Table I. Selected Distances and Angles for the $Cu_2(SR)_2$ Core of $[Co(en)_2(SCH_2CH_2NH_2)\cdot Cu(CH_3CN)_2]_2(ClO_4)_6\cdot 2H_2O$

Type	Distance, Å	Type	Angle, deg
Cu-S	2.406 (4)[a]	S-Cu-S	97.0 (1)
	2.342 (5)		
Cu-N	1.951 (1)	N-Cu-N	118.3 (5)
	1.951 (2)		
Cu-Cu	3.146 (2)	N-Cu-S	117.1 (5)
			105.4 (5)
S-S	3.557 (6)	Cu-S-Cu	83.0 (1)
S-Co	2.273 (5)	Cu-S-Co	137.2 (2)
			127.7 (2)
S-C	1.84 (2)	Cu-S-C	102.8 (5)
			105.2 (5)
Cu-Co	4.356 (3)	Co-S-C	96.9 (6)
	4.142 (3)		

[a] Estimated standard deviations are in parentheses.

unit. Pertinent bond lengths and angles are presented in Table I.

Each copper is bound to two mercaptide sulfurs and two acetonitrile nitrogens in a distorted tetrahedral configuration. The copper–copper distance, although too great for consideration of substantial metal–metal bonding, is not out of line with that expected for a reduced type 3 copper site in view of the predicted *maximum* separation of 5–6 Å for antiferromagnetically coupled coppers in oxidized type 3 copper sites.[1b] The S–Cu–S bond angle (97°) indicates that the planar ring imparts, or at least allows, a geometry about the copper atoms intermediate between that preferred by copper(I) (tetrahedral) and copper(II) (tetragonal), a fact which may be of importance in the oxidation–reduction behavior of type 3 copper.

A disulfide bond can be ruled out on the basis of the sulfur–sulfur distance. Of note, however, is the fact that each sulfur is simultaneously bound to the two coppers, one sp^3 carbon and one cobalt. It is thus conceivable that in the multicopper oxidases a cysteine sulfur atom, in addition to its function as a bridge between the two metals of the type 3 copper unit, serves as a further ligand bridge and as a mediator of intramolecular electron transfer between type 3 and type 1 or 2 copper chromophores. The possibility of such a structural arrangement in proteins, either in the ground state or in an electron-transfer transition state, seems worthy of serious consideration in view of the known facile inner-sphere electron-transfer mediating ability of coordinated mercaptide[5,6] and the kinetics of reduction of *Rhus vernicifera* laccase wherein reduction by hydroquinone indicated intramolecular electron transfer from type 2 to type 3 copper[7] and reduction by ferrocyanide suggested a common rate-determining step for reduction of type 1 and type 3 copper sites.[8]

Irradiation of the Co(III)–S–Cu(I) species (anaerobic, acidic solution) at 366 nm results in a decrease in intensity of the 365-nm absorption of the complex with concomitant production of aqueous Co(II) which suggests that the 365-nm absorption is due to either a primarily S → Co(III) or Cu(I) → S charge-transfer transition. The 365-nm band may thus result from a red shift of the S → Co(III) transition upon incorporation of Cu(I) into the complex. Alternatively coordination of Cu(I) to sulfur may give rise to a Cu(I) → S charge transfer centered at 365 nm while the S → Co(III) transition is shifted further into the ultraviolet where it is lost under other intense bands. From the available data we are unable to definitively choose between these alternatives. However, incorporation of CH_3Hg^+ into the starting cobalt complex results in a blue shift of the S → Co(III) charge-transfer band of ~10 nm while Ag(I) yields a red shift of <5 nm.[9] Since there is no a priori reason to expect Cu(I) binding to result in a red shift of the S → Co(III) transition of over 80 nm, and since Cu(I) → ligand transitions in the vicinity of 360 nm have previously been observed,[10] we prefer the second possibility.

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Gas Phase Basicity of Silanamines

Sir:

There is abundant evidence for the dichotomous donor-acceptor behavior of a trimethylsilyl (TMS) group.[1] For example, the relative basicities of the amines $Me_3MCH_2NH_2$[2] and acidities of the carboxylic acids $Me_3MCH_2CO_2H$[3] (M = C, Si) indicate that a trimethylsilyl group releases electrons more strongly than a *tert*-butyl group (Table I); the reported δ values for Me_3SiCH_2– range from −0.1 to −0.2.[4] This behavior is commensurate with the relative electronegativities and polarizabilities of carbon and silicon.[5] The trend is reversed, however, upon direct attachment of a trimethylsilyl group to a π-electron system. Under many, but not all, circumstances, the TMS group behaves as a weak electron acceptor. Examples of this phenomena are numerous and can be found in qualitative studies of basicity of silanamines and ethers,[6] linear free-energy relationships,[7] and spectroscopic investigations of unsaturated organosilicon derivatives.[8] The most frequently cited explanation for this observation involves $d\pi$–$p\pi$ bonding,[9] although the necessity of including d orbitals in the bonding description has been questioned.[10]

The importance of determining intrinsic, solvent-free, substituent effects in simple acid–base chemistry is well recognized.[11] In this communication we describe the results of our efforts to obtain a quantitative measure of the proton affinities of a number of silanamines and their carbon analogues. Our

Table I. Aqueous pK_A Values for Me_3MCH_2X (25 °C)

	X	
M	NH_2[a]	CO_2H[b]
C	11.0	5.0
Si	10.2	5.22

[a] Reference 2. [b] Reference 3.

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Table II. Gas Phase Proton Affinities of Tertiary Carbon and Silicon Amines

Compd	Proton affinity,[a] kcal mol^{-1}	Compd	Proton affinity,[a] kcal mol^{-1}
$Me_3Si(CH_2)_3NMe_2$	227.6		
$Me_3Si(CH_2)_2NMe_2$	227.6	$Me_3C(CH_2)_2NMe_2$	226.3
$Me_3SiCH_2NMe_2$	227.1	$Me_3CCH_2NMe_2$	225.8
$(t\text{-Bu})Me_2SiNMe_2$	225.6	$(t\text{-Bu})Me_2CNMe_2$	230.7

[a] Based upon a proton affinity (NH_3) = 201.0 ± 2 kcal/mol;[12] relative values are precise to ±0.2 kcal mol^{-1}.

data permit an assessment of the direction and magnitude of the electronic effects of a trimethylsilyl substituent in systems that are unencumbered by solvent effects.

Pulsed ion cyclotron resonance (ICR) mass spectrometry was used to measure equilibrium constants for proton-transfer reactions between amines and various reference bases.[12] Double resonance between protonated base pairs was observed for all base pairs and multiple overlaps with reference bases were employed whenever possible. The data, summarized in Table II, show the effect of alkyl groups on the relative basicity of tertiary amines. In particular the results confirm the electron releasing properties of a Me_3SiCH_2 group; dimethylaminomethyltrimethylsilane is 1.5 kcal more basic than the analogous carbon amine. Homologation produces identical changes (0.5 kcal/mol) in both carbon and silicon systems. Comparison with solution phase basicities (Table I) reveals the extent of attenuation of these differences in going from gas to solution phase.

The logical parent silanamine, dimethylaminotrimethylsilane (**1**) is not included in Table II. The proton affinity of this base could not be obtained by the ICR technique; indeed, most simple amines with silicon directly attached to nitrogen do not achieve equilibrium. Rather, these compounds undergo a facile proton-catalyzed, transamination reaction under the proton exchange conditions.[13]

$$Me_3SiNMe_2 + BH^+ \rightleftarrows Me_3SiNMe_2H^+ + B$$

1

$$Me_3SiNMe_2H^+ + NMe_3 \rightarrow Me_3SiNMe_3^+ + HNMe_2$$

The transamination reaction manifold can be eliminated by replacement of a methyl substituent with a *tert*-butyl group, an approach that has proven successful in the condensed phase to reduce the hydrolytic lability of trialkylsilyl protecting groups.[14] *tert*-Butyldimethylsilyldimethylamine does not undergo transamination under the ICR conditions and equilibrium could be achieved. This base, together with its carbon analogue, is included in Table II. The difference in proton affinity is striking. The silicon base is now 5 kcal/mol *less* basic than its carbon analogue—despite polarizability and inductive effects that operate to oppose this trend (i.e., the more electropositive and polarizable silicon is expected to increase the basicity of the silanamine). The electronic effects of the TMS group are best understood in terms of a ground-state perturbation between the nitrogen lone pair (n) and the HOMO–LUMOs of the substituent groups (π,π^*). This is illustrated in Charts I and II. When the substituent is silicon (Chart I, a), the dominant interaction produces a net stabilization, while net destabilization results when the substituent is carbon (b). In the second case, Chart II, both substituents produce a net destabilization; the magnitude of this destabilization is greatest with CH_2SiMe_3. This interpretation is consistent with recent spectroscopic investigations[8] and does not *require* the inclusion of silicon d orbitals.

Finally, it should be noted that the absence of a significant

Chart I. Qualitative Interaction Diagram for a Nitrogen Lone Pair with (a) $SiMe_2$ (*t*-Bu) and (b) CMe_2 (*t*-Bu)

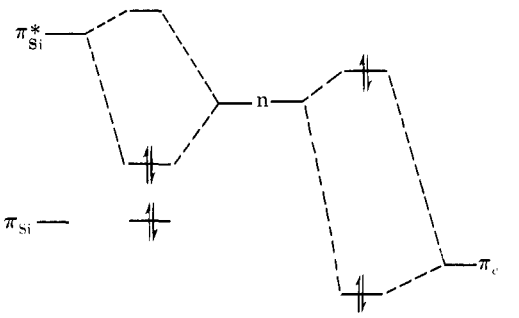
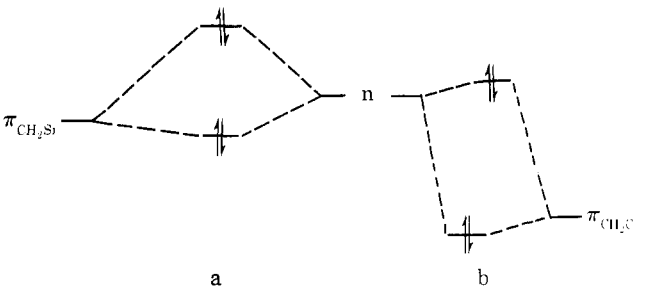
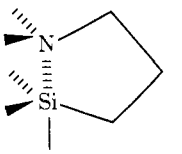


Chart II. Qualitative Interaction Diagram for a Nitrogen Lone Pair with (a) CH_2SiMe_3 and (b) CH_2CMe_3



diminution in basicity of $Me_3Si(CH_2)_3NMe_2$ argues against cyclic structures such as **2** from making an important contri-



2

bution to the ground state conformation of long chain silanamines.

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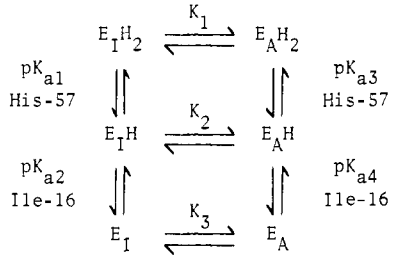
Thermal Characteristics of a Refolding Transition. The Alkaline Transition of α-Chymotrypsin[1]

Sir:

The alkaline transition of the serine proteases has already attracted considerable attention and has been studied in some depth with the chymotrypsin members of the family.[2-14] The apparent ubiquitousness of the transition and the participation of the "buried" ion pairs in the transition suggest possible clues to catalytic mechanism. Similarly, charge rearrangements leading to formation of the ILE-16 to ASP-194 ion pair are similar to those in chymotrypsinogen activation, thus providing promise for information of general importance in zymogen activation. Less attention has been given to the transition as a model protein "refolding" process (defined[15] as having large activation enthalpies and entropies but small overall standard enthalpy and entropy changes). Our recent studies have been directed toward the last aspect but produce information of broader applicability.

The stopped-flow, proflavin-binding method described by Fersht and Requena[6] was used to monitor the transition of α-chymotrypsin (Worthington Biochemical Corp.) at 30 to 40 pHs from pH 6 to pH 11, at each of six temperatures from 1 to 31 °C. Four to six determinations were made at each pH and temperature. This extensive data collection was required to achieve the small standard deviations essential for establishing the pH dependence of the equilibrium constant between active and inactive species. The pH data are fit by a minimal two-ionization mechanism (eq 1) at all temperatures.[16] Equation



(1)

1 was used by Fersht[7] to describe this equilibrium in α-CT, which also did not fit a one-ionization mechanism. van't Hoff plots for two of the fitted equilibrium constants are shown in Figure 1 and other "best-fit" values of thermodynamic parameters are given in Table I.

The most striking result is the magnitude of the curvature in the van't Hoff plots for K_1 and K_2 (Figure 1), since this may

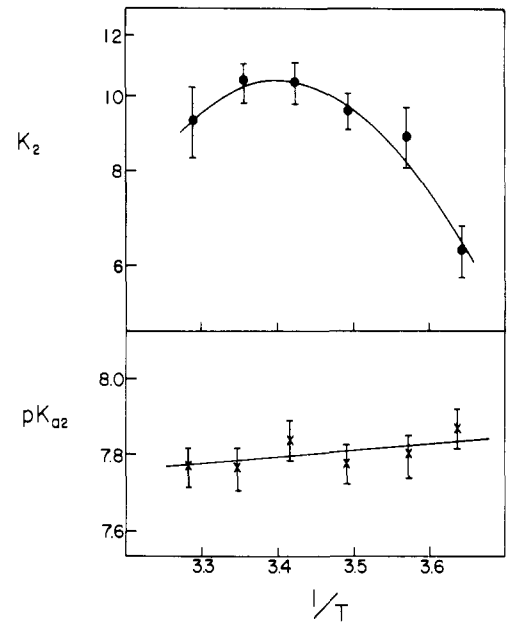


Figure 1. van't Hoff plots for two of the fitted equilibrium constants of eq 1 at ionic strength 0.2 (maintained with KCl in .005 M phosphate buffer). Error bars are estimates determined from the fitting procedure. The lines were drawn using the thermodynamic constants given in Table I: ●, K_2; ×, pK_{a2}. Consult ref 25 for further experimental details.

Table I. Thermodynamic Values for Processes in Eq 1 at Ionic Strength 0.2 at 25 °C[a]

	ΔG^b	ΔH^b	ΔS^c	$\Delta C_p{}^b$
$K_1{}^d$	−1.03 ± 0.04	0.17 ± 0.80	4.02 ± 3.0	−0.43 ± 0.200
$K_2{}^d$	−1.38 ± 0.04	−1.62 ± 0.90	−0.78 ± 3.0	−0.43 ± 0.200
$K_3{}^d$	1.81 ± 0.12	−4.55 ± 1.00	−21.4 ± 3.0	0 ± 0.200
pK_{a1}	9.52 ± 0.13	6.88 ± 1.30	−8.83 ± 3.0	
pK_{a2}	10.61 ± 0.07	1.14 ± 0.50	−31.8 ± 2.0	

[a] Conditions as in Figure 1. [b] In kilocalories/mole. [c] In entropy units. [d] Defined as $K_1 = (H_2E_A)/(H_2E_I)$; etc.

reflect large heat capacity changes. Overall $\Delta G°$, $\Delta H°$, and $\Delta S°$ values for these steps are small, suggesting that the active and inactive forms are very similar, but the large $\Delta C_p°$ values are not a priori consistent with this conclusion. The standard heat capacity change for the transition is ~10% of the $\Delta C_p°$ observed for thermal unfolding of α-CT at similar conditions.[17] It can be argued from protein unfolding studies that heat capacity differences reflect hydrophobic bonding changes in protein conformational changes;[18,19] therefore, one might speculate that the transconformation of HE_A to HE_I (or H_2E_A to H_2E_I) involves a considerable increase in water-polypeptide interaction. According to data from models for such effects, a relatively large negative entropy change should accompany this increased interaction,[15] but we observe very small $\Delta S°$ values (Table I). It is possible that the negative "hydrophobic" entropy change is balanced by a positive configurational entropy change, with a consequent reduction in configurational entropy for the active species. This rationalization agrees with some current proposals for enzymic catalysis, but it is based on the very tentative assumption that the heat capacity changes in a protein conformational transition are primarily a measure of water-polypeptide interaction.

The value of pK_{a1} and the corresponding ionization enthalpy suggest ionization process 1 is due to one of the two histidine residues. Studies of *N*-methyl-HIS-57 α-CT[20] support this assignment, identifying the residue as HIS-57.[21] According to conventional wisdom, pK_{a2} applies to the α-ammonium group of ILE-16[22] when exposed to solvent in form E_I.[2-8] However, although the pK_{a2} value is consistent with pK_a values

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