interactions can contribute to the stability of the cluster.

The solution simulations using nonadditive many-body potentials have also provided some new interesting observations. In particular, the waters are very mobile between the first and second hydration shells, resulting in a nonzero first minimum in the calculated $g_{\text{Na-O}}$. The calculated enthalpies for both clusters and solution simulations and the coordination numbers in solution are in good agreement with the experimental data.

Thus, a model has been developed that gives energies in ion–water clusters and energies and structural features of ionic solutions in near quantitative agreement with experiment. This lets us suggest with some confidence that both the Na^+ and Cl^- ions have significantly different coordination geometries in ion–water clusters and solution. Our model has included both polarization and exchange repulsion nonadditive effects. We have carried out some simulations without the exchange repulsion nonadditivity, and the agreement with experiment is poorer. One cannot totally rule out that another choice of parameters might allow one to exclude the exchange term, but it appears to be important on the basis of quantum mechanical calculations[4,27] and its inclusion does not cause very large computational demands, the polarization part of the nonadditivity being the most time-consuming part of the model.

There are many directions for further development of this model. What are properties of solutions with more highly charged ions? What role do nonadditive effects play in solvation of nonpolar or neutral solutes? What are the potentials of mean force for the ion–ion and neutral–neutral association including nonadditive effects? Inclusion of the Ewald summation method[28] for the evaluation electrostatic potentials and forces would be worthwhile. Studies on these and related questions are in progress. Nevertheless, the results presented in this report, we feel, have been a significant step toward the understanding of the physics and chemistry of solvation.

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Calculated Heat of Formation of Ammonia

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Abstract: The heat of formation, $\Delta H^\circ_{f,0}$, of NH_3 has been determined using ab initio calculations including extrapolation to the complete basis set (CBS) limit. The extrapolated value for $\Delta H^\circ_{f,0}$ is −8.83 ± 0.5 kcal/mol, which is in good agreement with the best experimental measurement, −9.34 ± 0.01 kcal/mol.

Calculations of the heats of formation of molecules involving multiply bonded or highly polar species are of considerable interest as they offer a more stringent test of theoretical models than simpler systems. An example of one of these more complex systems is the Haber process[1] for the synthesis of ammonia:

$$N_2 + 3H_2 \rightarrow 2NH_3$$

Because of the relatively drastic changes that occur in the bonding characteristics in going from reactants to products, the energy change for this simple reaction is very difficult to calculate accurately. For example, the G1 model chemistry[2] of Pople, Head-Gordon, Fox, Raghavachari, and Curtiss generally gives excellent results for energy changes in chemical reactions. However, the heat of formation of ammonia obtained[2] with the G1 model (−6.52 kcal/mol) is significantly smaller than the experimental value[3] (−9.34 ± 0.01 kcal/mol). We have therefore subjected this system to a detailed theoretical study including our CBS-QCI model chemistry.[4] The calculated CBS-QCI value of $\Delta H^\circ_{f,0}$ for ammonia, −8.83 ± 0.5 kcal/mol, is in good agreement with the experimental value. The slow convergence of the calculations with both the basis set and the order of perturbation theory illustrates the difficulty one encounters with such systems.

Method and Results

To calculate the heat of formation, $\Delta H^\circ_{f,0}$, of NH_3, we have studied the gas-phase reaction of H_2 with N_2. The standard heats of formation at 0 K of H_2, N_2, and NH_3 are known by definition and experiment[3] to be 0.0, 0.0, and −9.34 kcal/mol, respectively. For our calculations of the total energy, we used the experimental geometries of the reactants and product. The observed internuclear distances for H_2 and N_2 are 0.7414 Å and 1.109 76 Å, respectively.[5] The internuclear distance and H–N–H angle for NH_3 are[6] 1.0124 Å and 106.68°. The determination of $\Delta H^\circ_{f,0}$ requires that the calculated total energy change for the reaction be cor-

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Table I. The Convergence of the SCF Energy (in hartrees) for the Reaction $N_2 + 3H_2 \rightarrow 2NH_2$ and the Resulting $\Delta H^\circ_{f,0}(NH_3)$, in kcal/mol

basis set	H_2	N_2	NH_3	reaction	$\Delta H^\circ_{f,0}(NH_3)$
STO-3G[a]	−1.11668	−107.49587	−55.45409	−0.06227	−9.23
4-31G[a]	−1.12673	−108.75367	−56.10243	−0.07100	−11.97
6-31G[a]	−1.12673	−108.86777	−56.16103	−0.07410	−12.94
6-31G**[a]	−1.13128	−108.94268	−56.19520	−0.05388	−6.60
DZ + P; APNO[b]	−1.13028	−108.98690	−56.21350	−0.04926	−5.15
TZ + DP; APNO[c]	−1.13167	−108.98822	−56.22079	−0.05835	−8.00
QZ + TP; APNO[d]	−1.13338	−108.98881	−56.22303	−0.05711	−7.61
QZ + TP + 2*f*[e]	−1.13338	−108.99188	−56.22358	−0.05514	−7.00
[6s6p3d2f,4s2p1d][f]	−1.13334	−108.99210	−56.22390	−0.05568	−7.20
l^{-6} extrap	−0.00002	−0.00087	−0.00004	+0.00085	
CBS SCF	−1.13336	−108.99297	−56.22394	−0.05483	−6.93 ± 0.3

[a] Reference 17. [b] This frozen core DZ + P size basis set is obtained from the {KK,KL,LL} full DZ + P basis set in ref 10 by deleting the 2s′ and 2p′ functions which correlate the (1s,1s) pair. [c] This frozen core TZ + DP size basis set is obtained from the {KK,KL,LL,LL′] full basis set in ref 10 by deleting the 2s′ and 2p′ functions which correlate the (1s,1s) pair. [d] The most diffuse s, p, and d primitives of the TZ + DP basis set were *not* contracted. [e] The two *f* functions of the [6s6p3d2f,4s2p1d] basis set were added. [f] Reference 4.

Table II. The Convergence of the Correlation Energy (in hartrees) for the Reaction $N_2 + 3H_2 \rightarrow 2NH_3$ and the Resulting Contribution to $\Delta H^\circ_{f,0}(NH_3)$, in kcal/mol

method/basis set	H_2	N_2	NH_3	reaction	$\Delta H^\circ_{f,0}(NH_3)$
MP2(FC)[a]					
6-31G**	−0.02634	−0.30991	−0.18799	+0.01294	+4.06
DZ + P; APNO	−0.02801	−0.33775	−0.20476	+0.01226	+4.03
TZ + DP	−0.02932	−0.35487	−0.21997	+0.00289	+0.91
QZ + TP	−0.03040	−0.36278	−0.22584	+0.00239	+0.75
QZ + TP + 2*f*	−0.03040	−0.38771	−0.23975	−0.00059	−0.19
[6s6p3d2f,4s2p1d]	−0.03164	−0.38687	−0.24321	−0.00463	−1.45
CBS2(FC)[b]					
6-31G**	−0.03246	−0.40019	−0.24939	−0.00121	−0.38
DZ + P; APNO	−0.03422	−0.41057	−0.26015	−0.00707	−2.22
TZ + DP	−0.03454	−0.42373	−0.26701	−0.00667	−2.10
QZ + TP	−0.03469	−0.42569	−0.26778	−0.00580	−1.82
QZ + TP + 2*f*	−0.03469	−0.42720	−0.26852	−0.00577	−1.81
[6s6p3d2f,4s2p1d]	−0.03390	−0.41526	−0.26075	−0.00454	−1.42
MP3(FC)[a]					
6-31G**	−0.00552	+0.00504	−0.01277	−0.01402	−4.40
DZ + P; APNO	−0.00648	+0.00882	−0.01102	−0.01142	−3.58
TZ + DP	−0.00631	+0.00936	−0.01026	−0.01095	−3.44
QZ + TP	−0.00593	+0.01002	−0.00970	−0.01163	−3.65
QZ + TP + 2*f*	−0.00593	+0.00954	−0.01024	−0.01223	−3.84
[6s6p3d2f,4s2p1d]	−0.00574	+0.00897	−0.01028	−0.01231	−3.86
MP4(FC)[a]					
6-31G**	−0.00142	−0.02312	−0.00541	+0.01656	+5.20
DZ + P; APNO	−0.00159	−0.02883	−0.00748	+0.01864	+5.85
TZ + DP	−0.00156	−0.03088	−0.00979	+0.01598	+5.01
QZ + TP	−0.00154	−0.03180	−0.01001	+0.01640	+5.15
QZ + TP + 2*f*	−0.00154	−0.03164	−0.01011	+0.01605	+5.04
[6s6p3d2f,4s2p1d]	−0.00150	−0.03127	−0.01004	+0.01569	+4.92
QCI(FC)[c]					
6-31G**	−0.00055	+0.00289	−0.00070	−0.00264	−0.83
DZ + P; APNO	−0.00054	+0.00354	−0.00030	−0.00250	−0.78
TZ + DP	−0.00057	+0.00524	+0.00016	−0.00321	−1.01
QZ + TP	−0.00062	+0.00539	+0.00020	−0.00313	−0.98
QZ + TP + 2*f*	−0.00062	+0.00555	+0.00024	−0.00321	−1.01
[6s6p3d2f,4s2p1d]	−0.00062	+0.00564	+0.00033	−0.00312	−0.98

[a] Møller-Plesset perturbation theory (ref 9) as included in GAUSSIAN 88 (ref 17). [b] Complete basis set extrapolation of the MP2 energy (ref 10). [c] QCISD(T) (ref 15).

rected for the zero-point energy changes including anharmonicity differences. The harmonic zero-point energy changes can be calculated using the experimental fundamental frequencies. The vibrational frequency of hydrogen[5] is 4160.2 cm^{-1}, and that of nitrogen[5] is 2331 cm^{-1}. Ammonia has six vibrational degrees of freedom, but only four frequencies since two are doubly degenerate. The two doubly degenerate bands appear[7] at 3444 and 1627 cm^{-1}; the other vibrational frequencies occur[7] at 950 and 3337 cm^{-1}. The anharmonicity corrections to the zero-point energies for hydrogen,[5] nitrogen,[5] and ammonia[8] are 88.4 cm^{-1}, 10.8 cm^{-1}, and 240 cml–^{1}, respectively.

The total energy change for a chemical reaction can be expanded in a Møller–Plesset perturbation expansion.[9] A reliable calculation of the energy change requires that *each* order of perturbation theory be converged with respect to expansion of the basis set *and* that enough terms have been included in the perturbation series to achieve a converged result.

In Table I we present the self-consistent-field (SCF) contribution to the heat of formation calculated using basis sets ranging from the simple STO-3G to the large (14s9p4d2f,6s3p1d)/[6s6p3d2f,4s2p1d] atomic pair natural orbital (APNO) basis set.[4] An l^{-6} extrapolation[10] is used to estimate the contributions from *g*, *h*, and higher angular momentum functions. As the basis set is improved, the SCF contribution to the heat of formation converges to the complete basis set (CBS) SCF limit of −6.93 kcal/mol. The convergence is somewhat erratic. However, two trends are evident. The calculated heat of formation becomes more

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Table III. The Components of the Total Energy (in hartrees) for the Reaction $N_2 + 3H_2 \rightarrow 2NH_3$ and the Resulting Contributions to $\Delta H^\circ_{f,0}(NH_3)$, in kcal/mol

method/basis set	H_2	N_2	NH_3	reaction	$\Delta H^\circ_{f,0}(NH_3)$
CBS2-QCI(FC)[a]					
6-31G**	-0.039 95	-0.415 38	-0.268 27	-0.001 31	-0.41
DZ + P; APNO	-0.042 83	-0.427 04	-0.278 95	-0.002 35	-0.74
TZ + DP	-0.042 98	-0.440 01	-0.286 90	-0.004 85	-1.53
QZ + TP	-0.042 78	-0.442 08	-0.287 29	-0.004 16	-1.31
QZ + TP + $2f$	-0.042 78	-0.443 75	-0.288 63	-0.005 17	-1.62
[6s6p3d2f,4s2p1d]	-0.041 76	-0.431 92	-0.280 74	-0.004 28	-1.34
CBS-QCI(FC)[a]					
[6s6p3d2f,4s2p1d]	-0.040 57	-0.421 74	-0.274 13	-0.004 80	-1.51 ± 0.3
CBS-QCI(core)[a]					
{KK,KL,LL,LL′}	0.	-0.116 02	-0.058 64	-0.001 26	-0.40 ± 0.1
CBS-SCF[a,b]					
[6s6p3d2f,4s2p1d]	-1.133 36	-108.992 97	-56.223 94	-0.054 83	-17.20 ± 0.3
ZPE (exp)	0.009 93	0.005 36	0.033 95	0.032 75	+10.27 ± 0.01
total					
[6s6p3d2f,4s2p1d]	-1.164 00	-109.525 37	-56.522 76	-0.028 14	-8.83 ± 0.5
experiment	-1.164 55	-109.537 7	-56.530 5	-0.029 77	-9.34

[a] Refer to text for definitions. [b] See Table I.

Table IV. Summary of the Direct Calculations of $\Delta H^\circ_{f,0}$ for NH_3

	method					
basis set	SCF	MP2(FC)[a]	MP3(FC)[a]	MP4(FC)[a]	QCI(FC)[b]	QCI(full)[b]
STO-3G	-9.23					
6-31G**	-6.60	-2.54	-6.94	-1.74	-2.57	
DZ + P; APNO	-5.15	-1.12	-4.70	+1.15	+0.37	
TZ + DP; APNO	-8.00	-7.09	-10.53	-5.52	-6.63	-7.03[c]
QZ + TP; APNO	-7.61	-6.86	-10.51	-5.36	-6.34	-6.74[c]
QZ + TP + $2f$	-7.00	-7.19	-11.03	-5.99	-7.00	-7.40[c]
[6s6p3d2f,4s2p1d]	-7.20	-8.65	-12.51	-7.59	-8.57	-8.97[c]
experiment						-9.34

[a] Møller–Plesset perturbation theory (ref 9) as included in GAUSSIAN 88 (ref 17). [b] QCISD(T) (ref 15). [c] This calculation included the KK and KL basis functions for the inner shell (ref 10).

negative as the basis set becomes more flexible if no new angular momentum terms are added, and the calculated heat of formation becomes less negative if new angular momentum terms are added. The small changes in the calculated heat of formation in going from the QZ + TP + $2f$ to the [6s6p3d2f,4s2p1d] basis set, and in going from the [6s6p3d2f,4s2p1d] basis set to the CBS extrapolation,[10] suggest that the CBS SCF contribution to the heat of formation is converted to within ±0.3 kcal/mol.

In Table II we examine the convergence of the correlation energy contribution to the heat of formation. These calculations use the frozen core (FC) approximation in which we include only the correlation energy of the valence electrons. The first set of calculations in Table II shows that, as the basis set is improved, the direct Møller–Plesset second-order (MP2) contribution changes appreciably from +4.06 kcal/mol with the smallest basis set and converges from above to a value of −1.45 kcal/mol with the largest basis set. The second set of calculations employs extrapolation to the complete basis set second-order (CBS2) limit using the N^{-1} asymptotic convergence of the N-configuration pair natural orbital expansions.[11-14] The CBS extrapolations use a minimum number, N, of five pair natural orbitals for the smaller basis sets and ten pair natural orbitals for the largest basis set, which includes f functions on the nitrogens and d functions on the hydrogens. The presence of these f functions and d functions ensures that the 10 lowest lying pair natural orbitals can be adequately described. The CBS2 estimate of the MP2 contribution to the heat of formation converges from below to −1.42 kcal/mol in excellent agreement with the direct calculations. The CBS method is less sensitive to basis set than the direct MP2 method is by a factor of about 5.

The higher order contributions, MP3, MP4, and QCISD(T),[15] each show rapid convergence with the basis set. However, they dramatically illustrate the difficulty with convergence of the Møller–Plesset perturbation series. The magnitude of the Møller–Plesset perturbation terms increases from second to third to fourth order. This is indeed a pathological example of poor convergence for the MP expansion and demonstrates the need for coupled cluster methods such as QCISD(T), which include single and double excitations through infinite order in the MP expansion. The poor convergence of the MP expansion for this example results from the third-order overestimate of the large positive pair coupling terms from the triple bond of N_2. The four-order triple excitations must then correct for this overestimation. The result is the observed oscillation in the sign of the MP perturbation series. If the triple excitations are omitted from the QCI calculations, the resulting errors in the energies (1 mE_h = 0.001 hartree) of the individual species are quite large (16.83 mE_h for N_2 and 8.18 mE_h for NH_3). However, in this particular case the error for N_2 happens to almost exactly cancel the error for $2NH_3$. The error from omission of triple excitations does not in general cancel. For example, the error from omitting triple excitations for the ${}^4S_0$ ground state of the nitrogen atom is only 2.59 mE_h, and thus the triple excitations contribute 11.65 mE_h to the dissociation energy of N_2.

In Table III, we present the individual components of the total energy obtained with the CBS-QCI model chemistry. The first set of calculations, labeled CBS2-QCI, is the sum of the CBS2, MP3, MP4, and QCISD(T) contributions with the given basis set. The CBS-QCI result includes the interference correction[12] to the higher order terms. The CBS2 extrapolation gives the

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Table V. Summary of the CBS Extrapolated[a] Values of $\Delta H^\circ_{f,0}$ for NH_3

	method					
basis set	SCF	MP2(FC)[b]	MP3(FC)[b]	MP4(FC)[b]	QCI(FC)[c]	QCI(full)[c]
6-31G**	−6.60	−6.98	−11.38	−6.18	−7.01	
DZ + P; APNO	−5.15	−7.37	−10.95	−5.10	−5.88	
TZ + DP; APNO	−8.00	−10.10	−13.54	−8.53	−9.64	−10.04[d]
QZ + TP; APNO	−7.61	−9.43	−13.08	−7.93	−8.92	−9.32[d]
QZ + TP + 2*f*	−7.00	−8.81	−12.65	−7.61	−8.62	−9.02[d]
[6s6p3d2f,4s2p1d]	−6.93	−8.35	−12.38	−7.45	−8.43	−8.83[d]
experiment						−9.34

[a] Complete basis set extrapolation (ref 10). [b] Møller–Plesset perturbation theory (ref 9) as included in GAUSSIAN 88 (ref 17). [c] QCISD(T) (ref 15). [d] This calculation included the KK and KL basis functions for the inner shell.

Table VI. Comparison of the CBS-QCI Components[a] with the G1 Components[b] of $\Delta H^\circ_{f,0}$ for NH_3

	component					
method/geom	SCF	MP2(FC)[c]	MP3,4,QCI(FC)[c,d]	core	ZPE	total
G1/6-31G*	−22.01	5.93	−0.56	0.	10.08	−6.52
G1/exp	−16.90	0.81	0.05	0.	10.08	−5.96
CBS-QCI/exp	−17.20	−1.42	−0.09	−0.40[e]	10.27	−8.83[e]
experiment						−9.34

[a] Complete basis set quadratic CI as defined in text (ref 4). [b] Reference 2. [c] Møller–Plesset perturbation theory (ref 9) as included in GAUSSIAN 88 (ref 17). [d] MP3 + MP4 + QCISD(T) (ref 15). [e] This calculation included the KK and KL basis functions for the inner shell.

correct sign for the correlation energy even with the smallest basis set. The CBS2-QCI correlation energy converges rapidly and is stable after the TZ + DP level of basis set. The root-mean-square error for the CBS-QCI model chemistry in a set of test cases was 0.5 kcal/mol per bond dissociation.[4] However, since the number of bonds formed is equal to the number of bonds broken, this error estimate is not applicable to the Haber process. Examination of the convergence of the components with respect to basis set allows us to make reasonable estimates of the accuracy of each of the components (Table III), from which we are able to conclude that the CBS-QCI model is accurate to ±0.5 kcal/mol. This is, in fact, equal to the size of the error in our calculations.

The convergence of the calculated heat of formation of NH_3 as a function of the basis set used and the order of Møller–Plesset theory is summarized in Table IV. The values in this table are cumulative; e.g., the MP4 value includes the ZPE, SCF, MP2, MP3, and MP4 contributions. The most striking result in Table IV is the accuracy of the simple STO-3G model. Unfortunately, the accuracy of the STO-3G model for this particular example is fortuitous and not at all representative of the generally reliability of STO-3G energies.[16] Several trends in Table IV are more typical of reactions in which the number of bonds and lone pairs are conserved. First, the SCF energy change is qualitatively correct and a reasonable approximation to the total energy change regardless of which basis set is used. Second, the MP2 energy change gives a realistic account of the effects of electron correlation, but the MP2 correction can be grossly in error (even having the wrong sign!) unless a very large basis set is used. Third, the MP3 energy change can be less reliable than the MP2 energy change because of cancellation with fourth-order effects. Improvement over the MP2 result requires at least MP4 and preferably a CCSD(T) method such as QCISD(T). Finally, the effect of core correlation is small and needs to be included only if very accurate results are desired.

Since the dominant basis set convergence problem involves the MP2 contribution, extrapolation to the CBS2 limit will clearly be helpful. The summary of CBS extrapolations in Table V demonstrates the marked improvement in convergence that is achieved. The CBS2 result for $\Delta H^\circ_{f,0}$ is in reasonable agreement with experiment regardless of which basis set is used. Although there is almost no change in this particular case, the general reliability of the CBS-QCI model[4] is substantially better than that of the CBS2 model.

Having determined accurate values for each of the components of the calculated $\Delta H^\circ_{f,0}$, we can now determine the source of the error in $\Delta H^\circ_{f,0}$ from the readily available[17] G1 model.[2] The components of the G1 heat of formation for ammonia are given in Table VI, along with the components from the "G1 method" using the experimental geometry and the components of the CBS-QCI model. Although small changes in geometry have little effect on the total energy, they cause significant but compensating changes in the SCF and MP2 components individually. Comparisons of different methods must therefore use the same geometry. The separate contributions in Table VI, indicate that the MP2 contribution to the G1 value for $\Delta H^\circ_{f,0}$ (+0.81 kcal/mol) is in error by 2.23 kcal/mol and accounts for the bulk of the error in the G1 heat of formation for NH_3. This is a result of using a single *f*-basis function on nitrogen and no *d*-basis functions on the hydrogens. The G1 model generally accounts for the omission of such basis functions with the semiempirical "higher level correction", ΔE(HLC),[2] which is equal to −5.76 mE_h times the number of doubly occupied orbitals. This corrects the intraorbital pair energies, but makes no attempt to correct the interorbital pair energies for the use of an incomplete basis set. Since the interorbital pair energies are more important in $2NH_3$ than in N_2 plus $3H_2$, this results in a relative underestimation of the correlation energy for NH_3, and hence values for ΔE(MP2) and $\Delta H^\circ_{f,0}$ that are too small.

Conclusions

The Haber process presents some interesting contrasts. On one hand, the number of bonds and lone pairs on nitrogen is preserved, which leads to a rather modest change in the electron correlation energy. This results in qualitatively correct SCF calculations, without regard to basis set. On the other hand, the calculation of the electron correlation energy is extremely difficult because of the changing nature of the bonding in going from reactants to products: the reactant molecules contain three nonpolar single bonds in H_2 and one nonpolar triple bond in N_2, while the product contains six polar NH bonds. The net result is that there is no cancellation of the bonding characteristics between reactants and products. The number of interorbital pair energies is larger in $2NH_3$ than in N_2, and H_2 does not have any interorbital pair energies. As a result of all of these factors, it is essential to include *f*-basis functions on N_2 to obtain the correct sign for the correlation energy contribution to the heat of formation. In addition, *d*-basis functions on the hydrogen must be included to obtain an accurate correlation energy contribution. These difficulties can be circumvented by extrapolation to the complete basis set limit using the asymptotic convergence of pair natural orbital expansions. The

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CBS-QCI model chemistry gives a value for $\Delta H^\circ_{f,0}$ (−8.83 ± 0.5 kcal/mol) in good agreement with experiment (−9.34 ± 0.01 kcal/mol).

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Evidence for the Stochastic Nature of Base Pair Opening in DNA: A Brownian Dynamics Simulation

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Abstract: The time dependence of the opening of the central thymine base in a B-DNA $(dA)_5\cdot(dT)_5$ oligomer has been simulated by Brownian dynamics using a previously developed opening model where the base is allowed to rotate toward the major groove of the double helix around an axis perpendicular to the base plane and passing roughly through the center of the sugar moiety. From an analysis of the considerable variations of this rotation angle as a function of time, it is possible to estimate the lifetime of the base pair as well as the activation energy for the opening process. These values are found to be in good agreement with the corresponding experimental measurements obtained by hydrogen exchange. This study thus points to the stochastic character of the base pair opening process in double-stranded nucleic acids.

It is now well-acknowledged that the helices formed by double-stranded nucleic acids are not rigid entities, but present rather a high degree of flexibility characterized by numerous thermally excited motions of atoms or groups of atoms. These motions are generally very fast; for example, the motions detected by NMR spectroscopy involving the phosphodiester backbone or the torsional motions localized in the base pairs revealed by fluorescence depolarization studies have relaxation times in the nanosecond time range.[1-6]

In contrast, the so-called opening reaction, leading to a state with disrupted base pairs, is surprisingly slow and occurs on a millisecond time scale.[7] The existence of this open state has been inferred principally from hydrogen-exchange experiments where the exchange occurs between water protons and base imino protons. In the native conformation these protons are completely shielded from the water molecules by being hydrogen bonded within Watson–Crick base pairs, and thus, for the exchange to occur, the formation of a transient open state where these protons become accessible to the solvent, is required.

Despite many experimental hydrogen-exchange studies, which have successfully delineated the base pair opening time range[7,8] and the overall reaction scheme of the proton-exchange process in double-stranded nucleic acids,[9] a detailed description, as well as a basic theoretical understanding, of the opening reaction is still lacking. One aspect of this understanding involves the conformational features of the open state which remain completely unknown (the low stability of the open state compared to the native state precludes any direct measurements by NMR spectroscopy or X-ray crystallography). Most notably, nothing is known about either the molecular opening trajectory or the underlying mechanism by which the energy barrier involved in breaking the base pair can be overcome.

In order to improve our fundamental understanding of the opening reaction in double-stranded nucleic acids, we have recently undertaken a theoretical study on a B-DNA $(dA)_5\cdot(dT)_5$ oligomer by molecular modelling techniques.[10,11] Using an algorithm specifically designed for nucleic acid energy optimization,[12] the energetics of the different opening pathways available for the central AT base pair have been computed. These energies were found to be comparable to the experimental activation energies determined from hydrogen-exchange experiments, thus indicating that this single base pair opening model could account correctly for the energies involved in the real DNA opening process.

In the present work we address more specifically the question of the time dependence of the opening reaction, with the aim of finding, at the molecular level, a mechanism which can explain the surprisingly slow opening kinetics. Therefore, as a first step in this direction, we have simulated the opening kinetics of the central thymine in the $(dA)_5\cdot(dT)_5$ oligonucleotide using Brownian dynamics. The results of this study are found to be in good agreement with experimental values, thus supporting the stochastic character of the opening reaction mechanism and the basic premises of the model we have employed.

Methods

The present Brownian dynamics simulation of opening the central thymine in the $(dA)_5\cdot(dT)_5$ oligonucleotide refers to the molecular opening model described by Ramstein and Lavery.[10] According to this model, based on the results of preliminary investigations by molecular

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