to model the *non*-bonded interactions adequately. We developed a new and more rational strategy of optimization,[8] involving heavy optimization on crystal structures, which resulted in our best potential energy function so far, with the parameter set **PEF95SAC**. This has been documented in much detail.[9]

The present paper records further tests of the force fields, and directions for improvement are indicated.

SUMMARY OF THE CFF CONCEPT

The most essential point of the Consistent Force Field concept[3,10] is optimization of the potential energy function parameters on different types of observables of a series of related substances. The energy functions which are presently handled with the Consistent Force Field are shown in Table 1. Currently the Consistent Force Field is able to optimize the energy function parameters on: (1) the static geometrical structure including bond lengths, valence angles, torsional angles and *non*-bonded distances; (2) condensed phase packing as represented by unit cell dimensions; (3) condensed phase packing energies (lattice energies); (4) degree of molecular rigidity as expressed by vibrational frequencies in gaseous and crystalline phases; and (5) dipole moments of gases. Each observable can be and usually is individually weighted with the reciprocal of its experimental uncertainty taken, as a rule, as three times the standard deviation.

Selection of experimental data is an integral and very important part of the optimization process. Two examples will illustrate this: For the static representation of molecular geometry in the gas phase we use the r_z structure where most people, at least in earlier days,

have used the r_g structure which is temperature dependent for comparison. For vibrational frequency we use, as a rule, a standard deviation of 25 cm^{-1}, because the uncertainty must reflect also the error due to lack of anharmonic corrections and other imperfections in the interpretation of the measured spectra.

MAIN APPROACHES

We try to use as simple potential energy functions as possible. This is in almost complete contradiction to the current trend, where a new term is added when some calculated result is not perfectly satisfactory. This is acceptable only if you do not want to do optimization, or are unable to do so. Optimization requires parameter sets which are uncorrelated, and this is difficult even with simple functions. The functions we use require almost a doubling of the number of parameters when one more atom type is added, and this also forces us to keep the number of terms as low as possible. The number of parameters in **PEF95SAC** is rather large, even for a simple set intended for a limited range of compounds. In **PEF91L** which contains parameters also for amide and phosphate groups there are several times as many parameters.

Among the present possible choices for potential energy functions used in the Consistent Force Field, see Table 1, we use Morse functions for all bonded interactions, and Lennard-Jones 12-6 functions for non-bonded interactions.

It is not due to forgetfulness that no specific term for hydrogen bonding appears. Following ideas which originally were strongly advocated by Charles Coulson decades ago,[11] we treat hydrogen bonding as an overlay of van der Waals and electrostatic interactions, in other words, as any other non-bonded interaction. We are aware that this strong stance may have to be relaxed but maintain that the simple approach has not yet been fully exploited.

During all our work over the years we have tried to improve our strategies of optimization. Our goal is to obtain a force field applicable to both gas phase and condensed phase simulations. With this approach we approximate an explicit environment potential as closely as possible by adjusting non-bonded parameters to condensed phase observables, so far preferably low temperature neutron diffraction data.

In the case of **PEF91L** we developed the following strategy of optimization:[8]

(1) An initial potential energy function with "reasonable" parameter values is neces-

Table 1. Potential energy functions

Type	Function	Mathematical expression
Bonded	Harmonic	$V = \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2$
	Morse	$V = \sum_{bonds} D_e \left[e^{-2\alpha(b-b_0)} - 2e^{-\alpha(b-b_0)} \right]$
	Inverse power	$V = \sum_{bonds} \left[A\, b^{-1} + B\, b^{-5} + C\, b^{-9} \right]$
Non-bonded	Lennard-Jones n-6-1	$V = \sum_{i<j} \left[A_{ij}\, r^{-n} - B_{ij}\, r^{-6} + e_i e_j\, (Dr)^{-1} \right]$
	Lennard-Jones n-6-1	$V = \sum_{i<j} \left[\epsilon_{ij} \left(\frac{\sigma_{ij}}{r} \right)^n - 2\epsilon_{ij} \left(\frac{\sigma_{ij}}{r} \right)^6 + \frac{e_i e_j}{Dr} \right]$
	Buckingham exp-6-1	$V = \sum_{i<j} \left[A_{ij}\, e^{-B_{ij} r} - C_{ij}\, r^{-6} + e_i e_j\, (Dr)^{-1} \right]$
Correction	Harm. valence angle	$V_\theta = \sum_{angles} \frac{1}{2} K_\theta (\theta - \theta_0)^2$
	Torsional angle	$V_\phi = \sum_{torsions} \frac{1}{2} K_\phi (1 \pm \cos k\phi)$
	Torsional angle	$V_\phi = \sum_{torsions} \frac{1}{2} [K_{\phi 1} (1 + \cos(\phi - \phi_{01})) + K_{\phi 2} (1 + \cos(2\phi - \phi_{02})) + K_{\phi 3} (1 + \cos(3\phi - \phi_{03}))]$
	Out-of-plane angle	$V_\chi = \sum_{oopl} \frac{1}{2} K_\chi (\chi - \chi_0)^2$

sary. (2) Optimize Lennard-Jones parameters on crystal structures, freezing all other parameters. (3) Freeze Lennard-Jones and charge parameters, optimize all others on gas phase data. (4) Repeat the crystal phase optimization, then the gas phase optimization, until no further improvement is seen. (5) Optimize charge parameters on dipole moments. (6) Repeat the entire process until no further improvement is seen.

For **PEF95SAC** we changed the strategy: We kept the charge parameters fixed all way through, after having adapted them to Mulliken charges at the Hartree-Fock level at the outset. Dipole moments were kept in the gas phase optimization database.

The costly optimization on crystal structure plays a dominant part in both strategies. This is an absolutely necessary condition if an adequate representation of *non*-bonding is to be achieved, and it is by no means a sufficient condition.

The weight we place on the use of crystal structure in optimization prompts a note on charge assignment. Atomic charge is assigned to each atom by a rather complicated algorithm, and in exactly the same way for crystals as for single molecules. Exact charge neutralization is always secured. The algorithm has been described in some detail,[12] as has the choice of dielectric constant.[10,12]

SUCCESSES AND FAILURES

PEF91L is in many ways a satisfactory force field, particularly in respect of gas phase structure, and to a certain extent also for crystal properties. Even lattice energies are pretty well reproduced. This applies certainly to alkanes. Only five carbohydrate crystals were included in the optimization, and there is no doubt that the results for saccharides were not as satisfactory as we had hoped for. The reproduction of the gentiobiose crystal is an example, see Table 2.

We expected that a better treatment of *non*-bonded and especially electrostatic interactions, and optimization on a much larger set of saccharide crystal structures, now exclusively from neutron diffraction, would improve our description of hydrogen bonding and other energetic properties. We started as usual from scratch with a large set of alkanes, gaseous and crystalline, and proceeded to ethers, both straight-chain and cyclic. When this work was just finished, we could compare with *ab initio* calculations on 2-methoxy-tetrahydropyran carried out by Tvaroska and Carver[14] at the same time. This comparison came out quite favorably for both structure and energetics.[12] The next step would then be to add the alcohol groups.

In the optimization of **PEF95SAC** we locked the parts of the potential energy function dealing with only alkanes and ethers, and optimized on structures and spectra of small alcohols and on neutron structures of 16 saccharides.[9] We believe that this is the most extensive optimization on crystal structures so far done for saccharides. The resulting

Table 2. Details of gentiobiose structure

	Crystal[13]	PEF95SAC	PEF91L
C1'-O6-C6	113.3	114.1	116.9
ϕ	63.2	62.8	52.0
ψ	-156.3	-158.9	-175.7
ω	-177.9	173.1	-179.9
-C5-C6-	g'g	g'g	g'g
H1'---H_R	240	236	248
H1'---H_S	312	329	307
A	8.8693	8.452	
B	22.8460	22.835	
C	7.2011	7.290	
Vol	1459.2	1406.9	

parameter set[9] was then checked against some additional neutron and x-ray structures, and on a variety of other data. The resulting calculated properties are of such quality that **PEF95SAC** should be useful in a broader context, and be applicable to gases as well as solids. The *ab initio* charges used in the force field are also quite similar to those used by most established water potentials; therefore also realistic condensed phase molecular dynamics simulations are within the scope.

Yet even **PEF95SAC** is not perfect. In some of the saccharide crystal structures, one or two *exo*cyclic alcohol groups are given wrong torsions which shows that the hydrogen bonding description is not yet in place. Some crystalline alcohols are reproduced neatly, such as ethanol, where the unit cell contains both the *anti* and the *gauche* conformer, and *meso*-erythritol;[9] see also Table 3. Estimates of barriers to rotation in small alcohols are quite reasonable; see Table 4.

These results indicate that small adjustments of the properties of the H-on-O atom should further improve the parameter set.

TESTING TOWARDS *AB INITIO* CALCULATIONS

A hope to get an indication of the direction the change should take might come from an analysis of a selection of glucose conformers. Barrows *et al.* performed series of large-

Table 3. Crystalline alcohols in PEF95SAC

			exp	PEF95SAC	error, %
Ethanol[15]	*anti*	H'OCC	179(2)	173	3
monoclinic	*gauche*	H'OCC	-63(2)	-58	8
Pc		A	5.337(4)	5.496	-3.0
Z=4		B	6.882(5)	6.373	7.4
x-ray		C	8.225(8)	9.042	-8.7
		β	102.2(1)	109.6	-7.2
		Vol	298.6	298.3	0.1
meso-Erythritol[16]		H'OCC	-80.2 (1)	-69.1	13.8
tetragonal		H'OCC	-80.6 (1)	-87.6	-8.7
$I4_1/a$		A	12.713 (5)	13.395	-5.4
Z=8		C	6.747 (2)	6.228	7.7
neutron		Vol	1090.5	1147.6	-5.2

Table 4. Energy Differences and Barriers in PEF95SAC. Unit of energy: $kJmol^{-1}$

substance		barrier or rel. energy	exp	method
methanol		4.02	4.45	microwave spectrum[17]
ethanol	*gauche*	0.00		
	anti	1.34		
	a → *g*	2.2		
	g → *a*	3.3	5.0	microwave spectrum[18]
2-propanol	*anti*	0.00		
	gauche	0.58		
	a → *g*	6.3		
	g → *a*	5.7	7.0	microwave spectrum[19]

scale *ab initio* calculations,[20] and their 11 conformers were examined with the Consistent Force Field using **PEF95SAC**. A comparison is seen in Table 5 where the MM3 and *ab initio* data are taken from an early version of their manuscript. The crystal structure is well represented, see Table 6 and Figure 1. The molecular conformation is marginally better reproduced than with the more elaborate methods, and the unit cell is quite correct. Inspection of stereo drawings showed that α conformers 7 and 8, and their structurally analogous β conformers 3 and 5 whose occurrences are underestimated, have too different energies. There is no obvious explanation. α conformers 10 and 11 are overestimated. Conformers 10 and 11 have a neat round-the-clock system of hydrogen bonding which is probably the reason for the low energy. In spite of the rather large amount of work, very little indication as to improvement was obtained from this exercise.

MAPPING OF SUCROSE

A mapping of the relevant part of the conformational space of sucrose was then undertaken, inspired by the dedicated work of French;[22,23] it was done with the program **MoleCast** used in earlier studies.[7]

The map is shown in Figure 2, and some conformational details are given in Table 7. A few notes on the technical details may be relevant. The map was made by dragging the two central torsions through the interesting ranges, starting near a minimum. This is the reason why the top and the bottom of the map do not fit properly, and the procedure runs contrary to what we usually recommend.[7] It was necessary in this case, as the extreme flexibility of the side groups, coupled with the pseudorotation of the furanose ring, made the preferred procedure of minimizing in each point of the grid independently, starting from the same conformation, impossible. A grid of 30° was used, and in each grid point minimization was rather stringent, as it was carried through to an energy gradient norm of 10^{-4} $kJmol^{-1}pm^{-1}$. These data are the basis of the map shown. In addition, a mapping over the same grid, and over this grid moved by (15°,15°) was carried out with the "proper" procedure. A multitude of point sets were identified because of trapping in high-lying minima. Accordingly, no map could be made. The crudeness of the map shown in Fig. 3 can be seen in the location of the three lowest minima. On the whole, the map conforms to earlier and more elaborate mappings[22,24,25] as three minima are identified, and the crystal

Table 5. 11 glucose conformers in the gas phase

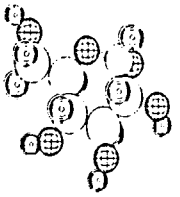
Conf. no.	PEF95SAC ΔE kcalmol^{-1} 0 K	*ΔG* kcalmol^{-1} *298 K*	Boltzmann distribution	MM3[20] ΔE kcalmol^{-1} 0 K	*ΔG* kcalmol^{-1} *298 K*	Boltzmann distribution	*ab initio*[20] comp. ΔE kcalmol^{-1} 0 K	*comp. ΔG* kcalmol^{-1} *298 K*	Boltzmann distribution
1	5.21	*4.88*	0.00	3.54	*-0.5*	0.10	3.8	*3.1*	0.00
2	4.47	*4.05*	0.00	2.30	*-1.0*	0.13	4.1	*3.3*	0.00
3	4.19	*3.93*	0.00	0.00	*-0.8*	0.12	1.1	*0.4*	0.13
4	3.30	*3.03*	0.00	2.41			1.9	*1.3*	0.03
5	3.30	*3.03*	0.00	0.64	*-0.7*	0.11	0.9	*0.4*	0.14
6	4.48	*4.31*	0.00	0.11	*-0.3*	0.10	1.3	*1.0*	0.05
7	1.39	*1.44*	0.03	0.53	*-0.1*	0.09	0.1	*0.0*	0.25
8	0.00	*0.00*	0.36	1.26	*0.0*	0.09	0.0	*0.0*	0.25
9	1.71	*1.86*	0.02	0.61	*0.5*	0.07	0.2	*0.5*	0.12
10	0.23	*0.14*	0.29	2.99	*0.0*	0.09	1.3	*1.2*	0.03
11	0.25	*0.12*	0.30	2.19	*-0.4*	0.10	3.1	*2.8*	0.00
α : β			1.00 : 0.00			0.44 : 0.56			0.65 : 0.35

Table 6. Glucose in the crystal

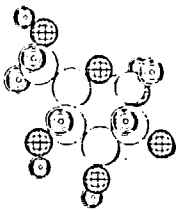
	neutron crystal	PEF95SAC crystal		PEF95SAC conf. 7	MM3 conf. 7	*ab initio* conf. 7
C1-C2	1.534	1.521		1.521	1.523	1.529
C2-C3	1.525	1.536		1.536	1.518	1.524
C3-C4	1.520	1.538		1.535	1.520	1.518
C4-C5	1.529	1.533		1.535	1.524	1.523
C5-C6	1.511	1.524		1.529	1.525	1.519
C1-O5	1.427	1.409		1.408	1.416	1.412
C1-O1	1.391	1.397		1.396	1.429	1.414
C2-O2	1.417	1.428		1.428	1.434	1.422
C3-O3	1.416	1.422		1.422	1.433	1.422
C4-O4	1.426	1.422		1.421	1.432	1.418
C5-O5	1.428	1.426		1.428	1.442	1.446
C6-O6	1.414	1.420		1.420	1.431	1.416
mean error		*-0.004*		*-0.003*	*0.005*	*0.002*
mean abs error		*0.006*		*0.008*	*0.011*	*0.008*
C5-O5-C1	113.8	113.5		113.8	115.2	113.9
O5-C1-O1	111.5	107.0		107.7	108.4	113.2
O5-C1-C2-C3	54.1	56.3		56.2	53.8	53.8
C1-C2-C3-C4	-51.3	-54.0		-53.0	-55.6	-54.0
C2-C3-C4-C5	53.3	54.6		52.8	58.0	56.5
C3-C4-C5-O5	-57.5	-56.4		-55.0	-59.0	-57.9
C4-C5-O5-C1	62.2	61.3		61.3	59.7	60.1
C5-O5-C1-C2	-60.9	-61.7		-62.2	-56.6	-57.9
mean error		*0.0*		*-0.5*	*-0.2*	*0.3*
mean abs error		*1.5*		*1.5*	*2.8*	*1.7*
a	10.3662	10.2798	0.8 %			
b	14.8506	15.2977	3.0 %			
c	4.9753	4.8527	2.5 %			
Vol	765.919	763.123	0.4 %			

sucrose conformation is placed in the most prominent minimum region. Other minima than the ones shown were found, up to 150 kJmol^{-1}.

An examination of some details of the minimum conformations is interesting, see Table 7. First, three minima were identified in the three minimal regions. Their coordinates



from Brown and Levy[21] (neutron diffraction)



by the Consistent Force Field using PEF95SAC

Figure 1. Glucose in the crystal

were taken to another machine and run with CFF, resulting in slightly changed conformations, and an interchange on the energy scale. This may be due to -OH groups having turned. When the coordinates from this calculation were taken back to Molecast, a third set resulted, of which one, no. 3, was identical to no. 3 in the first set; nos. 1 and 2 had changed slightly. The difference between the Consistent Force Field and the MoleCast runs reflect the combined inaccuracies, mostly due to round-off errors, between two different programs using different energy units, written in different languages, and running on different machines.

The crystal structure was reproduced rather neatly when subjected to minimization utilizing convergent lattice summation, see Table 7 and Figure 2. The high relative energy of 26 $kJmol^{-1}$ reflects that some extra molecular strain must be accepted in the crystal towards a gain in lattice energy of 199.80 $kJmol^{-1}$. When the crystal conformation was minimized as a gaseous molecule it converged to near minimum 1.

It would seem that we have reached the limit of what is meaningful doing with static minimization; a partial conclusion of this exercise is then that in the mapping of the

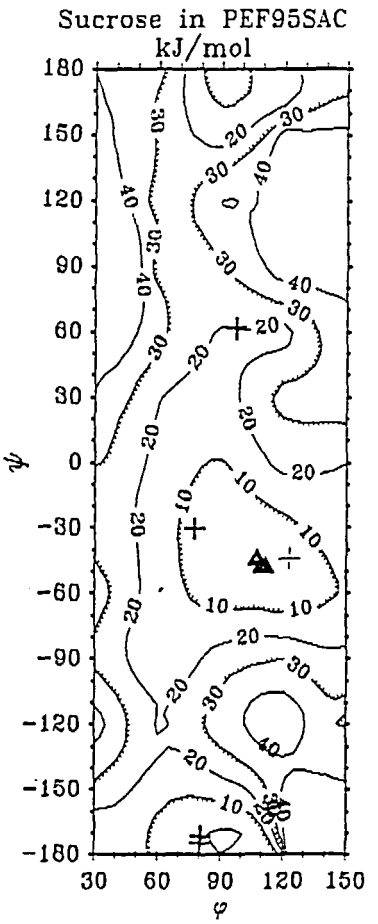


Figure 2. *Mapping of sucrose*

conformational space of extremely flexible molecules, molecular dynamics runs are necessary. As an example, the reader is referred to the recent work of Engelsen and Pérez[25] who carried out an MD modeling of sucrose in water using CHARMM,[26] with Brady's[27] and Jorgensen's[28] force fields. No static simulation, like the present, or those of French,[22,23] can match a proper dynamic simulation using a good force field. That force field may well be CHARMM,[26] as just shown,[25] or it may be MM3.[24]

A static simulation which does not reproduce experimentally known structural details does not necessarily show that the force field employed is inadequate. Accordingly, there is hardly any reason for doing quantum corrections on a map gotten with molecular statics methods.[23]

Table 7. Sucrose: Minima in PEF95SAC. E in kJmol^{-1}

No	E	ΔE	φ	ψ	ω_g	ω_t	χ_t	C2C3	C3C4	C4C5	C5O5	O5C2
Molecast:												
1	-17783.19	0.00	77	-31	-65	64	-176	35	-40	35	-14	-14
2	-17773.69	9.50	80	-171	-61	63	-62	-43	46	-36	11	20
3	-17763.11	20.08	94	62	-62	64	-177	37	-40	33	-10	-17
CFF:												
1'	-17667.67	4.90	80	-31	-66	64	-175	35	-41	36	-16	-12
2'	-17672.57	0.00	81	-173	-64	63	-64	-44	46	-36	9	22
3'	-17651.34	21.23	92	66	-64	65	-176	38	-41	34	-10	-18
Molecast:												
1''	-17782.03	1.16	103	-43	-63	-59	-176	-39	46	-41	188	13
2''	-17775.45	7.74	80	-174	-62	63	-62	-44	46	-36	10	21
3''	-17763.11	20.08	94	62	-62	64	-177	37	-40	33	-10	-17
CFF:												
crystal min. as gas	-17672.34	0.23	110	-47	-62	-62	-175	-40	45	-39	15	16
crystal min. as cryst.	-17646.90	25.67	116	-49	-64	-64	-177	-40	44	-37	13	17
crystal exp.			108	-45	-56	-70	+171	-31	35	-27	8	15

unit cell	exp[21]	min	error, %
a	10.8648	10.4563	3.8
b	8.7028	9.2341	-6.1
c	7.7578	7.5052	3.3
β	102.956	107.250	-4.1
V	714.859	692.071	3.2

This corroborates my opinion that the clue to the development of still more accurate and reliable force fields for saccharides is to be found in optimization on a much larger selection of crystalline alcohols and saccharides rather than trying to reproduce even large *ab initio* calculations on molecules in the gas phase.

THE FUTURE APPROACH

Many similar analyses of calculated structures using **PEF95SAC** were made in order to detect directions of improvement. Rather than just refining on parameters for H-on-O, it is now decided to embark on an entire new series of optimization along the following lines:

(1) We shall stick to Morse functions, but the values of the dissociation energy of a bond *may* be based on *ab initio* calculations[29] and not on thermochemical measurements. (2) Charge assignments of individual atoms will still be based on one charge parameter for each atom type and the unfortunately rather complicated algorithm, but the reference charge to be approximated will be the result of the CHELPG[30] modeling or a similar method based on an analysis of the electrostatic potential.[31] *Non*-bonded interactions will be treated with Lennard-Jones 9-6 instead of 12-6 potentials which will make the atoms softer and should have a beneficial effect on the description of hydrogen bonding.

The optimization data set is being enhanced with a few more alkanes and with many alcohol crystals. The strategy of optimization will be the same as for **PEF95SAC**. The working name for the new parameter set is **PEF98SAC**.[32] So far, the new potential energy function has proceeded to a neat reproduction of charges, selection of dissociation energies for the Morse functions, and the preparation of the increased data set for optimization.

POINTS FOR DISCUSSION

I want to raise some questions in respect of molecular modeling, in the hope that they will provoke discussion.

One is the choice of r_e *vs* r_z in the modeling of gas phase structure. My question is whether we are now going to have so many reliable equilibrium structures from *ab initio* calculations that we should use these rather than the r_z structure derived from electron diffraction. How will the two different crystal structures (x-ray and neutron) fit in ? - The neutron structure at low temperature is supposed to correspond to the r_e.[33]

Another question is whether it is now time to stop comparing potential energies ΔV, or at least to supplement them with comparisons of free enthalpies ΔG. This question is closely related to the problem of approximations in statistical mechanics. Almost all authors use the same approximations, in short: harmonic motion with small amplitudes and in the gas phase stiff rotors. This means that we do very well with even rather large molecules provided they are reasonably stiff, whereas thermodynamic functions of even small but very flexible molecules are badly represented. It is a major programming effort to do better than the traditional approximations.

A third question: How accurately do we want to calculate vibrational spectra ? - An accuracy corresponding to the experimental uncertainty is ridiculous, if only due to imper-

fections in assigning the spectra, and it will cost so many terms in the potential energy functions that optimization on a rational basis is impossible. My choice is to strive to get zero *average* errors for spectrally isolated regions, such as O-H stretching and C-H stretching and the mid-IR, and to try to obtain good individual accuracy in the low frequencies, because they contribute most to the Einstein functions of the statistical-mechanical calculations. Examples of results from these efforts can be seen in the papers on ethers[12] (Figure 4 and Table 7), and on alcohols[9] (Table 4). A mere reproduction of vibrational spectra has no purpose, as it in itself cannot bring about any deeper understanding of atomic interactions.

A fourth question: Which NMR properties should we try to calculate? - This field is constantly undergoing rapid development, and maybe it is timely to look into the models behind evaluation of NOE experiments (the pure r^{-6} term) and of spin couplings (the Karplus equation and its modifications).

Finally: Which other properties should we try to calculate? - In our group it has of late become possible to calculate such thermodynamic properties as phase equilibria in one- and two-component systems[34-37] by other models with parameters derived from Consistent Force Field parameters.

A CAVEAT

Praeterea censeo: ***No force field should be used with confidence outside the scope for which it was developed, and with caution when used with another program than that employed in its development.*** If you violate these rules, you have only yourself to blame for your possible failure.

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REFERENCES AND NOTES

1. Presented at the *XIXth International Carbohydrate Symposium*, San Diego, California, USA, Aug 9-14, 1998.
2. Email: kjr@kemi.dtu.dk .

3. S. Lifson and A. Warshel, *J. Chem. Phys.*, **49**, 5116 (1968).
4. S.R. Niketić and K. Rasmussen, *The Consistent Force Field: A Documentation. Lecture Notes in Chemistry*, Vol. **3**, Springer-Verlag, Berlin, 1977.
5. K. Rasmussen, *THEOCHEM*, **395**, 91 (1997).
6. K. Rasmussen, *Potential Energy Functions in Conformational Analysis. Lecture Notes in Chemistry*, Vol. **37**, Springer-Verlag, Berlin, 1985.
7. S.B. Engelsen and K. Rasmussen, *Int. J. Biol. Macromol.*, **15**, 56 (1993).
8. S.B. Engelsen, J. Fabricius and K. Rasmussen, *Acta Chem. Scand.*, **48**, 548 (1994).
9. J. Fabricius, S. B. Engelsen and K. Rasmussen, *J. Carbohydr. Chem.*, **16**, 751 (1997).
10. K. Rasmussen, S.B. Engelsen, J. Fabricius and B. Rasmussen, *NATO ASI Series C*, **406**, 381-419 (1993).
11. C.A. Coulson and U. Danielsson, *Arkiv för Fysik*, **8**, 239, 245 (1954).
12. J. Fabricius, S.B. Engelsen and K. Rasmussen, *New J. Chem.*, **19**, 1123 (1995).
13. D. C. Rohrer, A. Sarko, T. L. Bluhm and Y. N. Lee, *Acta Crystallogr.*, **B36**, 650 (1980).
14. I. Tvaroska and J. P. Carver, *J. Phys. Chem.*, **98**, 9477 (1994).
15. P.-G. Jönsson, *Acta Crystallogr.*, **B32**, 232 (1976).
16. H. S. Kim and G. A. Jeffrey, *Acta Crystallogr.*, **B25**, 2607 (1969).
17. R. M. Lees and J. G. Baker, *J. Chem. Phys.*, **48**, 5299 (1968).
18. R. K. Kakar and P. J. Seibt, *J. Chem. Phys.*, **57**, 4060 (1972).
19. S. Kondo and E. Hirota, *J. Mol. Spectrosc.*, **34**, 97 (1970).
20. S.E. Barrows, J.W. Storer, C.J. Cramer, A.D. French and D.G. Truhlar, *J. Comput. Chem.*, **19**, 1111 (1998).
21. G. M. Brown and H. A. Levy, *Acta Cryst.*, **B29**, 790 (1973).
22. A. D. French and M. K. Dowd, *J. Mol. Struct. (Theochem)*, **286**, 183 (1993).
23. A. D. French, A.-M. Kelterer, M. K. Dowd and G. P. Johnson, *XIX International Carbohydrate Symposium*; San Diego, California, USA, Aug 9-14, 1998, *Abstracts of Papers*, Abstract AO 001.
24. F. Casset, A. Imberty, C. H. du Penhoat, J. Koca and S. Pérez, *J. Mol. Struct. (Theochem)*, **395-396**, 211 (1997).
25. S. B. Engelsen and S. Pérez, *J. Mol. Graphics Model.*, **15**, 122 (1997).
26. C. L. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan and M. Karplus, *J. Comput. Chem.*, **4**, 187 (1983).
27. S. N. Ha, A. Giammona, M. Field and J. W. Brady, *Carbohydr. Res.*, **180**, 207 (1988).
28. W. L. Jorgensen, *J. Am. Chem. Soc.*, **103**, 335 (1981).
29. S. Fliszár, *Atoms, Chemical Bonds and Bond Dissociation Energies. Lecture Notes in Chemistry*, Vol. **63**, Springer-Verlag, Berlin, 1994.
30. C. M. Breneman and K. B. Wiberg, *J. Comput. Chem.*, **11**, 361 (1990).
31. E. Sigfridsson and U. Ryde, *J. Comput. Chem.*, **19**, 377 (1998).
32. K. Rasmussen, *to be published.*
33. K. Kuchitsu, *private communication.*
34. S. Ó. Jónsdóttir, K. Rasmussen and A. Fredenslund, *Fluid Phase Equilib.*, **100**, 121 (1994).

35. S. Ó. Jónsdóttir, K. Rasmussen, P. Rasmussen and W. J. Welsh, *Comput. and Theor. Polymer Sci.*, **8**, 75 (1998).
36. S. Ó. Jónsdóttir, W. J. Welsh, K. Rasmussen and R. A. Klein, *New J. Chem.* 153 (1999).
37. S. Ó. Jónsdóttir and P. Rasmussen, *Fluid Phase Equilib.*, (1999) *in press.*