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Excess Free Energy of Liquids from Molecular Dynamics Simulations. Application to Water Models[†]

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Abstract: Thermodynamic integration and perturbation methods have been applied to calculate the excess free energy, ΔA_e, of several models of liquid water. The results for the SPC and TIP models agree well with the experimental excess free energy of liquid water computed from the vapor pressure. The precision of the calculation, in which the nonbonded interaction of all molecules is coupled to a forcing parameter, is demonstrated by the agreement of the computed temperature dependence of ΔA_e with that expected. Some results are presented that show the apparent equivalence of the stepwise perturbation and continuous integration algorithms for this calculation. Finally, it is suggested that the excess free energy of liquids should be among the most important observables used in the parameterization of interatomic potential functions for application in free energy simulations of biological molecules.

The application of molecular dynamics simulations to problems of thermodynamics of biological macromolecules has been explosive. This is due in part to the rapid increase in available computing power and in part to the realization[1-3] of methods for applying molecular dynamics simulations to the calculation of interaction free energies for proteins and small molecules. The differences in affinities of an enzyme for different inhibitors,[4] and of mutant forms of the same enzyme for the same inhibitor or substrate,[5,6] have been estimated by computer modeling of the molecular dynamics. Significantly, these results are found to be in substantial agreement, i.e. quantitative and qualitative agreement, with experimental results.

In parallel developments, these techniques have been applied to estimate free energies of interaction for compounds of low molecular weight with water.[7-11] These results were also found to be in substantial agreement with experimental values, the free energies of transfer for these compounds from vapor to water.[12,13]

In this paper we present a rapid calculation of the excess free energy of the liquid, which is defined as the free energy of transfer of all molecules in a sample of liquid to the state of ideal gas without a change in volume. This calculation uses the methods of thermodynamic perturbation and integration. Molecular dynamics provides the means for retaining the sample in thermal equilibrium. The approach taken is based on the same principles that have been used for studies of the transfer of a single molecule, in which the interactions between *one* molecule and all other molecules in the sample are varied. When the interactions between *all* molecules in the sample are varied, accuracy is improved, as the statistical error per molecule is less. We report applications to two test systems, soft spheres and liquid argon, and to four models of water, SPC,[14] SPCE,[15] TIP3P, and TIP4P.[16]

Thermodynamic perturbation and integration methods have been applied before to models of liquid water, in ways similar to the present approach. One begins with the expression of the free energy in terms of the partition function (eq 1).[2,17,18] The perturbation method proceeds via differences between states B and A (eq 2), i.e., the mean Boltzmann factor for the difference in energy for the two states, at thermal equilibrium of state A. Here, B can indicate the liquid, and A, the ideal gas, the ideal gas potential U_A not containing any nonbonded forces. If the states are very different, this method requires an inordinately large sampling of system configurations for convergence. Many small steps more efficiently bridge the difference between the two extreme states, which requires a series of simulations with intermediate force fields.

$$A = -kT \ln z$$
$$z = \int \exp(-U/kT)\,\mathrm{d}X \qquad (1)$$

$$z_B/z_A = \int \exp(-U_B/kT)\,\mathrm{d}X \Big/ \int \exp(-U_A/kT)\,\mathrm{d}X = \langle \exp[-(U_B - U_A)/kT] \rangle_A \qquad (2)$$

One may also proceed continuously from one state to another and perform an integration (eq 3).[2] Here, U is written as a function of a coupling parameter λ, such that U varies from U_A to U_B as λ is varied. The derivative of U is averaged over a Boltzmann distribution corresponding to $U(\lambda)$.

$$\Delta A = \int \mathrm{d}A = \int \langle \partial U(\lambda)/\partial\lambda \rangle\,\mathrm{d}\lambda \qquad (3)$$

Earlier calculations of the excess free energy of water used variations of both methods and maintained thermal equilibrium by use of Monte Carlo methods. Sarkisov et al.[19] and Mezei et

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al.[20] report results for water models that are not presently widely applied to simulations of biological macromolecules and aqueous solutions. Mezei[21] reported results for several other models of liquid water, of which one, the SPC model, is widely used at this time. The excess free energy for this model has now been recomputed by us using thermodynamic integration, with a different result, which is in much better agreement with the experimental value.

Methods

Computations. Molecular dynamics calculations were performed with the program CEDAR.[22] Bond lengths were kept fixed by the SHAKE algorithm.[23] A time step of 2 fs was used (4 fs for simulations of liquid argon and 0.5 fs for TIP4P, where problems were encountered, which are probably connected with the presence of a very short bond in the TIP4P model). Temperature and pressure were restrained by relaxation[24] with a time constant of 0.2 ps. Calculations at constant mean temperature and pressure were done to establish the equilibrium density of the models, while for the free energy calculations volume and mean temperature were constant. Nonbonded forces were calculated for pairs of molecules at separation distances below a cutoff (values are given below for each case).

The excess Helmholtz free energy of the liquid, ΔA_e, was computed as follows.[2] The nonbonded potential energy is calculated as the sum of pairwise contributions over all atom pairs in different molecules (eq 4).

$$U = \sum U_{ij} \qquad (4)$$

The energy for each nonbonded atom pair was written as the sum of a Lennard-Jones potential and an electrostatic potential with the following choice for the multipliers (cf. also ref 10, eq 16 and 17).

$$U_{ij} = -f_a(\lambda_a)A/r_{ij}^6 + f_b(\lambda_b)B/r_{ij}^{12} + f_c(\lambda_c)C/r_{ij} \qquad (5)$$

$$f_a(\lambda_a) = \lambda_a^3 \qquad f_b(\lambda_b) = \lambda_b^5 \qquad f_c(\lambda_c) = \lambda_c^3 \qquad (6)$$

Thus, the state determined by $\lambda = (\lambda_a, \lambda_b, \lambda_c) = (1, 1, 1)$ corresponds to the liquid, and the state determined by $\lambda = (0, 0, 0)$ corresponds to the ideal gas. The molecular dynamics calculation was begun in one of these states, and in each step λ was varied by a small increment, $\delta\lambda$. When eq 7 is accumulated with very small step-size $\delta\lambda$, one closely

$$\sum \delta A = \sum \partial U/\partial\lambda \cdot \delta\lambda \qquad (7)$$

approximates the integral of eq 3. (Here, $\partial U/\partial\lambda\cdot\delta\lambda$ is a scalar product and stands for $\partial U/\partial\lambda_a\delta\lambda_a + \partial U/\partial\lambda_b\delta\lambda_b + \partial U/\partial\lambda_c\delta\lambda_c$.) It was necessary to let the components of λ vary independently, in order to prevent the occurrence of states having a negative pressure, which might collapse to a smaller volume of liquid and an empty space. In practice, we accomplished this by monitoring the potential energy of the system. E.g., if λ was being reduced, λ_b was not reduced unless U was positive. As a consequence, the changes in λ follow different paths in the forward and reverse trajectories. (In the calculations on water models, λ_c was set equal to λ_a.)

Test Systems. Calculations were performed for two test systems: soft spheres and argon. In both cases, 216 particles were used, with periodic boundary conditions. For the soft-sphere model, the cutoff distance for nonbonded forces was (12/23) the edge of a cube containing 216 particles, with the same mass and number density as liquid argon. A single calculation was done, in which λ varied from 0 to 1. In this model, monoatomic particles interact with a simple inverse 12th power repulsion potential (second term of eq 5), and the entire equation of state follows from a single calculation.[25] The pressure and excess entropy were p = 19.2 (18.8)kT/V and ΔS = 3.82 (3.85)k, values in parentheses being those reported by Hoover et al.[25] from a Monte Carlo simulation. These figures are for the highest energy parameter used by Hoover et al.[25]

Liquid argon was used for the second test system with parameters the same as used by Rahman, i.e., with $\epsilon = 120k$ and σ = 3.4 Å.[26] Simulations were performed at 90 K, i.e., at reduced temperature $T^* = kT/\epsilon$ = 0.75 and reduced particle density $\rho^* = \sigma^3 N/V$ = 0.80. Calculations were done with a 10-Å cutoff on nonbonded interactions. First, the system was equilibrated at constant pressure and temperature for 5 ps. Second, the value of λ was reduced to 0, and, third, λ was again brought to 1, each run taking approximately 14 000 steps (56 ps). The net change in free energy upon going through this entire cycle was ca. 0.05 kcal/mol, which is a measure of thermodynamic reversibility. A longer calculation (200 ps) was performed, and this gave a result very close to the mean of $-\Delta A$ for the forward and ΔA for the reverse calculation. This supports the reasonable contention that each value of the change in free energy calculated by simulation is too high but that the excess decreases as the number of steps is increased; i.e., the system remains closer to equilibrium when the number of steps for a given change of λ are increased.[27] We obtained a value of the excess free energy of −0.735 kcal/mol; the corresponding configurational free energy differs from this by $[\ln(\rho^* - 1)]kT$ and is equal to -3.98ϵ. This value may be compared with values in the range −4.21 to -4.28ϵ obtained by others with the same force field but with three quite different methods.[27-29] The difference corresponds closely to the correction that must be applied to our result for the use of a finite cutoff radius.

Table I. Geometry, Lennard-Jones Parameters, and Partial Changes for Water Models

	SPC	SPCE	TIP3P	TIP4P[a]
r(OH), Å	1.0	1.0	0.9572	0.9572
∠HOH, deg	109.47	109.47	104.52	104.52
$B \times 10^{-3}$, kcal Å^{12}/mol	629.4	629.4	582.0	600.0
A, kcal Å^6/mol	625.5	625.5	595.0	610.0
q(O)	−0.82	−0.8476	−0.834	0.0
q(H)	+0.41	+0.4238	+0.417	+0.52
q(M)	0.0	0.0	0.0	−1.04
r(OM), Å	0.0	0.0	0.0	0.15

[a] The negative charge is moved off the oxygen and toward the hydrogens at a point (M) on the bisector of the HOH angle.

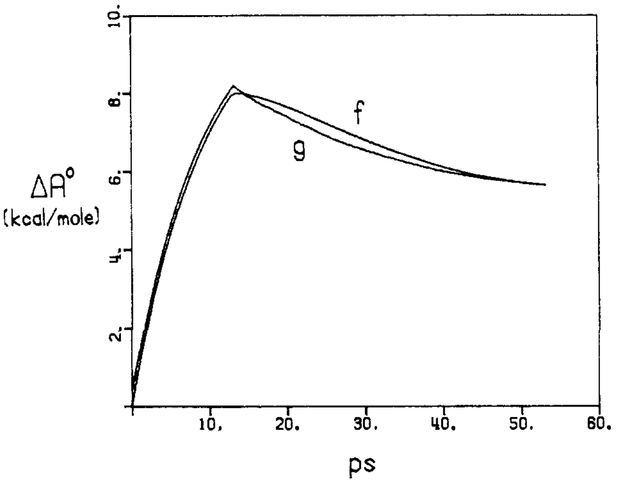

Figure 1. Excess free energy of the SPC water model computed by thermodynamic integration. After each step of the molecular dynamics calculation, the energy function was changed according to eq 5 and 6, λ varying from (1, 1, 1) on the left to (0, 0, 0) on the right (curve marked f). The calculation was reversed (curve marked g, for which time is counted backward). The near coincidence of start and end point (on the left) is a measure of the extent of thermodynamic reversibility.

Calculations on Water Models. We have studied the properties of four water models, SPC,[14] the very similar TIP3P,[16] a recent modification of SPC, SPCE,[15] and TIP4P.[16] The parameters used in these models are summarized in Table I. Most of the calculations were done with 80 molecules under periodic boundary conditions and a 6-Å cutoff on nonbonded interactions.

For all water molecules thermodynamic integrations were performed in a simulated time of 50 ps in each direction, i.e., in 25 000 dynamic steps. In addition, we performed integrations of different lengths and a

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Table II. Molar Excess Free Energies for the SPC Model of Liquid Water

temp, °C	cutoff, Å	density, g/cm^3	$-U_{pot}$, kcal/mol	$-\Delta A_{calcd}$, kcal/mol	$-\Delta A_e{}^a$ kcal/mol
27	10	1.017	10.1	5.8	5.74
0	6			6.0	6.10
27	6	0.995	9.9	5.6	5.74
100	6			4.6	4.74

[a] Calculated as $\Delta A_e = \Delta G_e - \Delta(pV) \cong -kT \ln \alpha + kT$, where α is the ratio between molar volumes of vapor and liquid at equilibrium.

Table III. Excess Free Energies Calculated for the SPCE, TIP3P, and TIP4P Models at 27 °C, with Use of a 6-Å Cutoff

model	$-\Delta A_e$, kcal/mol
SPCE	5.5 (6.4)^a
TIP3P	5.4
TIP4P	5.3

[a] The higher value is that reported by the simulation; the lower value is that value corrected for the polarization self-energy.

perturbation calculation for the SPC model at 300 K, as described below.

Results

Figure 1 shows results of varying all nonbonded forces for SPC water at 300 K. The lack of coincidence of the results for forward and reverse calculations is due, at least in the right-hand portion of the figure, to the independence of the changes in λ_a ($=\lambda_c$) and λ_b, and the use of different criteria for when to change both λ's rather than only one. In the left-hand portion only λ_a ($=\lambda_c$) changed in both calculations, and the difference between the two curves corresponds to a lack of closure of the thermodynamic cycle.

For calculations in which λ varied at different rates, the hysteresis, or net change of the free energy in the cycle, decreased as the rate of change of λ was decreased, from 2.2 kcal/mol, if the rate of change was 1 in 2000 steps, to 0.6 kcal/mol for a rate of 1 in 20000 steps to 0.16 kcal/mol for a rate of 1 in 50000. The mean of $-\Delta A$ and ΔA for the two calculations constituting the cycle was, however, independent of the rate, within 0.2 kcal/mol. The best value for the excess free energy, ΔA_e, was therefore taken to be given by this mean and was found to be -5.6 kcal/mol.

The above results were obtained with floating-point arithmetic of 64 bits. When the same calculations were done with 32-bit precision, the same mean values were obtained but the closure error in the slowest run was 0.4 kcal/mol. These thermodynamic integration runs were begun from a starting configuration of the liquid equilibrated by a molecular dynamics calculation of several picoseconds. I.e., in the first calculation λ was decreased to zero. Usually, the end point of this calculation was used as the starting point for the calculation in which λ was changed back to unity. For rapid variation of λ, the two runs were separated by several picoseconds of equilibration at $\lambda = 0$. In the calculation at the less rapid rate of change of λ of 1 in 20000 steps, the reverse calculation was done from two different starting points separated by a similar equilibration. The resulting free energy change for the preequilibrated run differed by -0.15 kcal/mol, which may be just outside the statistical error.

The excess free energy for the SPC model is given in Table II, together with values for the density and the nonbonded energy of the liquid (at atmospheric pressure). The latter values are in agreement with the previously published values for the SPC model. Also given are values obtained at temperatures of 273 and 373 K, as well as the corresponding experimental values. The values of ΔA_e calculated for the model are slightly lower than the experimental values, by 0.1 kcal/mol at all three temperatures. This demonstrates the method's precision. (As the energy of the model matches the experimental excess energy of liquid water, the temperature dependence of ΔA_e is not an independent result.) Table III gives values of ΔA_e calculated for the SPCE, TIP3P, and TIP4P models. The results for the last two models were checked by a pair of perturbation calculations involving the TIP3P and TIP4P models, in which the free energy difference was estimated from the mean Boltzmann factor for the energy difference for the two models, according to eq 1 and 2. The energy difference was found to fluctuate in the range between -15 and $+15$ kcal/mol (of an 80-molecule sample), and the free energy of the TIP4P model was found to be 0.1 kcal/mol higher than that of the TIP3P model.

Most of the results reported here were calculated with a 6-Å cutoff on nonbonded interactions. The reasons for using a short cutoff distance, r_c, in a study of liquids are obvious: Both minimum sample size and the number of nonbonded atom pairs per atom vary as r_c^3, and the total calculation varies as r_c^6. We have investigated the dependence of the results on the value of r_c by additional calculations, in which r_c was 10 Å. This was done with 640 molecules, in order to have a linear repeat greater than twice r_c. Internal energy, volume at constant mean pressure, and excess free energy were found to be only slightly different from the values obtained with use of a 6-Å cutoff. Accordingly, results for the other water models were not extended with use of a larger cutoff distance.

Calculations were performed on the SPC model with use of thermodynamic perturbation, i.e., by calculation of ΔA for discrete steps in λ according to eq 2 and 4–6.

A comparison of the behavior of the methods appears to favor neither. On the one hand, the stepwise method requires a separate equilibration period for each interval, followed by an accumulation of the sum of the Boltzmann factor, while in the continuous method equilibration and accumulation of the derivative proceed simultaneously. On the other hand, each simulation at intermediate λ with the perturbation method produces increments $\Delta\Delta A$ in both directions, whereas thermodynamic integration has to be run twice, once with increasing and once with decreasing λ, to test reversibility.

A priori one might expect that the stepwise method will give improved results when the Boltzmann factor is accumulated over a longer period at each intermediate λ or when the step in λ is decreased or both. In order to determine an economical strategy for computing large free energy differences by stepwise perturbation, we have computed the free energy difference for three different steps of λ_a (and λ_c), of magnitude 0.05, 0.1, and 0.2, respectively, in a single simulation at $\lambda_a = 1$, lasting 20 ps. The results are shown in Figure 2. It will be seen that after initial rapid changes little further change occurs, except that the system twice passes briefly through states in which the Boltzmann factor is very large and in which the mean increases very significantly. After these abrupt changes the mean slowly drops as the number of steps increase, whereas the sum remains nearly constant. In contrast, the derivative $\partial U/\partial\lambda$ was found to converge extremely rapidly. The values of ΔA computed by the perturbation method, together with the corresponding values from continuous integration, are given in Table IV. By comparison the last two columns of this table, one sees that an adequate ΔA value was obtained for the smallest change in λ but that for bigger changes of λ considerable systematic error occurred. Strikingly, the progress of ΔA with time of accumulation does not indicate that one value has converged, and the other two have not. Thus, we find that it is more effective to do the calculation of ΔA in many steps with small increments of λ, with a relatively short simulation at each step. Using stepwise perturbation, one must rely on a comparison of results obtained with increasing and decreasing λ, to determine if the calculation was done with a sufficiently small increment of λ. Techniques and conditions for free energy calculations are also discussed by Jorgensen and Ravimohan[8] and Straatsma,[9,31] with similar, but not identical, conclusions.

A complete calculation by stepwise perturbation was done as follows. For each of 21 configurations along a 100000-step trajectory along which the potential energy function had been varied continuously during thermodynamic integration, values of $\Delta\Delta A_e$ for changing the potential energy function to that for the preceding and the following selected configurations were calculated over 1000 time steps (2 ps). The magnitudes of $\Delta\Delta A_e$ for the same

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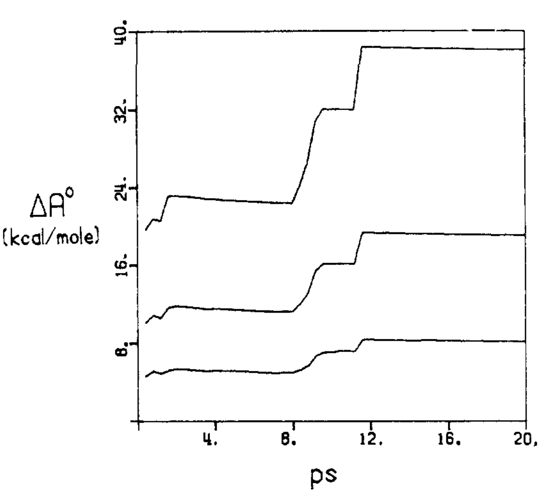

Figure 2. Effect of the magnitude of the increment in λ on the convergence of the (partial) free energy change, ΔA, in a perturbation calculation. Mean free energy differences were accumulated for three states B corresponding to three different values of λ_B in a single molecular dynamics calculation relative to a state A with $\lambda_A = (1, 1, 1)$ according to eq 2. The plotted values are relative to different origins, given in Table III. The difference between the potential functions for states A and B is largest for the upper curve and smallest for the lower curve.

Table IV. Comparison of Stepwise and Continuous Methods for Three Different Stepsizes

$\lambda_a = \lambda_c$[a]	ΔU_0	$-RT \ln \langle \exp(-\Delta\Delta U/kT) \rangle_{20}$	ΔA_{step}	ΔA_{cont}[b]
0.95	172	−9.5	162	164
0.9	328	−20.4	308	297
0.8	591	−39.4	552	487

[a] $\lambda_b = 1$ in all three cases. [b] Values in kilocalories per mole of sample (80 water molecules): ΔU_0, energy difference, $U(\lambda_a, 1, \lambda_c) - U(1, 1, 1)$, for the starting configuration; $\langle \exp(-\Delta\Delta U)/kT) \rangle_{20}$, Boltzmann factor for the change in the difference $\Delta\Delta U = \Delta U - \Delta U_0$, averaged over 20 ps; ΔA_{step}, sum of the preceding two columns; ΔA_{cont}, value from continuous integration.

interval calculated with increasing and decreasing λ systematically differed by small amounts. The value of ΔA_e obtained by adding $\Delta\Delta A_e$ for all intervals with increasing λ was −5.3, and with decreasing λ, −5.9. The mean of −5.6 kcal/mol is in excellent agreement with the mean from continuous integration.

Discussion

As was mentioned in the introduction, the excess free energy of the SPC water model calculated here disagrees with a value reported earlier.[21] Mezei (personal communication) has determined that the earlier value is affected by a programming error (which influenced the result for the SPC model, only). Correction of the error has made the disagreement vanish. Very recently Jorgensen et al.[32] have computed the free energy of liquid TIP4P water as the free energy of transfer of a single water molecule from a vacuum to liquid water. They obtain −5.4 kcal/mol, in excellent agreement with the value of −5.3 kcal/mol found here.

It is useful to summarize the basis of the force fields for liquid water that have been studied here. To begin with, these force fields are easy to use and are economical in terms of computer time. They have very few parameters, which has made it possible to determine these parameters uniquely by requiring that the model optimally reproduce experimentally observable properties of liquid water. These properties are the "structure", as described by the oxygen–oxygen radial distribution function derived from X-ray diffraction experiments,[33] the specific volume, and the internal energy, as derived from the heat of vaporization. Comparison of other properties of these models with experimental observations provides criteria for judging how successful these models are. The extent of agreement should be used as a basis for deciding what kind of problems to study when applying the models to more complicated systems. This suggests that use of one of several (slightly) different models may be preferable, depending on the problem. For example, in a study of motion of molecules through liquid water, it would be advisable to use a water model that gave a good value for the diffusion coefficient of liquid water, as does the SPCE model.[15]

Extensive use of molecular dynamics simulations for the estimation of thermodynamic properties, especially free energies, suggests that the force fields should be parametrized on free energies, rather than energies. It is clearly feasible to search for "best" parameters (in terms of free energies) with the method described in this paper. In a study of a series of liquids it is possible to optimize a few of the force field's parameters at a time with great accuracy.[34] Parameters describing the hydration of solutes can be obtained by modeling water–solute interactions by application of thermodynamic integration methods to free energies of transfer and free energies of liquid mixtures. Recent results[7-11] indicate that current potential functions account very well for hydration free energies and would need to be modified only slightly to give perfect agreement.

No adjustment of the SPC model is suggested by the results presented in this paper. The good agreement between the theoretical and experimental excess free energies of liquid water is as expected on the basis of the agreement between calculated and experimental free energy differences in more complicated systems.

Real water molecules become more polarized when transferred from a vacuum to the liquid, whereas the polarized state of the water *models* studied here is independent of the environment. Berendsen et al.[15] have analyzed this further and proposed a modified model, SPCE. They point out that the intermolecular energy of the model should not simply be equated with the observed excess energy as a reference, as was done for the SPC and TIP models, but that this reference datum should be modified by an amount equal to the energy needed to change the molecular polarization when the molecules are transferred from a vacuum to the liquid state. The resulting SPCE model is slightly more polar than the original SPC model, and the SPCE model gives lower energy and free energy for the liquid by the same amount, 0.9 kcal/mol. This difference is just the energy required to change the polarization of the water molecules. The diffusion coefficient of the SPCE model is in much better agreement with the experimental value than that of the SPC model,[15] the value for TIP4P being intermediate;[35] however, it is not yet known which of the two models is preferable in thermodynamic studies, for example, calculations of free energies of transfer of guest molecules of different polarity.

The very small differences in the calculated properties of the water models when the cutoff distance for nonbonded forces is varied have been noted successively for several different water models.[36-38] This is contrary to experience with models of apolar molecules, for which both energy and volume change in significant proportion. Use of a short cutoff distance may also give good results in other simulations in which a considerable volume of bulk is present, i.e., in studies of small molecules and macromolecules in aqueous solution. At the very least, it may be possible to model the interactions between water molecules with a short cutoff distance.

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Iron(I)-Induced Demethanation of *tert*-Butyl-Substituted Nitriles in the Gas Phase. A Case of Remote Functionalization of Carbon–Carbon Bonds†

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Abstract: Experiments are described that indicate that the Fe^+-induced reductive demethanation of 8,8-dimethylnonanenitrile (**11**) follows a 1,2-elimination mode in which 90% of the CH_4 is generated from the *tert*-butyl group. The actual reaction sequence seems to commence with oxidative addition of a remote C–C bond to the complexed transition-metal ion, followed by a β-hydrogen migration. There is no experimental evidence for the operation of the long-sought-after β-methyl migration in the system studied. Other processes examined include the collision-induced losses of H_2, H_2/CH_4, CH_4/CH_4, C_4H_8, and H_2/C_4H_8 versus C_4H_{10}, C_5H_{12}, and C_6H_{12}, respectively, from the RCN/Fe^+ complex. Deuterium-labeling experiments are mandatory for an understanding of the reaction pathways.

The selective functionalization of C–H bonds remains one of the major focuses of catalytic and organic chemistry. High selectivity is often achieved by the presence of activating groups, which induce the reactivity of the neighboring C–H bonds. The functionalization of *remote* C–H bonds, i.e. several carbon atoms away from the activating group, represents a great challenge. While such reactions are common to enzymes, which corrdinate a functional group and *geometrically* select a specific site of the substrate, only a few cases in solution chemistry are reported[1] where a similar principle seems to be operative. Breslow[1d] has coined the term "remote functionalization" for this method of coordination of a functional group followed by selective reactions at sites away from the complexed functionality. We have recently demonstrated that a similar system exists in the gas phase.[2] The reaction of aliphatic, unbranched nitriles with bare transition-metal ions, e.g. Fe^+, is very unique, in that selective C–H activation occurs only at positions remote from the cyanide functionality. This unprecedented behavior contrasts with that of other unsaturated systems, such as alkenes[3] and alkynes,[4] where allylic and propargylic activations, respectively, of the C–C and/or C–H bonds are reported to be the major mode of reaction. The primary reason for the unique behavior of nitriles is due to the initial interaction of the cyanide group with the transition-metal ion Fe^+. The preferred coordination leads to an "end-on" complex **1** characterized by a "linear"[5] $-CH_2C{\equiv}NM^+$ entity (M = transition-metal atom). The linear fragment in turn constrains the remainder of the molecule such that Fe^+ activates C–H bonds while trying to minimize the strain. For nitriles containing four to seven carbon atoms, this deformation results in the exclusive activation of the terminal methyl group by oxidative addition of the C–H bond to the (complexed) Fe^+ (Scheme I, **1** → **2**). This insertion is followed by either a β-hydrogen shift (**2** → **3**) to produce eventually H_2 in a site-specific 1,2-elimination mode or cleavage of the C–C bond (**2** → **4**). The latter intermediate may then undergo reductive elimination of C_2H_4 to generate RCN/Fe^+ complexes being shortened by the C_2H_4 unit, which originates exclusively from the ω and $(\omega - 1)$ positions of the alkyl chain.[6]

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