mL) with 0.1 mL of chloroform added as internal standard in an NMR tube. The NMR spectrum of the solution was recorded and the ratio of TMD to chloroform was determined. The mixture was cooled to −78 °C and gaseous boron trifluoride was bubbled through the solution for 10 s. The reaction mixture was allowed to stand at −78 °C for 30 min, and 50 μL of methanol was then added to dissociate complexes. The solution was allowed to warm quickly to room temperature, and the yields of products (average of ten experiments) were determined by integrations of product absorptions relative to that for internal standard ($CHCl_3$) in the ambient temperature NMR spectrum of the reaction mixture. Thus the product yields directly reflect the percentage of dioxetane that was converted to each product. Total recovery of material was 90%, of which 27% was recovered TMD. The remaining 63% of the material consisted of 70% pinacolone, 25% cyclic pinacolone diperoxide, and 5% acetone.

The combined reaction mixtures were washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Solvent and volatile products were removed at reduced pressure, yielding light yellow crystals. Recrystallization from ethanol (at −78 °C) gave 9 mg (10% based on TMD consumed) of white crystals of pinacolone diperoxide, mp 121.5–122.5 °C (mixed mp with an authentic sample). The IR spectrum (0.1 mm cell vs. CCl_4) 3030 (s), 1485 (m), 1470 (w), 1460 (w), 1405 (m), 1380 (m), 1170 (m), 1120 (s), 1015 (w), 920 (m), 730 (s) cm^{-1}; and the NMR spectrum (CCl_4) singlet at δ 0.97 (9 H) and singlet at 1.66 (3 H) were in agreement with those of an authentic sample.

Determination of the Total Peroxide Content in the Low Temperature Reaction of TMD with Boron Trifluoride. TMD (8.3 mg, 0.0716 mmol, purified by sublimation) was dissolved in 0.4 mL of dichloromethane and 0.1 mL of chloroform (internal standard). The NMR spectrum of the solution was recorded; the sample (in an NMR tube) was cooled to −78 °C and gaseous boron trifluoride was bubbled rapidly through the cold solution for 10 s. The NMR tube was then tightly capped and allowed to stand at −78 °C for 20–30 min. Methanol (45 μL) was added to the cold reaction mixture, and the resulting solution was allowed to warm quickly to room temperature (~5 min). The NMR spectrum of the reaction mixture was recorded and product composition was determined by integrations of product absorptions relative to that for chloroform (internal standard). Total peroxide content in the reaction mixture was determined by iodometric titration as described below.

Glacial acetic acid (5 mL) was added to 0.5 mL of saturated aqueous potassium iodide solution in an Erlenmeyer flask. Several lumps of dry ice were added to sweep out the air and the flask was loosely stoppered. The TMD–BF_3 reaction mixture was added to the acetic acid–KI solution, and the resulting solution was allowed to stand at room temperature for 15 min. The liberated I_2 was then titrated with 0.137 M $Na_2S_2O_3$. Under these conditions pinacolone diperoxide does *not* liberate iodine.

The results of this experiment and two others are shown in Table I.

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Relative Energies of Diprotonation of Small Neutral Molecules

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Abstract: The proton affinities of a group of cations have been determined by ab initio molecular orbital calculations. For both first and second row bases, the proton affinity for diprotonation on the same atom is found to be negative; for diprotonation on neighboring atoms, the proton affinity is sufficiently large (and positive) to allow possible experimental determination in the gas phase. A simple electrostatic theory for estimating the difference between first and second proton affinities is surprisingly accurate when the results of such calculations are compared with the results of the ab initio calculations.

We have been intrigued by the fact that the cyclization of creatine (*N*-methylguanidinoacetic acid) to form creatinine (1-methyl-2-amino-2-imidazolin-4-one) occurs under very strongly acidic conditions (~9 N HCl),[1] an effective acidity far removed from the pK_a of creatine's guanidinium group (~13).[2] One possibility is that the small amount of free guanidine base present in this highly acidic medium behaves as the nucleophile in the formation of the new C–N bond. Another

Table I. Calculated Proton Affinities[7]

Molecule protonated	Proton affinity, kcal/mol
CH_3OH	188
$CH_3OH_2^+$	−32
CH_3SH	171
$CH_3SH_2^+$	−12
NH_2NH_2	223
$NH_2NH_3^+$	64
$NH_2CH_2NH_2$	227
$NH_2CH_2NH_3^+$	108
$HNC(NH_2)_2$	260[a]
$H_2NC(NH_2)_2^+$	70

[a] Reference 12.

possibility is that the guanidinium ion itself of creatine is behaving as the attacking base or nucleophile. The same two choices of nucleophilic species exist in the reversible phosphorylation of creatine by ATP, catalyzed by the enzyme creatine kinase.[3] In considering these reactions, we asked ourselves the following question: How likely is guanidinium to be nucleophilic?[4] We thus decided to examine, using theoretical calculations, the proton affinities of a group of cations, using the relative proton affinity values as a first approximation to the relative nucleophilicities[5] for this group of cations. We chose to study mono- and diprotonation of methanol, methanethiol, hydrazine, diaminomethane (DAM), 1,2-diaminoethane (DAE), and guanidine by ab initio molecular orbital methods using a 431G basis set and a standard geometry model.[6]

Results and Discussion

The proton affinities are reported in Table I. It should be emphasized that this level of basis set is capable of giving proton affinities in good agreement with experiment. Trends are very well reproduced, with the absolute proton affinities generally overestimated by 10–20 kcal/mol.[7]

Our first interesting result is that diprotonation of methanol is *repulsive*. After these calculations were completed, we learned of the work of Daudel et al.,[8] who studied multiple protonation of H_2O, HF, and Ne, and found similar results as we did for CH_3OH.

We felt that diprotonation of methanethiol might be less repulsive, since sulfur is more polarizable than oxygen. It is clear from Table I that S diprotonation is still unfavorable, albeit significantly less unfavorable than O diprotonation. A complete geometry optimization on $CH_3SH_2^+$ and $CH_3SH_2^{2+}$ might decrease the energy difference between them, but it still is not likely that one will be able to observe diprotonated S experimentally in the gas phase.

We next considered diprotonation on adjacent atoms, hydrazine being a simple model for this. In this case, protonating $N_2H_5^+$ is favorable, but only by 64 kcal/mol, a value far less than that found for protonating N_2H_4 (223 kcal/mol).[9]

We then considered protonation of diaminomethane. The proton affinity of DAM is similar to that of methylamine, but the proton affinity of $DAMH^+$ is only 108 kcal/mol.

Finally, we considered the proton affinity of the guanidinium ion. Guanidine has an unusually high proton affinity (calculated to be 260 kcal/mol),[10] but we calculated the proton affinity of guanidinium to be only 70 kcal/mol. Thus, guanidine has a second proton affinity of comparable magnitude to that of hydrazine, which is consistent with the picture that the lone pairs of both molecules are still "available" for attack on strong electrophiles.[3,4]

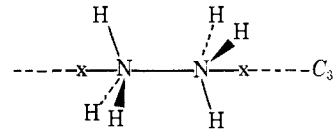
What general model can one come up with to rationalize these proton affinities of cations? A simple electrostatic repulsion model is consistent with the magnitude of the second

Table II. Dependence of Diprotonation on Distance

Molecule	Proton affinity, kcal/mol
$NH_2CH_2CH_2NH_2$ (*trans*) (**3**)	231.3
$NH_2CH_2CH_2NH_2$ (*gauche*) (**5**)	229.3[a] (244.9)[b]
$NH_2CH_2CH_2NH_3^+$ (*trans*)	140.3
$NH_2CH_2CH_2NH_3^+$ (*gauche*) (**7**)	131.3
NH_3	222.2
$NH_3\cdots NH_3$ (**4**)	217.8
$NH_3\cdots NH_4^+$	138.0

[a] $\Delta E = E(7) - E(5)$. [b] $\Delta E = E(6) - E(5)$.

proton affinities of N_2H_4 and $NH_2CH_2NH_2$. If one places the positive charge along the C_3 axis at the location where the hydrogen coordinates project onto this axis (see x's in structure **1**), one calculates an electrostatic repulsion ($\epsilon = 1$) for diprotonation of hydrazine of 155 kcal/mol. Thus, if this repulsion is the cause of the lowered proton affinity of the cation, one predicts from this model that the second proton affinity of hydrazine should be 68 kcal/mol, remarkably close to the calculated value (64 kcal/mol). Applying the same model to diaminomethane by placing the + charges in an analogous manner as for hydrazine (see structure **2**) leads to a predicted second proton affinity of 114 kcal/mol. Again, this compares well with the calculated value (108 kcal/mol). If one considers diprotonated methanol to involve a repulsion between the two hydrogens added (using the H–H distance to determine the repulsion), then one calculates this repulsion to be 212 kcal/mol and a second proton affinity of −24 kcal/mol, close to our ab initio results of −32 kcal/mol for this process.



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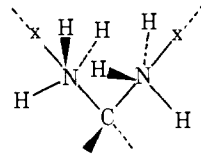

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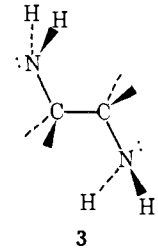
Finally, we consider the trans conformation of 1,2-diaminoethane (DAE, **3**) just using the electrostatic model and assuming a first proton affinity equal to that of DAM. In DAE, one predicts diprotonation to be less energetically favorable than monoprotonation by only 76 kcal/mol. Thus, the second proton affinity of this compound would be expected to be ~150 kcal/mol.

We decided to carry out explicit ab initio calculations on 1,2-diaminoethane as well as a model system ($NH_3\cdots NH_3$) designed to assess the role of "through-space" vs. "through-bond" effects.

We first studied *trans*-1,2-diaminoethane (**3**) (Table II) and found a first proton affinity similar to that for CH_3NH_2; the



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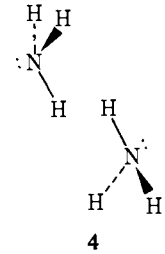

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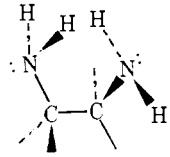
second proton affinity of 140 kcal/mol is somewhat smaller than the ~150 kcal/mol expected from the simple electrostatic model. We also studied mono- and diprotonation of two NH_3 molecules (**4**) located exactly as they are in the trans conformation of 1,2-diaminoethane. Here the difference between the first and second proton affinities is 80 kcal/mol, a value quite close to that estimated from the electrostatic model (76 kcal/mol). This agreement is probably as good as could be expected, in view of the simplicity of the model.

We calculated the proton affinities of *gauche*-1,2-diaminoethane (**5**). The first proton affinity is highly dependent on



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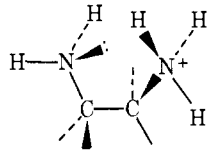
conformation, as one would expect. Conformation **6** is more stable than conformation **7** by 15.6 kcal/mol, which makes



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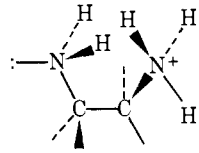

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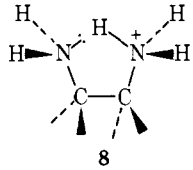
sense since the former conformation allows a favorable $^{+}N\text{-}H\cdots{:}N$ interaction. This type of an interaction is important in explaining the pK_a's of small bifunctional acids. Eberson[11] has pointed out that the Kirkwood-Westheimer[12] theory works well for small bifunctional acids only if one takes into consideration the possibility of $-COO^{-}\cdots H\text{-}O$ hydrogen bonding of the monoanion. The second proton affinity (relative to **7**) is 98 kcal/mol less than the first, whereas the simple electrostatic model leads to the prediction of an electrostatic repulsion of 103 kcal/mol.

Why is the difference between diprotonation of the gauche and trans forms (9 kcal/mol) so much smaller than that predicted by the electrostatic model (27 kcal/mol)? We suggest that this is one more example of the gauche effect,[13] where the second $^{+}NH_3$ group trans to the first does not allow as effective hyperconjugation of the $^{+}NH_3$ groups with the adjacent CH_2 groups.

In view of the interesting gas phase experimental data which estimate the enthalpy of H-bond formation of 1,2-diaminoethane as >9.7[14] and 12.6 kcal/mol,[15] we decided to carry out an additional calculation on the protonated H-bonded form of 1,2-diaminoethane in which the "optimum" H-bonded complex was formed. Structure **8** involves eight eclipsed bonds



8

and, reasoning from the experimental rotational barriers in ethane, methylamine, and methylammonium, a tortional strain energy of ~8 kcal/mol. However, we calculate its total energy to be 1.3 kcal/mol lower than **6**, leading to a *net* H-bond energy of 13.1 kcal/mol, in good agreement with experiment. This "H-bond energy" comes from a comparison of the total energies of **8** and the singly protonated *trans*-1,2-diaminoethane. The fact that Yamdagni and Kebarle[15] find a "strain energy" of 10.4 kcal/mol for H-bonded $NH_2CH_2CH_2NH_3^{+}$ is consistent with our estimated "strain energy" of 8 kcal/mol for structure **8**; the remaining "strain energy" might come from internal bond angle and bond length distortions.[16] Although it is presently too expensive for us to carry out a complete geometry optimization for $NH_2CH_2CH_2NH_3^{+}$ at the 431G level, it would be an interesting calculation to do either using molecular mechanics or using STO-3G. In our opinion, it is unlikely the results of a more complete geometry optimization at the ab initio level will change the above results substantially.

Why is **8** more stable than **6**, given the tortional strain energy of the former? We suggest that this is due to the more favorable H-bond structure of **8**. The $N\cdots H^{\delta+}$ distance in **8** is 1.85 Å (for the proton involved in the H bond); for **6**, the corresponding distance is 2.50 Å. The optimum $N\cdots H^{\delta+}$ distance in the $H_3N\cdots HNH_3^{+}$ complex has been calculated to be ~1.77 Å.[17]

Can one expect to detect dications in the gas phase? Even though the proton affinities we have calculated suggest that diprotonation on adjacent (and further separated) atoms is energetically more favorable than protonation of He (and thus proton transfer from HeH^{+} to hydrazinium would be thermodynamically favorable[18]), one still needs to consider the activation barrier for the approach of a proton to an already positively charged molecule. For hydrazinium, we calculate an activation barrier for proton approach along the lone pair direction of ~60 kcal/mol, with the maximum energy occurring at $r(N\cdots H)$ ~3.5 Å. Thus, it does not appear that hydrazinium dication will be amenable to gas phase detection at room temperature. An ab initio evaluation of the activation energy for diprotonation of *trans*-1,2-diaminoethane (**3**) leads to a $\Delta E^{\ddagger}$ of 37 kcal/mol. Although this is still somewhat large compared to "normal" reactions which proceed at an observable rate room temperature, there are two factors which might increase the rate: (a) proton tunneling and (b) HeH^{+} instead of H^{+} as the approaching electrophile might sufficiently delocalize the plus charge to reduce the electrostatic repulsion. In any case, extrapolating the results from our hydrazine and 1,2-diaminoethane calculations, we expect that molecules where the two basic centers are held further apart (~5 Å) might well be detectable as diprotonated species in the gas phase.

An important question for experimental studies is whether our "scale" for proton affinities of cations ($N_2H_5^{+}$ ~ guandinium^{+} < $DAMH^{+}$ < $DAEH^{+}$) is correct for other electrophiles beside the proton or for solution basicities. It is difficult to predict the solution basicities from the gas phase proton affinities of the cations, since there are many examples where solution pK_a's do not parallel proton affinities, the relative pK_a's and proton affinities of the alkylamines being among them.[19] However, the second pK_a's of hydrazinium and guanidinium are similar, consistent with their relative diprotonation affinities.

There is good evidence that a simple electrostatic model is applicable to the estimation of the difference between pK_1 and pK_2 values in solution, providing one uses an appropriate dielectric constant to estimate the electrostatic repulsions. Kirkwood and Westheimer[12] found that the "effective" dielectric constant for dissociation of *small* bifunctional *acids* in H_2O was significantly smaller than that of the solvent. Our electrostatic model suggests that the second pK_a of DAE would be 0.69 smaller than the first pK_a for a dielectric constant of 80; the observed ΔpK_a, corrected for the statistical effect, is 2.55.[20] Thus, it appears that an effective dielectric constant much smaller than that of water can also be used to estimate ΔpK_a's for organic bases. This point has been emphasized before by Kokesh and Westheimer[21] in their study of the "anomalous" pK_a of a lysine residue of acetoacetate decarboxylase. These authors[21] also pointed out that in the interior of proteins, where the effective dielectric constant is rather low, these through-space interactions between lysine residues would

be of a much longer range and larger magnitude than expected for analogous solution pK_a's. One of us is currently using an electrostatic model to try to rationalize the anomalous pK_a's in proteins whose crystal structures are known.[22]

Summary and Conclusions

In this study we have examined proton affinities of cations by theoretical methods. Our results show clearly that diprotonation on both oxygen and sulfur are energetically unfavorable, but neighboring atom protonation (e.g., on the unprotonated nitrogen of hydrazinium or a nitrogen of guanidinium) is energetically favorable. We also suggest guidelines for finding possible candidates for gas phase measurements of diprotonation.

These calculations provide further support for Kirkwood and Westheimer's assumption[12] that the *predominant* effect in both bifunctional acidity and basicity is *through-space,* as well as elucidating an interesting case (*gauche*- vs. *trans*-1,2-diaminoethane) where *through-bond* effects play an important role.

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(4) We already know (ref 2) that the 1,1,2,2-tetramethylguanidinium ion can be protonated in H_2SO_4 solutions to produce a dicationic species with a $pK_a = -11$.
(5) We are aware that nucleophilicity and basicity do not always correlate, especially if one compares atoms in different rows in the periodic table [see J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962)].
(6) All internal angles were assumed to be tetrahedral in CH_3OH, N_2H_4, $(CH_2NH_2)_2$, and $CH_2(NH_2)_2$ and the protonated forms of these molecules. The bond lengths used were: r(C–O) = 1.43; r(C–N) = 1.47; r(N–N) = 1.47; r(C–S) = 1.818; r(S–H) = 1.325; r(C–H) = 1.1; r(N–H) = 1.0; r(O–H) = 0.96 Å. For CH_3SH the angles around the methyl were tetrahedral, but ∢(CHS) = 100.3°. The dihedral angles were chosen to stagger adjacent bonds with the lone pairs in hydrazine trans and lone pairs in diaminomethane both trans to the neighboring C–N bond. We are aware that these are not the minimum energy conformations of hydrazine and diaminomethane (because of the gauche effect; see L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 2376 (1972)), but the conformational energy differences are far too small to affect the qualitative conclusions we reach here. Similar reasoning can be used to justify our choice of idealized internal geometries for the above molecules. For the guanidinium dication we used the calculated geometry found for amidinium (P. Kollman, J. McKelvey, and P. Gund, *J. Am. Chem. Soc.*, **97**, 1640 (1975)) and used the hydrazinium-like geometry for the C–NH_3^+ fragment. The calculations were carried out with the program GAUSSIAN 70 (QCPE No. 236) using a 431G basis set: R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
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(16) It should be emphasized that the authors in ref 15 determined their strain energy in $NH_2(CH_2)_nNH_3^+$ by comparing the proton affinity of the $n = 2$ compound with those of higher n. Thus, their "strain energy" could be interpreted as being due to either a nonoptimum H-bond geometry or to the "tortional strain" discussed here. Our calculations suggest that $^+NH_3CH_2CH_2NH_2$ will have considerable tortional strain, compensated by the much better H bond in **8** compared to **6**.
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