filtration[23] removes the unincorporated ^{32}P, and a plot of scintillation counts converted to concentration versus time yields rate constants. Because of the sensitivity of the assay, kinetic studies can be completed in 1 day even when the hydrolytic rate is quite slow. Studies done at approximately equal equivalents of **1** and RNA phosphates (37 °C and pH 7.05) at concentrations of 7–500 μM yield rate enhancements of 8–20-fold over 250 mM imidazole alone.[24]

Scheme I shows a mechanistic proposal in which imidazole acts as a general base to deliver the 2′-OH to the phosphodiester linkage.[25] The phosphorane transition state is stabilized by ion pairing and/or guanidinium general-acid proton transfer from **1**.[16] It is often postulated that guanidiniums play the role of electrophilic catalysts at the active sites of phosphoryl transfer enzymes.[26] These mRNA results corroborate, in a totally synthetic system, the role of guanidinium groups as electrophilic activators.

In conclusion, the RNA cleavage catalyzed by **1** at micromolar concentrations in aqueous solution at neutral pH and 37 °C, along with the parallel recent study on an RNA analog,[17] demonstrates that mimicking the arginine functionalities of SNase is a successful approach for catalyzing phosphodiester cleavage. Further rate enhancements can be expected by expanding the structure of **1** to include additional SNase functionalities such as an intramolecular general base and a metal binding site. In addition, the design of **1** includes an ester group for potential coupling of an RNA recognition moiety.

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Theoretical Characterization of the Transition Structure for an S_N2 Reaction at Neutral Nitrogen

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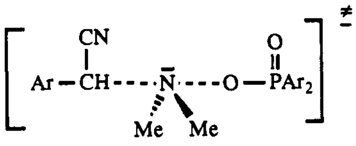
Nucleophilic displacement reactions at nitrogen, intriguing analogies to the classical organic S_N type reactions, are attracting an increasing amount of attention.[1-7] The preparation of amines via reaction of organometallic compounds with *N*-haloamines is a useful example of reaction umpolung.[1] The reaction of ultimate carcinogens of aromatic amines with bionucleophiles has been studied in detail; while nitrenium intermediates have been proposed,[2] model reactions have been shown to follow an S_N2 mechanism.[3,4] Recently, experimental evidence for a classical S_N2 transition state involving nitrogen (**1**) has been given by means of double labeling experiments.[6]



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While the S_N2 reaction at carbon has been studied theoretically in detail,[8,9] little is known about the corresponding nitrogen species. We now report ab initio quantum mechanical evidence[10] for the degenerate model reaction

$$F^- + H_2NF \rightarrow F^-{\cdot}H_2N{-}F \xrightarrow{[F{-}NH_2{-}F]^{-*}} F{-}NH_2{\cdot}F^- \rightarrow NH_2F + F^- \quad (1)$$

supporting the existence of transition structures like **1**. We chose this particular system as a model since it allows treatment at relatively high levels of theory.

As in gas-phase S_N2 reactions at a carbon center,[11] the first step in our model reaction is the formation of an ion–dipole complex, $F^-{\cdot}NH_2F$. This complex possesses C_1 symmetry and is characterized by a single, essentially linear $F^-{\cdots}H{-}N$ hydrogen bond (**2b**, see Figure 1). The C_s symmetry complex **2a** with two $F^-{\cdots}H$ contacts is the transition state for migration of the F^- from one H to the other. This situation is somewhat different from that in the analogous $F^-{\cdot}CH_3F$ complex (with C_{3v} symmetry and three $F^-{\cdots}H{-}C$ contacts), but is in agreement with theoretical findings for the related $F^-{\cdot}H_2O$ complex.[12] The actual dis-

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Table I. Absolute and Relative Energies of $NH_2F_2^-$ Species[a]

level of theory[b]	absolute energy, −au (rel energy, kcal/mol)			
	$NH_2F + F^-$	$F^-\cdots H_2NF$, C_s (**2a**)	$F^-\cdots H_2NF$, C_1 (**2b**)	$F-NH_2-F^-$, C_{2v} (**2c**)
DZP/SCF	254.421 63 (32.9)	254.466 04 (5.0)	254.474 03 (0.0)	254.434 59 (24.7)
DZP+/SCF	254.456 54 (25.1)	254.491 02 (3.5)	254.496 59 (0.0)	254.456 26 (25.3)
DZP2++/SCF	254.456 76 (25.1)	254.491 21 (3.5)	254.496 81 (0.0)	254.456 42 (25.3)
TZP+/SCF	254.481 83 (25.0)	254.516 06 (3.5)	254.521 68 (0.0)	254.481 14 (25.4)
TZ2Pfd++/SCF	254.488 67 (24.4)	254.521 96 (3.6)	254.527 62 (0.0)	254.487 60 (25.1)
DZP+/CISD	254.996 15[c] (27.1)	255.032 15 (4.5)	255.039 40 (0.0)	255.002 56 (23.1)
DZP+/CCSD	255.065 99 (27.1)	255.101 87 (4.6)	255.109 21 (0.0)	255.077 34 (20.0)
TZP+/CISD	255.079 93[c] (26.9)	255.115 50 (4.6)	255.128 85 (0.0)	255.084 57 (24.0)
ZPE (TZP+/SCF)[d]	18.8 [0]	19.3 [1]	19.3 [0]	18.5 [1]

[a] The relative energies are referenced to the most stable structure, complex **2b**. [b] Fully optimized in the given symmetry. [c] Since the CISD method is not size consistent, single-point calculations were performed on a "supermolecule", i.e., NH_2F (optimized at the level indicated) and F^-, separated by $1000a_0$ (>500 Å), cf. ref 13. [d] Zero-point energies [in brackets: number of imaginary frequencies].

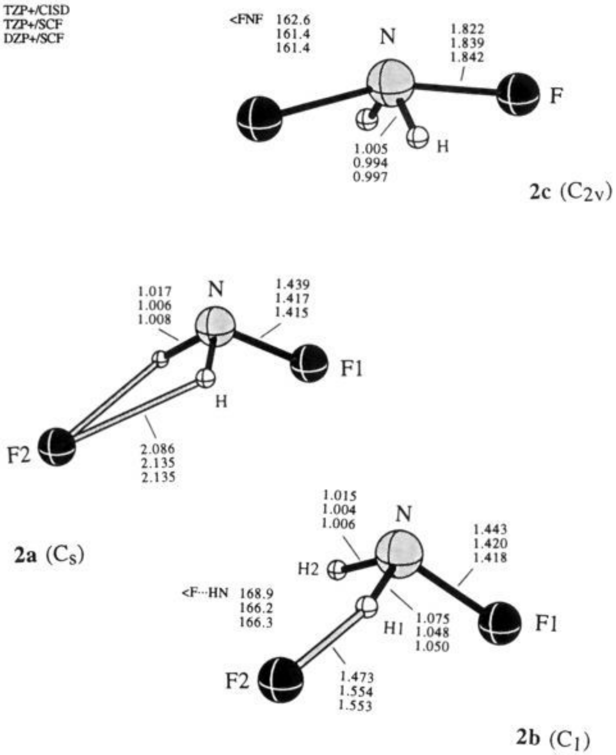

Figure 1. Ab initio equilibrium geometries of $NH_2F_2^-$ species **2a**–**2c** including selected bond lengths (in angstroms) and bond angles (in degrees).

placement reaction proceeds through transition structure **2c** (C_{2v} symmetry, Figure 1) with a nearly linear F–N–F arrangement. Vibrational frequency evaluations at the TZP+/SCF level confirm that **2c** is a true transition state with one imaginary frequency ($\nu = 626i$ cm^{-1}).

Most geometrical parameters of the isolated NH_2F and of structures **2a**–**2c** show only a moderate dependence on the level of optimization (see Figure 1 for selected levels). Except for the N–F1 and F2···H1 distances in **2b**, which is somewhat more susceptible to the inclusion of diffuse functions and electron correlation, changes in bond lengths and bond angles upon basis set improvement are less than 0.03–0.04 Å and 1–2°, respectively.

Due to basis set superposition error (BSSE), the theoretical complexation energies are very sensitive to the inclusion of diffuse functions on the heavy atoms (compare DZP and DZP+ values, first column in Table I). Stepwise improvement of the theoretical level results in relatively small further changes of the computed complexation energy: e.g., the effect of an additional set of diffuse functions on all atoms is very small (compare DZP+ and DZP2++ values), and inclusion of electron correlation increases the calculated complexation energy only slightly (compare TZP+/SCF and TZP+/CISD values).[14] Our best estimate, 26.4 kcal/mol (TZP+/CISD corrected for the TZP+/SCF zero-point energies), compares well to the experimental hydrogen bond energy of 26.8 kcal/mol for F^- and H_2NPh in the gas phase.[15]

Similarly to the complexation energy, the relative energies of **2a**–**2c** display only small variations with the theoretical levels employed (Table I). No significant changes are noticed upon inclusion of more and higher polarization functions (compare TZP+/SCF and TZ2Pfd++/SCF values) or inclusion of electron correlation (compare SCF and CISD values). While electron correlation is important for geometrical parameters associated with flat regions of the potential energy surface (like the F2···H1 distance in **2b**, see Figure 1), the relative energies are not affected drastically: The corresponding SCF and CISD values differ by less than 1–2 kcal/mol. A higher level of electron correlation, as assessed by means of the coupled cluster (CCSD) method, indicates a somewhat larger stabilization of the transition structure **2c** (by ca. 3 kcal/mol, compare DZP+/CISD and DZP+/CCSD values). However, in further studies of related species, even the rather modest DZP+/SCF level should give reliable results.

At the highest level employed, TZP+/CISD, the "intrinsic" barrier for model reaction (1), i.e., the energy difference between **2b** and **2c**, is 24.0 kcal/mol. While this barrier is somewhat larger than that for the isoelectronic reaction

$$F^-\cdot H_3C-F \xrightarrow{[F-CH_3-F]^{-\ddagger}} F-CH_3\cdot F^- \qquad (2)$$

at a carbon center (17.1 kcal/mol at the DZDP/CISD level),[10] it is of the same order of magnitude. However, as for the S_N2 reaction at carbon, a dramatic solvent effect is expected on the shape of the potential energy surface (and on the barrier height in particular),[8a,9] which precludes a direct relation of these results to experiments in solution.

In summary, the concerted nucleophilic displacement reaction of F^- and H_2NF shows the same characteristics as the S_N2 prototype reaction (2), namely, complex formation and a symmetrical transition state (i.e., a double-well potential). Although probably requiring a higher activation energy than the carbon analogue, the S_N2 reaction at neutral nitrogen is confirmed to be a viable pathway, in agreement with experimental findings.[3-7] Further studies involving other nucleophiles and leaving groups would provide a full theoretical picture of the S_N2 reaction at neutral nitrogen.

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