A computationally efficient alternative to the Buckingham potential for molecular mechanics calculations

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Summary

This paper describes a (6-8) variant of the Lennard-Jones (6-12) potential, for computing the energy of non-bonded interactions in molecular mechanics calculations, which combines the overall precision of the Buckingham (6-exp) potential with the computational efficiency of the standard Lennard-Jones (6-12) potential. There is also a note on the radius of convergence of the full matrix Newton–Raphson optimization procedure.

Following on from various updates of our molecular mechanics program [1,2] (VULCAN), we are about to embark on a major programme of precision force-field development. It seemed natural therefore to use our previously developed WBFF [3] for non-conjugated hydrocarbons as a starting point for this work.

When the WBFF was constructed, we experimented with both the Lennard-Jones (Eq. 1) and Buckingham (Eq. 2) potentials as a basis for describing the variation of non-bonded potential energy ($V(r)$) as a function of interatomic distance (r). The only alternative to Eqs. 1 and 2 that has seen widespread use in molecular mechanics calculations is the 6-9 potential (Eq. 3) employed by the Lifson group [4].

$$V(r) = \varepsilon\left[\left(\frac{r_m}{r}\right)^{12} - 2\left(\frac{r_m}{r}\right)^{6}\right] \qquad (1)$$

$$V(r) = \varepsilon\left[\exp\left(12\left\{1-\frac{r}{r_m}\right\}\right) - 2\left(\frac{r_m}{r}\right)^{6}\right] \qquad (2)$$

$$V(r) = \varepsilon\left[2\left(\frac{r_m}{r}\right)^{9} - 3\left(\frac{r_m}{r}\right)^{6}\right] \qquad (3)$$

We found, in common with other force-field developers [5,6], that the Buckingham potential yielded the best

overall results and so we incorporated it into the WBFF. At that time, we were not concerned with molecular mechanics calculations on either large molecules or large assemblies of small molecules, mainly due to limitations on available computing power. This situation has now changed, and the computational expense of evaluating the exponential term in the Buckingham potential, over millions of non-bonded interactions, would prove to be a major embarrassment in terms of overall program run time. In fact, the Buckingham potential takes about 4 times longer to compute than the Lennard-Jones potential; and as the evaluation of the non-bonded potential and its derivatives is the most time-consuming part of a molecular mechanics calculation, this factor of 4 feeds through fairly directly into the overall program run time.

A common solution to this difficulty involves using the computationally efficient Lennard-Jones potential instead of the Buckingham potential, and accepting the somewhat poorer overall accuracy that this choice entails. The 6-9 potential is not a contender because it uses an odd power of the interatomic distance, which entails the use of the computationally expensive (but not as expensive as the exponential) square-root function in evaluating the potential, as well as the first and second derivatives $\partial V(r)/\partial x_i$ and $\partial^2 V(r)/\partial x_i \partial x_j$ of the non-bonded energy with respect to the Cartesian coordinates.

Ideally, what is required is a potential function which will closely reproduce the results of the classical Bucking-
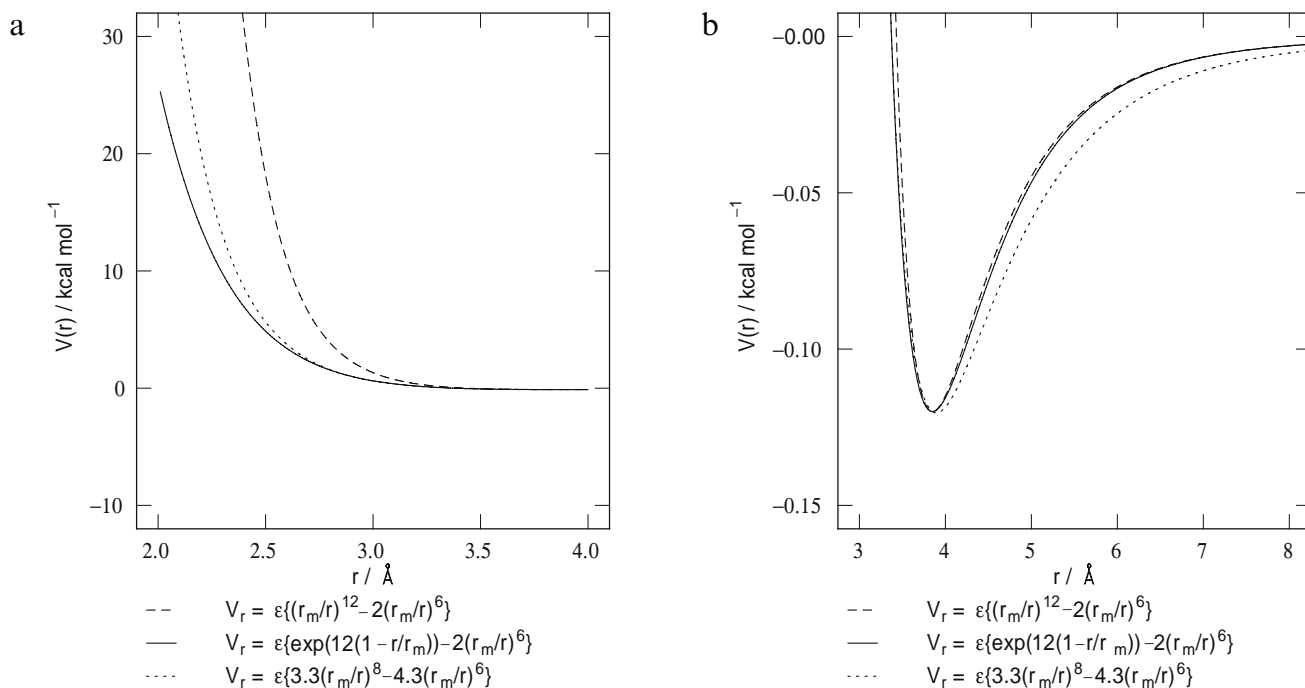
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Fig. 1. The 6-12, 6-exp and 6-8 potential energies, $V(r)$, plotted as a function of the interatomic distance, r, for a WBFF [3] $Csp^3\cdots Csp^3$ non-bonded interaction, showing (a) the repulsive portion of the curves and (b) detail around the minima.

ham potential (Eq. 2) but with the computational efficiency of the Lennard-Jones potential (Eq. 1). Such a potential would allow reuse of the r_m and values determined for the Buckingham potential in a computationally efficient potential with only modest reparametrization of the force field. Obviously such a potential function would be of use not only with force fields which currently use a Buckingham potential (it would enable the calculations to proceed more rapidly) but with new force fields and those force fields which currently use the 6-12 Lennard-Jones potential. In the latter case, a fair amount of reparametrization might be necessary, but there would be a useful gain in overall accuracy of prediction for structures and energies, particularly with strained compounds.

The graphs in Fig. 1, showing the variation of potential energy with interatomic distance for both the Buckingham and Lennard-Jones potentials using the WBFF values of r_m (3.85 Å) and ε (0.12) for a $Csp^3\cdots Csp^3$ interaction as an example, illustrate just how different are the energies calculated from these two functions using the same values of r_m and ε. When the interatomic separation is greater than or equal to r_m, where the attractive term $-2(r_m/r)^6$ predominates, the energies resulting from the two potential functions are indeed essentially equal; but when r is less than r_m, and the repulsive term dominates, the two functions behave quite differently. The $(r_m/r)^{12}$ term of the Lennard-Jones potential behaves as a veritable 'brick wall' function and the potential energy increases extremely sharply with decreasing r, whilst the exponential term of the Buckingham potential leads to a much gentler

increase in energy. Unfortunately, $Csp^3\cdots Csp^3$ interatomic distances from r_m down to about 1.8 Å less than r_m are frequently encountered in strained and not-so-strained hydrocarbons, so that the forms of the Buckingham and Lennard-Jones potentials given above are not interchangeable, at least in a molecular mechanics context, without extensive reparametrization of the force field. Similar considerations apply to non-bonded interactions between other types of atom pair (e.g. $H\cdots H$, $Csp^2\cdots H$, etc.). It has been noted before [4,5,6] that the 6-12 variant of the Lennard-Jones potential is too 'hard' a potential for accurate molecular mechanics calculations on strained as well as unstrained molecules; the fact that it is widely used today is a reflection of its computational efficiency, and the large number of calculations currently performed on relatively unstrained proteins.

As the whole idea of using the WBFF was to avoid an extensive reparametrization of the force field when switching to a new non-bonded potential, we sought a potential function, involving only even powers of r, which would closely emulate the Buckingham potential over the key distances of interest. In the event it transpired that the 6-8 potential of Eq. 4 came fairly close.

$$V(r) = \varepsilon\left[3\left(\frac{r_m}{r}\right)^8 - 4\left(\frac{r_m}{r}\right)^6\right] \qquad (4)$$

It could be improved a little by using a least-squares optimization procedure to give the expression shown in Eq. 5.

$$V(r) = \varepsilon \left[3.3 \left(\frac{r_m}{r} \right)^8 - 4.3 \left(\frac{r_m}{r} \right)^6 \right] \qquad (5)$$

This gives essentially the same potential energy as the Buckingham equation from $r = 2.6$ Å, through r_m, out to the limit of applicability. This is illustrated in Fig. 1. Notice that Eq. 5 does not have the property, as do Eqs. 1–4, that $\partial V(r)/\partial r = 0$ at $r = r_m$. However, this is of little importance, other than the fact that r_m and ε no longer precisely represent the equilibrium interatomic distance and well depth, because the primary objective is to reuse existing values of r_m and ε. The difference is more philosophical than practical mainly because most computer programs use Eq. 5 recast in the form of Eq. 6, which 'hides' r_m and ε, and also because any differences are small; for example the minimum in Eq. 4 occurs when $r = r_m$ and in Eq. 5 when $r = 1.01 r_m$. There is also some precedent in the molecular mechanics literature for this approach, as Allinger's [7] widely respected MM2 force field uses a 'non-standard' version of the Buckingham potential. However, for new force fields where it is desired to use the 6-8 potential with r_m and ε explicitly, it might be more advisable to use Eq. 4.

Another small difference between using Eq. 2 and Eq. 5 lies in the fact that at long ranges, where the attractive term dominates, the calculated energies will differ by a factor of a little over 2. This is not important as far as reproducing WBFF results is concerned because all of the force-field optimization was done using small molecules without any long-range non-bonded interactions. A fur-

ther factor which reduces the importance of long-range differences is that even calculations on large molecules usually operate with a non-bonded distance cutoff of between 4 and 8 Å where the difference factor is reduced to between 1.02 and 1.7. In any event, the long-range energies under consideration are very small, of the order of 10^{-3} kcal mol^{-1}. However, this may involve some re-parametrization when we come to consider large molecules, but that would still be the case had we continued to use Eq. 2. A similar argument applies to Lifson's 6-9 potential, as used in the CFF, but there were no problems dealing with long-range non-bonded interactions in the crystal structures considered [4].

It seems rather surprising to us, given the success of the Buckingham potential, that the 6-8 form of the Lennard-Jones potential does not appear to have been used previously for molecular mechanics (or molecular dynamics) calculations. The 6-9 potential used so successfully by the Lifson group produces very similar results to our 6-8 potential, but without the associated computational efficiency. It is interesting to note that Warshel and Lifson [4] investigated values of 8, 9, 10 and 12 for the exponent of the repulsive term in the Lennard-Jones potential, as well as the 6-exp potential. They found 9 to be the optimum choice for the repulsive exponent in the Lennard-Jones potential, although presenting little or no evidence against 8 or 10 (although the latter is probably too hard), whilst similar accuracy could be obtained with the 6-exp potential. Warshel and Lifson preferred to use the 6-9 potential because of its computational efficiency com-
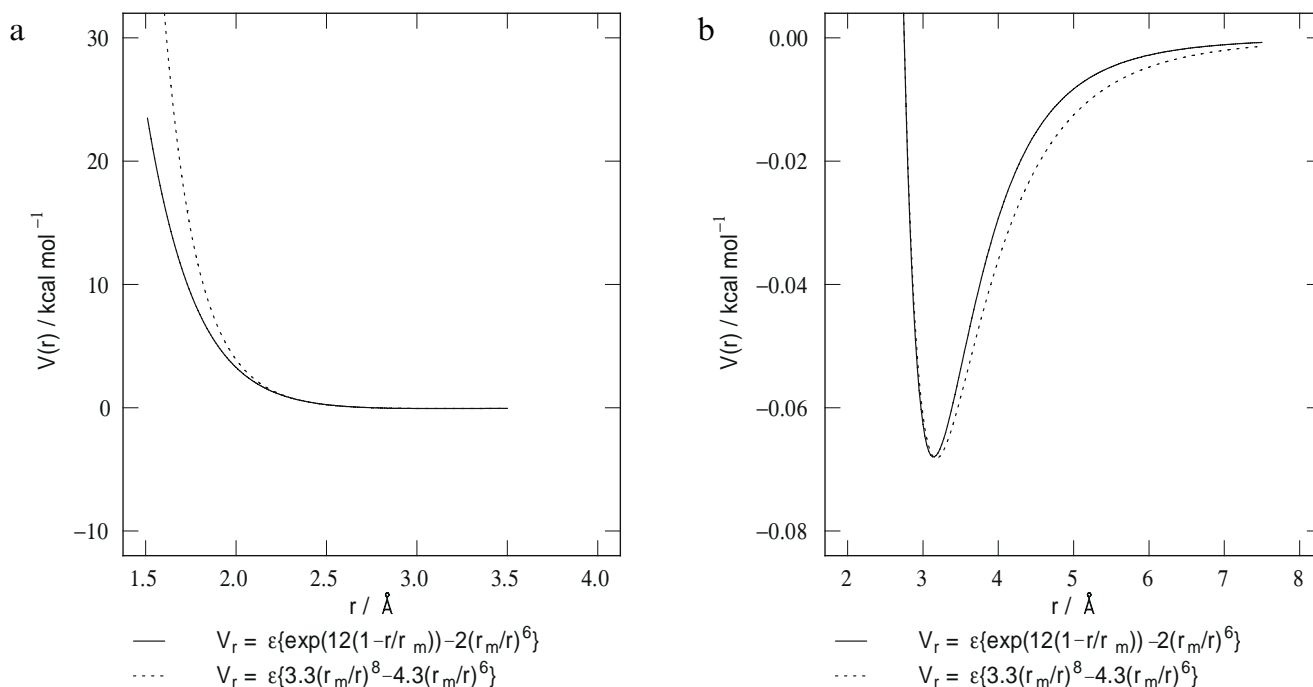

Fig. 2. The 6-exp and 6-8 potential energies, V(r), plotted as a function of the interatomic distance, r, for a WBFF Namide···Osp^2 non-bonded interaction, showing (a) the repulsive portion of the curves and (b) detail around the minima.

TABLE 1

DIFFERENCES BETWEEN CALCULATED AND OBSERVED HEATS OF FORMATION FOR A RANGE OF ALKANES AND ALKENES, ΔH_f° (gas, 25 °C)[a]

Compound	H_f°(calc) – H_f°(obs) (kcal mol^{-1})		
	WBFF	WFF97(O)	WFF97(R)
Ethylene	0.20	0.19	–0.02
Propene	0.03	0.01	–0.09
But-1-ene	0.10	0.08	–0.11
cis-But-2-ene	0.15	0.07	0.06
trans-But-2-ene	–0.10	–0.15	–0.16
Isobutene	0.54	0.50	0.43
2-Methylbut-1-ene	0.29	0.18	0.03
3-Methylbut-1-ene	0.42	0.35	0.14
2-Methylbut-2-ene	0.14	0.15	0.18
2,3-Dimethylbut-1-ene	0.47	0.51	0.43
2,3-Dimethylbut-2-ene	–0.14	–0.30	0.08
3,3-Dimethylbut-1-ene	0.01	–0.08	1.09
Pent-1-ene	0.25	0.17	–0.10
cis-Pent-2-ene	0.19	0.08	–0.01
trans-Pent-2-ene	–0.16	–0.23	–0.32
2-Methylpent-2-ene	–0.04	–0.11	–0.03
3-Methyl-trans-pent-2-ene	0.28	0.27	0.22
3-Methyl-cis-pent-2-ene	–0.27	–0.42	–0.47
4-Methyl-trans-pent-2-ene	0.55	0.42	0.31
4-Methyl-cis-pent-2-ene	0.88	–0.04	–0.15
4,4-Dimethylpent-1-ene	–0.99	–1.04	–0.05
2,4,4-Trimethylpent-1-ene	–1.60	–2.16	–1.04
Penta-1,4-diene	–0.10	–0.17	–0.22
trans-Hex-2-ene	–0.13	–0.27	–0.43
cis-Hex-2-ene	0.72	0.52	0.36
Hexa-1,5-diene	0.14	–0.01	–0.13
Methylcyclopentane	–0.16	–0.33	–0.75
Cyclopentene	0.53	0.45	0.46
1-Methylcyclopentene	0.48	0.28	0.32
3-Methylcyclopentene	–0.49	–0.59	–0.61
Cyclohexane	1.23	1.03	0.56
Methylcyclohexane	1.37	1.22	0.63
Cyclohexene	–0.27	–0.41	–0.49
1-Methylcyclohexene	0.02	–0.19	–0.24
Cyclohexa-1,4-diene	0.13	0.14	0.46
Average |H_f°(calc) – H_f°(obs)|	0.36	0.37	0.32

[a] Force fields used: the original WBFF [3] force field, the WFF97 force field with the original group enthalpy increments (WFF97(O)), and the WFF97 force field with reoptimized group enthalpy increments (WFF97(R)); WFF97 uses the 6-8 Lennard-Jones potential with no force-field reoptimization.

pared to the 6-exp potential. The 6-12 potential was found to be unsatisfactory because it could not simultaneously reproduce energetic quantities which depended on intermolecular (e.g. enthalpies of sublimation) and intramolecular (e.g. gas phase heats of formation) interactions.

The V(r) for the 6-8 non-bonded potential function can be calculated in the same number of steps ($r^{-2} * r^{-2} = r^{-4}$, $r^{-2} * r^{-4} = r^{-6}$, $r^{-2} * r^{-6} = r^{-8}$) as the V(r) for the 6-12 potential ($r^{-2} * r^{-2} = r^{-4}$, $r^{-2} * r^{-4} = r^{-6}$, $r^{-6} * r^{-6} = r^{-12}$), provided the potential functions are expressed in the form of Eq. 6. This means that Eqs. 4 and 5 have the same computa-

tional efficiency gain over Eq. 2 as does Eq. 1. If V(r) is expressed as a function of even powers of r, as in the 6-8 potential, then both the first and second derivatives, $\partial V(r)/\partial x_i$ and $\partial^2 V(r)/\partial x_i \partial x_j$, of the non-bonded energy with respect to the Cartesian coordinates, used by most molecular dynamics and molecular mechanics programs, also contain only even powers of r. This again removes the need for the computationally expensive square-root function required in order to evaluate odd powers of r. In fact, these derivatives can be calculated with one fewer floating point multiplication per non-bonded distance with a 6-8 rather than a 6-12 potential.

$$V(r) = \frac{A}{r^n} - \frac{B}{r^6} \qquad (6)$$

Notice that although we have used $Csp^3 \cdots Csp^3$ non-bonded interactions as an example, the previous discussion applies equally well to all types of non-bonded interaction, both for hydrocarbons (e.g. to $Csp^2 \cdots H$, $Csp^2 \cdots Csp^2$, $Csp^2 \cdots Csp^3$, $Csp^3 \cdots H$ and $Csp^3 \cdots Csp^3$) and in general. As the functional form of a non-bonded potential determines the overall shape of its V(r) as a function of the r_m curve, Eqs. 2 and 5 will always produce closely similar results, over all values of r_m and ε, provided identical r_m and ε values are given to each potential function. By way of example, Fig. 2 shows a comparison of the 6-8

TABLE 2

DIFFERENCES BETWEEN CALCULATED AND OBSERVED HEATS OF FORMATION FOR SOME ALDEHYDES AND KETONES, H_f° (gas, 25 °C)[a]

Compound	H_f°(calc) – H_f°(obs) (kcal mol^{-1})	
	WBFF	WFF97(R)
Ethanal	0.35	–0.41
Propanal	0.39	0.01
2-Methylpropanal	1.33	1.04
Butanal	–0.22	–0.67
Propanone	–0.07	–0.36
Butanone	0.25	0.42
Methylbutanone	–0.68	–1.16
Dimethylbutanone	–1.41	–0.25
2-Pentanone	0.01	0.06
3-Methylpentanone	0.04	0.03
4-Methylpentanone	0.72	0.48
3,3-Dimethylpentanone	–1.37	–0.11
4,4-Dimethylpentanone	–0.28	1.45
3,3,4-Trimethylpentanone	–1.27	0.29
3-Pentanone	0.05	0.68
Methyl-3-pentanone	0.04	0.62
Cyclopentanone	–0.01	–1.03
Cyclohexanone	–1.09	–1.71
Average |H_f°(calc) – H_f°(obs)|	0.53	0.59

[a] Force fields used: the original WBFF force field and the WFF97 force field with reoptimized group enthalpy increments (WFF97(R)); WFF97 uses the 6-8 Lennard-Jones potential with no force-field reoptimization.

and 6-exp non-bonded potentials for Namide$\cdots$Osp^2 ($r_m =$ 3.14, $\varepsilon = 0.068$).

It is all very well to match potential functions for one or more atom pair types, as described above, but the acid test is to see how the new potential function behaves in real molecular mechanics calculations.

We reminimized the steric energy and recalculated the heats of formation of the first 35 compounds in Table 2 of the WBFF [3] paper, using all the original force-field parameters and group enthalpy increments but using Eq. 5 rather than Eq. 2 to calculate the non-bonded energy and associated first and second derivatives (i.e. for all of Csp$^2\cdots$H, Csp$^2\cdots$Csp^2, Csp$^2\cdots$Csp^3, Csp$^3\cdots$H and Csp$^3\cdots$Csp^3). Subsequently, the group enthalpy increments were reoptimized by least-squares fitting to produce optimum values for the calculated heats of formation. The results of these calculations are shown in Table 1, which compares the observed heats of formation with those calculated by WBFF and the variants described in the previous sentence. The compounds used are a good mixture of unstrained, strained and hard to minimize alkanes and alkenes. Heats of formation are used as the basis for comparison because they are more difficult to calculate accurately than structural parameters.

In order to properly characterize all the minima of the 35 hydrocarbons mentioned above, we used the full matrix Newton–Raphson (FMNR) minimizer from VULCAN, essential if the torsion angles are to be really optimally adjusted during minimization. During this work we discovered a long-standing, but minor, bug in our FMNR routine which did not affect the calculated structures, energies, gradients or curvatures, but did lead to a moderate reduction in the radius of convergence. As a consequence, we may have misled others as to the necessity for preminimization with steepest descents or block diagonal Newton–Raphson procedures when using FMNR [8]. It is now our experience (having corrected the bug) that most unstrained structural models, built with a molecular graphics program, can be minimized with FMNR directly. Preminimization only appears to be necessary if the initial rms gradient is much greater than 10 kcal mol^{-1} Å^{-2}, which is often the case when building models of complex polycyclic systems. It is obvious from Table 1 that we have pretty much succeeded in our objective of reusing earlier force field parameters with a new, and computationally more efficient, functional form of the force field. The raw, unoptimized WFF97 force-field systematically underestimates heats of formation to a small extent and, as a consequence, gives marginally poorer results than the earlier (highly optimized) WBFF. However, when the group enthalpy increments are recalculated WFF97 gives markedly superior results to WBFF. It may be possible to improve on these figures somewhat by a small amount of force-field reoptimization. However, bearing in mind that comparable error estimates for MM3 [5] are a little larger than ours, and that the experimental estimated standard deviations for gas phase heats of formation are usually around ±0.5 kcal mol^{-1}, this may not be a worthwhile exercise.

In order to demonstrate that the new potential is not only applicable to hydrocarbons, we performed another set of heat of formation calculations on a small range of aldehydes and ketones, again using Eq. 5 for all the non-bonded interaction energies and associated first and second derivatives. The results are shown in Table 2 and it is once again obvious that the 6-8 potential function performs as well as the 6-exp function, *without any force-field reoptimization*. Global trial and error adjustments of the constants 3.3 and 4.3 from Eq. 5, followed by recalculation of the heats of formation shown in Tables 1 and 2, failed to yield any overall improvement, and so the original values of the constants were allowed to stand. Overall, Eq. 5 has been tested for Csp$^2\cdots$H, Csp$^2\cdots$Csp^2, Csp$^2\cdots$Csp^3, Csp$^2\cdots$Osp^2, Csp$^3\cdots$H, Csp$^3\cdots$Csp^3, Csp$^3\cdots$Osp^2, Osp$^2\cdots$H and Osp$^2\cdots$Osp^2 interactions, but it is obvious from the previous discussion that it will perform equally well over the full range of interactions in any force field that uses it.

We have developed a 6-8 non-bonded potential which gives sufficiently similar calculated structures and energies to the (6-exp) Buckingham potential previously employed for molecular mechanics calculations that only very minor force-field reparametrization is necessary when changing from the latter to the former potential. The new potential seems to have all the advantages of the 6-exp potential together with the computational efficiency of the 6-12 potential.

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