are the hydrogen bonds formed between the faces from bulk water. That is, these hydrogen bonds are more buried from bulk water, and thereby strengthened, when the cell-wall analogues are bound. In a similar way, the hydrogen bonds formed deep in the interior of proteins should in general be stronger than those near the surface. In this sense, the aggregates discussed in this paper model some aspects of protein folding. In relation to a possible biological role for dimerization, it should be noted that, with a dimerization equilibrium constant of 2×10^3 L M^{-1} at ristocetin concentrations of less than ca. 1 mM, the concentration of monomer outweighs that of dimer. The minimum inhibitory concentration (MIC) values for ristocetin[20] are of the order of 5 μM, which means that the antibiotic will occur as the monomer in solution (assuming the $K_{\text{dimerization}}$ for unbound ristocetin is similar to that for the tripeptide complex). However, this is not a measure of the concentration of antibiotic at the active site which would be expected to be much higher. Ristocetin may dimerize when bound to the bacterial cell wall unless the pulling together of two peptidoglycan termini is energetically restricted.

Conclusions

For ristocetin Ψ in the pseudoaqueous solvent 5:1 D_2O–acetonitrile-d_6, there is no evidence of sizable oscillations of rings 1 and 3. On addition of tripeptide, the NOEs of ring 3 are unchanged, whereas the changes of those of ring 1 indicate a rotation of the time-averaged orientation of the aromatic ring with respect to the peptide backbone. The major consequence of this is that it is energetically favorable for ring 1 to prevent solvent access to the carboxylate anion of the bound tripeptide but not to the polar groups of the binding pocket in the absence of peptide. This is consistent with our general observation of binding processes within the vancomycin group that the prevention of solvent access to the intermolecular electrostatic interactions is an energetically advantageous process. Intermolecular NOEs appropriate to the folding-in of ring 1 on addition of tripeptide are observed, e.g., between 1f and A_CCH, and 1e and A_NMe.

The different forms observed in a ristocetin A–tripeptide complex in D_2O–acetonitrile-d_6 solution are *not* the result of some slow intramolecular motion but represent the formation of either an asymmetric dimer or two symmetric dimers, with an association constant of ca. 2×10^3 L M^{-1}. The geometry of the two forms of the dimer, as determined by chemical shift changes and intermolecular NOEs, is such that the backsides of two molecules come together forming hydrogen bonds along the antibiotic amide backbone. This causes ring 6 of each molecule to lie close to the face of ring 4 of the other. The difference between the two forms of the dimer appears to be a result of the orientation of the tetrasaccharide attached to ring 4 of ristocetin. Primarily, it appears that the hydrophobic G_1, G_3, G_5 face of glucose occupies one side of ring 4 or the other. Also, in one form, the Rh_5, Rh_6 region lays over the face of ring 6.

Similar dimerization is observed in the ristocetin Ψ–tripeptide complex, although the off-rate of the dimer is considerably faster. This further implicates the tetrasaccharide in a specific role in dimer formation in addition to causing asymmetry. It appears that dimerization also occurs, but to a lesser extent, in DMSO solution and *may* be responsible for some of the NMR phenomena observed for vancomycin, A40926, and teicoplanin A_2. The geometry of the dimer is such that the intermolecular hydrogen bonds are shielded from the solvent by the coming together of large hydrophobic regions of the amino acid side chains within the antibiotic. This is analogous to the binding of the target peptide on the opposite face of the antibiotic.

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Registry No. Ac-Lys(Ac)-D-Ala-D-Ala-OH, 24570-39-6; ristocetin Ψ, 73412-13-2.

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A New Electronegativity Scale for the Correlation of Heats of Formation. 2. The Differences in Heats of Formation between Hydrogen and Methyl Derivatives

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Abstract: A new empirical equation $\Delta\Delta_f H^\circ(\mathrm{CH_3X/HX})/p = a' + b'V_X$ (5) has been found where $\Delta\Delta_f H^\circ(\mathrm{CH_3X/HX}) = \Delta_f H^\circ(\mathrm{CH_3X}) - \Delta_f H^\circ(\mathrm{HX})$, p is the number of hydrogen atoms in the HX molecule, V_X is the unshielded core potential of the atom in X attached to H, and a' and b' are constants. Heats of formation of some Si-, Ge-, Sn-, P-, As-, and Se-containing compounds are estimated with eq 5. Two sets of (a,b) constants are found to be very similar. One describes the relation when X is a monovalent atom and the other applies to polyvalent atoms.

Dating from the earliest efforts by Pauling in the 1930's to find quantitative relationships between heats of formation in homologous or otherwise related series of compounds and some measure of "electronegativity" of the atoms involved in bonding, there has developed a huge literature. Many of these efforts have been restricted to either single-bonded diatomic molecules or to substitutional effects in homologous compounds. Many of the authors have used different measures of electronegativity. Many of these efforts have been partially successful in correlating the empirical data in quantitative or semiquantitative terms. In recent years with greater facility by theoreticians in using various ab initio methods there has been a renewed effort to find empirical correlations for substituent effects in homologous series of organic compounds. Schleyer and co-workers have been among the most active in this field. Some of their findings and references to much of the earlier work will be found in a series of recent papers[1-3]

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Table I. Some Parameters and $\Delta_f H°$ (kcal/mol)[a]

X	V_X[d]	$\Delta_f H°(CH_3X)$	$\Delta_f H°(HX)$	p	$\Delta\Delta_f H°(CH_3X/HX)/p$
F	9.915	-55.9 ± 0.5[b]	-65.3 ± 0.2	1	9.4 ± 0.6
OH	8.11	-48.2 ± 0.1	-57.80 ± 0.01	2	4.8 ± 0.1
Cl	7.04	-19.6 ± 0.1	-22.06 ± 0.03	1	2.46 ± 0.2
NH_2	6.67	-5.5 ± 0.1	-11.0 ± 0.1	3	1.8 ± 0.1
Br	6.13	-8.5 ± 0.03	-8.67 ± 0.04	1	0.17 ± 0.4
SH	5.77	-5.5 ± 0.2	-4.9 ± 0.1	2	-0.3 ± 0.2
I	5.25	3.5 ± 0.3	6.33 ± 0.03	1	-2.8 ± 0.4
CH_3	5.19	-20.0 ± 0.1	-17.8 ± 0.1	4	-0.6 ± 0.1
SiH_3	3.41	-7.0 ± 1.0[c]	8.2 ± 0.5	4	-3.8 ± 0.3
H	2.70	-17.8 ± 0.1	0	2	-8.9 ± 0.1

[a] Data in Table I are from ref 7 unless specified. [b] Reference 8. [c] Reference 9. [d] The covalent radii of the diatomic molecules are taken from the bond lengths.[13] The other values are from ref 14 and 15.

dealing with both ions as well as molecules.

We have looked for such empirical relations for some time now in the hope of finding quantitative correlations with very limited success. Very recently however we have found a new measure for an electronegativity scale which seems to have quite general applicability and does meet our criteria for a quantitative correlation. This is described in the first of a series of papers[4] that are now starting to appear. In this first paper we describe a linear relationship between $\Delta_f H°(RX) - \Delta_f H°(MeX) \equiv \Delta\Delta_f H°(RX/MeX)$, where $R = CH_{3-m}(CH_3)_m$, and V_X, which is the unshielded core potential of the carbon-bonding atom in X. $\Delta\Delta_f H°(RX/MeX)$ depends only on m and V_X. We have found that

$\Delta\Delta_f H°(RX/MeX) =$

$$[0.9 - 1.5m(m-1)] - \frac{m}{0.67 + 0.21m} V_X = a_m + b_m V_X \quad (1)$$

where energy is in kcal mol^{-1} and $V_X = n_X/r_X$. n_X is the number of valence electrons in atom X and r_X is its covalent radius (Å). Equation 1 fits all measured data (over 35 compounds) to within 0.5 kcal/mol.

In the present paper, we report a similar linear relationship for differences in heats of formation between hydrogen and methyl derivatives.

Relation between $\Delta_f H°(CH_3X)$ and $\Delta_f H°(HX)$ vs V_X

Data on $\Delta_f H°(CH_3X)$ and $\Delta_f H°(HX)$ are listed in Table I. For X = F, Cl, Br, and I, $\Delta_f H°(CH_3X)$ and $\Delta_f H°(HX)$ decrease with increasing electronegativity of the X atom, that is, the molecules become more stable. Using the new electronegativity scale V_X we find that both $\Delta_f H°(MeX)$ and $\Delta_f H°(HX)$ vary linearly with V_X (Figure 1). Two different straight lines describe the two sequences for the halides. The differences $\Delta_f H°(CH_3X) - \Delta_f H°(HX) = \Delta\Delta_f H°(CH_3X/HX)$ are in consequence described very well by a single straight line (Figure 1), surprisingly, to within 0.4 kcal/mol.

Some time ago, Benson[5,6] pointed out that $\Delta\Delta_f H°(CH_3X/HX)$ is related to the electronegativity of X, where X = F, Cl, Br, I, OH, SH, NH_2, CH_3, and SiH_3. He was unable, however, to find any measure of electronegativity or formal charge that could correlate the data quantitatively.

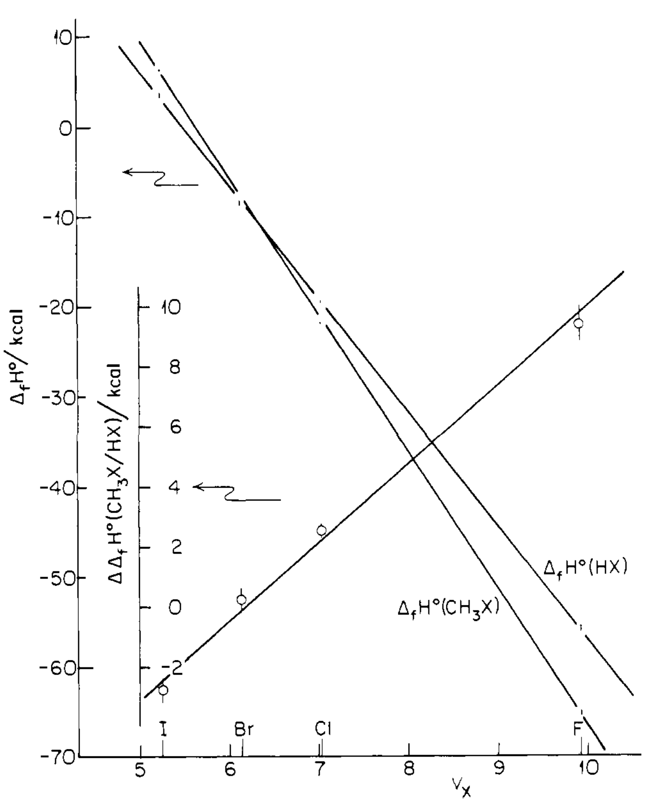

Figure 1. Relationship of $\Delta_f H°(CH_3X)$, $\Delta_f H°(HX)$, and $\Delta\Delta_f H°(CH_3X/HX)$ vs V_X.

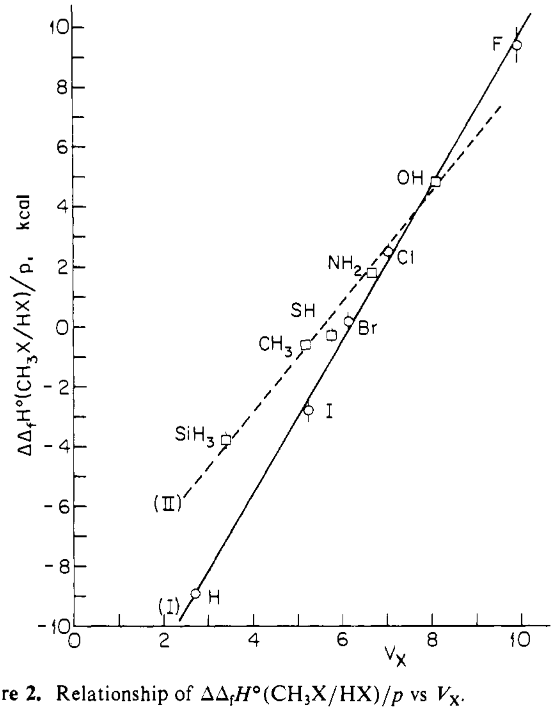

Figure 2. Relationship of $\Delta\Delta_f H°(CH_3X/HX)/p$ vs V_X.

The following observation was discovered recently in exploring our new electronegativity scale. If the value of $\Delta\Delta_f H°(CH_4/H_2)$, where X is now H, is divided by 2, the point falls exactly on the straight line of $\Delta\Delta_f H°(CH_3X/HX)$ vs V_X, for the halogens. This is shown by line I in Figure 2. The equation of line I is given by

$$\Delta\Delta_f H°(CH_3X/HX)/p = -15.8 + 2.58 V_X \quad (2)$$

where p is the number of hydrogen atoms in the HX molecule. The average and maximum deviation of line I are only 0.3 and 0.5 kcal per hydrogen atom in HX, respectively. Note that p = 1 for all the halogen atoms but p = 2 for HX = H_2.

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Table II. Some Estimated $\Delta_f H^\circ(CH_3X)$ (kcal mol^{-1})

X	V_X	$\Delta_f H^\circ(HX)^a$	p	$\Delta_f H^\circ(CH_3X)_{est}$
GeH_3	3.24	21.7	4	4.4 ± 2.0
SnH_3	2.83	38.9	4	18.6 ± 2.0
PH_2	4.55	1.3	3	-4.6 ± 1.5
AsH_2	4.20	15.9	3	8.1 ± 1.5
SeH	5.13	7.1	2	5.3 ± 1.0

[a] Reference 10.

Polyvalent Atoms, X

For polyvalent atoms X, a similar straight line has been found, as shown by line I in Figure 2. The equation for line II is given by

$$\Delta\Delta_f H^\circ(CH_3X/HX)/p = -10.2 + 1.81 V_X \qquad (3)$$

where X = OH, SH, NH_2, CH_3, and SiH_3. The average and maximum deviations from line II are also only 0.3 and 0.5 kcal per hydrogen atom in HX, respectively. It is interesting to note that the groups X = OH, NH_2, and SH fall equally close to lines I or II. Only X = CH_3 and SiH_3 fall uniquely on line II. Since the two lines are very close to each other it is possible to represent all the data by a single, mean linear relation having larger deviations. The maximum deviation is about 2 kcal per hydrogen atom in HX. This cruder linear equation is given by

$$\Delta\Delta_f H^\circ(CH_3X/HX)/p = -13.6 + 2.30 V_X \qquad (4)$$

In general, we have a relatively precise linear equation for the two categories:

$$\Delta\Delta_f H^\circ(CH_3X/HX)/p = a' + b'V_X \qquad (5)$$

Discussion

Empirical eq 5 can be used for estimating heats of formation of some compounds, CH_3X or HX. For example, we have derived from eq 3

$$\Delta_f H^\circ(CH_3X)_{est} = (-10.2 + 1.81 V_X)p + \Delta_f H^\circ(HX) \qquad (6)$$

Using known data for $\Delta_f H^\circ(HX)$, where X = GeH_3, SnH_3, PH_2, AsH_2, and SeH, we can estimate $\Delta_f H^\circ(CH_3X)$ (see Table II). The heats of formation of these CH_3X have not yet been measured.

Combining eq 1 with 5, we have a new linear equation

$$\Delta\Delta_f H^\circ(RX/HX) = (a_m + a'p) + (b_m + b'p)V_X \qquad (7)$$

If X is a polyvalent atom, then

$$\Delta\Delta_f H^\circ(RX/HX) = [0.9 - 1.5m(m-1) - 10.2p] + \left[1.81p - \frac{m}{0.67 + 0.21m}\right]V_X \qquad (8)$$

or

$$\Delta_f H^\circ(RX)_{est} = [0.9 - 1.5m(m-1) - 10.2p] + \left[1.81p - \frac{m}{0.67 + 0.21m}\right]V_X + \Delta_f H^\circ(HX) \qquad (9)$$

Equation 9 can be used for estimating heats of formation of many kinds of compounds, such as $CH_3CH_2SiH_3$, $(CH_3)_2CHGeH_3$, $(CH_3)_3CPH_2$, $(CH_3)_2CHAsH_2$, and C_2H_5SeH.

Thermochemists have sought for a long time to find methods for the quantitative estimation of the heats of formation of chemical compounds from carefully measured data on "key" members of homologous series. The need for and the utility of such methods are well documented.[6,11,12] With the discovery of V_X as a measure of the electronegativity and its successful application to differences in heats of formation we seem to have found such a method. We are currently exploring its application to a variety of other elements and properties such as ionization potentials where it again seems to produce remarkably quantitative correlations. We hope to report on these efforts in the near future. We shall also in these papers compare some of the results found by using other electronegativity scales.

$V_X = n_X/r_X$ is proportional to the (nucleus-core) potential, $e^2[Z - (Z - n_X)]/r_X$, experienced by a bonding electron at the covalent binding distance. it seems intuitively plausible that the strength of a covalent bond would show a dependence on V_X. It also seems reasonable that there will be a compensating potential in an actual compound due to the other bonding electrons, the nuclei to which they are attached, and their distances from the bond being considered. These latter influences might account in part for the appearance of p and m in our relationships.

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On the Electrostatic Bonding of CO to the Monocations of the First-Row Transition Elements

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Abstract: We have investigated the binding of a CO group to the early transition metal +1 ions Sc^+, Ti^+, V^+, and Cr^+ using ab initio electronic structure theory and find that the binding mechanism is electrostatic in nature with no more than 10% σ ligand-to-metal donations and practically no metal-to-ligand π donation. Our calculated M–C$^+$ bond lengths are very long, ranging from 2.25 Å in $CrCO^+$ ($^4\Pi$) to 3.38 Å in $ScCO^+$ ($^3\Sigma^+$). The calculated binding energies range from 3.4 kcal/mol in the $^3\Sigma^+$ state of $ScCO^+$ to 21.5 kcal/mol in the $^4\Pi$ state of $CrCO^+$ and correlate with the equilibrium M–C distance.

A well-known aspect of the first-row transition metal elements is their ability to form complexes with neutral ligands, most notably the carbonyl ligand,[1,2] CO. The mechanism through which carbon monoxide binds to neutral or (formally) low oxidation states of transition metal elements is of fundamental interest in organometallic chemistry.

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† On leave from the Department of Chemistry, University of Athens, Greece.

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