IMPROVED SCALES FOR METAL ION SOFTNESS AND TOXICITY

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Abstract—Ten scales relating to chemical hardness or softness of metal ions were compiled. These included eight published scales such as those of Pearson, Ahrland, Klopman, and Misono. Another scale consisted of the logs of the solubility products of metal sulfides, and yet another was a consensus scale constructed from $-\log K$ values for metal ion binding to seven soft ligands. These 10 scales were normalized and averaged. The resulting consensus scale for softness ($\sigma_{\text{con}}$) appeared to be superior to any of the 10 scales used in its construction based on correlations among the scales. Other possible indicators of softness were examined, including the standard electrode potential ($E^0$) and the bulk metal density ($p_{\text{metal}}$), both of which were also superior to most of the 10 scales just mentioned. Values for $\sigma_{\text{con}}$ may be computed from $E^0$, $p_{\text{metal}}$, and the first ionization potential ($I_p$), $R^2 = 0.867$, for the equation $\sigma_{\text{con}} = aE^0 + bI_p$. A consensus scale for toxicity ($T_{\text{con}}$) derived from studies with many different taxa correlated well ($R^2 = 0.807$) with $\sigma_{\text{con}}$ computed from the preceding equation, but incorporation of ion charge ($Z$) into the following equation, $T_{\text{con}} = a\sigma_{\text{con}} + b\sigma_{\text{con}}Z + cZ$, increased $R^2$ to 0.923. Substitution of other softness scales for $\sigma_{\text{con}}$ into equations to predict $T_{\text{con}}$ reduced the value of $R^2$. Thus, $\sigma_{\text{con}}$ appears to be a superior scale for metal ion softness and toxicity, the latter being an interactive function of both softness and charge.

Keywords—Hardness  
Metal ion  
Softness  
Toxicity

INTRODUCTION

Quantitative scales for metal ion hardness or softness were developed in the 1960s and subsequently, following earlier classification of ions into groups according to chemical lore accumulated for a century or more [1]. The groupings known as A and B came to be designated hard and soft, respectively, by Pearson [2], who specified a borderline class as well.

In general terms, hard and soft suggest greater or lesser resistance to deformation in response to a force—electric forces in the present case. Thus, hard ions have greater resistance to deformation of the electron cloud, are less polarized when chemically bound, and have a greater tendency to form ionic bonds. Soft ions have lesser resistance to deformation of the electron cloud, are more polarized when chemically bound, and have a greater tendency to form covalent bonds [2-5]. In the words of Owny and Newman [6], "The consequence of high polarizability is that the cation [metal ion] actually penetrates the anionic electron cloud [of the ligand] producing a predominantly covalent bond" (p 242). Hard metal ions bond more strongly with hard ligands (e.g., F- and O donors), and soft metal ions bond more strongly with soft ligands (e.g., I- and S donors) [4,7].

A modern version of metal ion classification (Leach MR. 2006. The Chemogenesis Web Book, http://www.meta-synthesis.com/webbook/43-hsah/HSAB.html), differing slightly from Pearson’s 1963 classification, is presented here for some of the 82 ions considered in the present study: hard ions: Al3+, Be2+, Ca2+, Ce3+, Co3+, Cr3+, Fe3+, Ga3+, H+, In3+, K+, La3+, Mg2+, Mn2+, Na+, Nb3+, Sc3+, Sn2+, Ti4+, U3+, and Zr4+; borderline ions: Bi3+, Co2+, Cu2+, Fe2+, Ir3+, Ni2+, Pb2+, Ru3+, Sn2+, and Zn2+; and soft ions: Ag+, Au+, Cd2+, Cu+, Hg+, Hg2+, Pd2+, Pb2+, Pt2+, Ti4+, and Ti4+.

Toxicologists and many physiologists will recognize that the soft ions are commonly very toxic but that the hard ions of charge ($Z$) $<$ 3 are commonly less toxic. All ions of $Z > 2$ appear to be toxic [8]. With regard to the latter point, one must remember that multivalent cations are very prone to hydrolysis and that the free metal ion is never the majority species when pH > pK(H2O) where pK(H2O) is $-\log$ of the first hydrolysis constant. For Al3+ that means that pH must be $<5.0$, and for Fe3+ the pH must be $<2.2$. This puts great restraints on toxicological studies, especially for ions injected into pH-neutral body fluids, for example, which contain numerous metal binding ligands in addition to OH-. For studies with aquatic organisms or plant roots, simple solutions of pH $<$ 4 can be used sometimes [9,10].

The most commonly cited scale for hardness or softness is the one computed by Pearson and Mawby [11], commonly denoted by $\sigma_p$. This scale is based on ion binding to the hard ligand F- and the soft ligand I-. It is computed as $[CBE(F^-) - CBE(I^-)]/CBE(F^-)$, where CBE is the coordinate bond energy. This is a hardness scale because values increase with increasing hardness, but a sign change converts the scale into a softness scale. Toxicologists in particular have used this scale in their attempts to relate ion toxicity to the chemical properties of the ions [8,12-16]. It is surprising, therefore, that $\sigma_p$ correlates poorly with other scales of chemical hardness or softness. Another well-known softness scale is that of Ahrland ($\sigma_A$) [17]. In the author’s own words, “It is postulated that the more completely the energy spent on the formation of a positive ion in the gas phase is regained by the introduction of the ion in a hard solvent like water, the harder the ion. Thus, the larger the difference between the total ionization potential for the formation of M+(g) and the dehydration energy $-\Delta H_o$ . . . . . . the softer the ion” (p 305). The $\sigma_A$ scale correlates relatively well with other scales of chemical softness.

The last scale discussed here appears to be a favorite with physical chemists [5,18,19]. The softness scale designated here as $\sigma_{\text{Pan}}$ is the reciprocal of a property referred to by its authors as absolute hardness ($\eta$). The authors of the scale [20] define hardness with these statements (pp 7512, 7513, 7516): “The
nonchemical meaning of the word ‘hardness’ is resistance to deformation or change.” Thus, “chemical hardness is resistance of the chemical potential to change in the number of electrons.” Also, “hardness is identically one-half of the energy change for the disproportion reaction S + S → S^+ + S^-.” They conclude with the statement: “The hardness of a chemical species, then, is half the derivative of its chemical potential with respect to the number of electrons: 2\eta = (\delta \mu / \delta N)_S. There seem to be no other acceptable definitions.”

Hardness is computed by the formula \eta_S = \frac{1}{2}(I_S - A_S)/2, where I_S is the ionization potential and A_S is the electron affinity for S. Later, Pearson [21] noted that 2\eta = (\delta \mu / \delta N)_S implies 2\eta = (\delta \mu / \delta p), where p is the electron density. Thus, \eta “has the meaning of resistance to change, or deformation, of the electron cloud” (p 8). Softness was defined as 1/\eta, which I shall denote as \sigma_{Parr}. However satisfying \sigma_{Parr} may be to physical chemists, \sigma_{Parr} is only intermediate in its agreement with other scales of chemical softness.

I undertook the present study after noting the great disparities among the scales for hardness or softness and wondering whether it would be possible to evaluate the scales one against the other and to devise a consensus scale (\sigma_{con}) for softness that was superior to any individual scale previously published. Superiority would be determined solely on the basis of correlations among published scales for softness and other possible indicators of softness, such as E^p, \rho_{metal}, Pauling electronegativity (Xp^p), metal sulfide solubility, and toxicity. Thus, \sigma_{con} is a composite scale also constructed by the normalization and averaging of log K values for metal ion binding to soft ligands (SLScale). Each scale was normalized by subtracting the scale mean from each number in the scale and dividing by the standard deviation. The units for each scale therefore ranged above and below 0.00, which was the mean. A scale value of -1.00 was one standard deviation below the mean, and 1.00 was one standard deviation above the mean. Finally, a consensus scale was constructed by averaging across the 10 normalized scales. The consensus scale, henceforth denoted as the observed \sigma_{conobs}, included 51 ions, which were the number of ions for which there were three or more values from the 10 scales used in the construction.

Values for \sigma_{conobs} were next analyzed in terms of common physical parameters for the ions. In addition to being possibly interesting in its own right, this analysis allows for the extension of the softness parameter beyond 51 ions. The analysis resulted in the equation \sigma_{conobs} = aE^p + b metals for which R^2 = 0.867, a = 0.0607, and b = 0.0454. Henceforth, \sigma_{concomp} will refer to values computed from the equation.

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of the correlations was complicated by the fact that the number of ions varied for the different correlations. Thus, \( n \) varies from \( n = 15 \) for \( \sigma_K \) versus SLScale to \( n = 51 \) for \( \sigma_{\text{par}} \) versus \( \sigma_Z \). However, the ranking of the scales (Table 3) did not change much when the set of ions was restricted to ensure a more similar suite of ions for each correlation.

The quality of the consensus scales, \( \sigma_{\text{Con,obs}} \) and \( \sigma_{\text{Con,comp}} \), was assessed by determining the correlation of each of these two with the 10 other softness scales and with the standard electrode potential \( (E^0) \), the bulk density \( (\rho_{\text{Meas}}) \), and the hard-borderline–soft classification noted in the Introduction. Other authors who construct or use scales for hardness or softness have also noted agreements or disagreements between the scales and the hard-borderline–soft classification [23,24]. For the present study, agreement was assessed by analysis of variance (ANOVA), and the scales were ranked according to \( F \) ratio (Table 3 and Fig. 1).

**Construction of a consensus toxicity scale (\( T_{\text{Con,obs}} \))**

Table 1 lists the sources of 10 published toxicity studies. The published scales were usually in the form of log concentration of metal ions required to induce 50% toxicity (death rate, inhibition of growth, and so on). These 10 scales were normalized and averaged, as in the case of the softness scales, in order to construct a consensus toxicity scale. One of the articles [25] presented a toxicity ranking based on 30 datum sets from the literature.

**RESULTS**

**Correlation and ranking of published softness scales**

The scales for softness are poorly correlated with one another (correlation matrix not shown; Table 3). In none of the 45 correlations did \( R^2 \) achieve 0.900, and in two cases \( R^2 < 0.100 \). For just over half the correlations, \( R^2 < 0.500 \). Figure 2 illustrates the poorest (Fig. 2a) and the best (Fig. 2d) correlations, and the figure presents two other correlations for the scales \( \sigma_F, \sigma_T, \sigma_{\text{par}}, \text{ and } \sigma_{\text{sl}} \). As mentioned earlier, \( n \) is variable for these correlations. For that reason the set of ions was restricted to the 23 common to all four scales in Figure 2, and the correlations were repeated. The new \( R^2 \) values are shown in the figure. Although \( R^2 \)s changed somewhat, the ranking of the four correlations did not. The ranking of the 10 scales with \( \sigma_K \) at the top and \( \sigma_F \) at the bottom represents a trend that changed only slightly with further analyses (Table 3). \( F \) ratios for ANOVA for the scales versus the hard-borderline–soft classification are presented in Table 3 and Figure 1. Again, \( \sigma_K \) was the top-ranked scale.

**Evaluation of \( \sigma_{\text{Con,obs}} \) and \( \sigma_{\text{Con,comp}} \) as softness scales**

The correlation of \( \sigma_{\text{Con,obs}} \) against the 10 scales used in its construction indicates that it may be superior to any of those scales. The mean \( R^2 \) of 0.689 exceeds the value for the mean \( R^2 \) of 0.572 for \( \sigma_K \), the individual scale most correlated with the others (Table 3). The scale, \( \sigma_{\text{Con,comp}} \) also appears to be superior to any of the 10 scales used to construct \( \sigma_{\text{Con,obs}} \). For the ANOVA, \( F \) ratios for \( \sigma_{\text{Con,obs}} \) and \( \sigma_{\text{Con,comp}} \) were large but ranked behind that of \( \sigma_K \). Correlations of \( \sigma_{\text{Con,obs}} \) with \( E^0 \) and \( \rho_{\text{Meas}} \) ranked behind \( \sigma_K \) and \( \sigma_{\text{sl}} \), respectively. Figure 3 illustrates the correlations of \( \sigma_{\text{Con,obs}} \) with \( E^0, \rho_{\text{Meas}}, \chi_F \), and \( Z \). As noted already, \( \sigma_{\text{Con,comp}} = aE^0 + b \rho_{\text{Meas}} \), for which \( R^2 = 0.867, a = 0.0607 \), and \( b = 0.0454 \), with each coefficient statistically significant.

**Evaluation of the binding scale for soft ligands**

The SLScale was one of the 10 scales used to construct \( \sigma_{\text{Con,obs}} \) and it has some interesting features. The SLScale correlated very well with six of the seven scales used for its construction (\( R^2 = 0.808–0.977 \), not shown); for \( \log K_{\text{NH3}} \), \( R^2 = 0.653 \). Table 3 lists \( R^2 = 0.759 \) for SLScale versus \( \sigma_{\text{Con,obs}} \), but a quadratic equation increased \( R^2 \) to 0.863 (Fig. 4a). Addition of \( Z \) in the equation SLScale = \( a + b \sigma_{\text{Con,obs}} + c \sigma_{\text{Con,obs}}^2 + dZ \) increased \( R^2 \) to 0.896. Finally, removal of \( H^+ \) from the regression raised \( R^2 \) to 0.922. Figure 4b illustrates that SLScale and HLScale are highly correlated for the harder ions (\( R^2 = 0.853 \) for ions with \( \sigma_{\text{Con,obs}} < -0.1 \); all the greater outliers for the drawn line are softer ions.

**Evaluation of \( \sigma_{\text{Con,obs}} \) and \( \sigma_{\text{Con,comp}} \) relative to toxicity**

The 10 toxicity scales are better correlated with one another than are the softness scales (not shown). The \( R^2 \) values ranged from 0.136 to 0.898, and \( R^2 > 0.500 \) for 32 of the 45 correlations. Figure 5 presents some notable features of the toxicity studies. The scale most poorly correlated with all others is \( T_{\text{Lewis}} \) (Fig. 5a), and the scale best correlated with all others is \( T_{\text{McClusky}} \) (Fig. 5b). One of the scales, \( T_{\text{Khirade}} \) for root elongation, has been presented previously only in graphical form,
Table 2. List of metal ions and H⁺ with the standard electrode potential (E°), bulk density (ρ_{tot}), first ionization potential (I₁), binding strengths to hard ligands (HLScale), binding strengths to soft ligands (SLScale), observed softness (σ_{obs}), computed softness (σ_{comp}), observed toxicity (T_{obs}), and computed toxicity (T_{comp}). For the normalization units, 0.00 is the mean, -1.00 is one standard deviation below the mean, and 1.00 is one standard deviation above the mean.

<table>
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<th>Metal Ion</th>
<th>E° V</th>
<th>ρ_{tot} g/cm³</th>
<th>First I₁ eV</th>
<th>HLScale</th>
<th>SLScale</th>
<th>σ_{obs}</th>
<th>σ_{comp}</th>
<th>T_{obs}</th>
<th>T_{comp}</th>
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<td>-2.30</td>
<td>7.35</td>
<td>5.64</td>
<td>-0.20</td>
<td>-0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Sm⁺</td>
<td>-0.14</td>
<td>7.31</td>
<td>7.34</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Sm²⁺</td>
<td>7.31</td>
<td>7.34</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
</tr>
<tr>
<td>Th⁺</td>
<td>-2.28</td>
<td>8.22</td>
<td>5.86</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>Th²⁺</td>
<td>-1.90</td>
<td>11.72</td>
<td>6.08</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Legend:
- **E° V**: Standard electrode potential
- **ρ_{tot} g/cm³**: Bulk density
- **First I₁ eV**: First ionization potential
- **HLScale**: Binding strengths to hard ligands
- **SLScale**: Binding strengths to soft ligands
- **σ_{obs}**: Observed softness
- **σ_{comp}**: Computed softness
- **T_{obs}**: Observed toxicity
- **T_{comp}**: Computed toxicity

Normalization units: 0.00 is the mean, -1.00 is one standard deviation below the mean, and 1.00 is one standard deviation above the mean.
and an additional ion, Tb\textsuperscript{3+}, has been evaluated. Therefore, \( T_{\text{Knnnke}} \) is presented here in the form of \( -\log \) of the ion activity at the plasma membrane surface required to reduce root elongation 50\%: Ag\textsuperscript{+}, 6.0; Al\textsuperscript{3+}, 5.1; Ba\textsuperscript{2+}, 1.7; Be\textsuperscript{3+}, 2.7; Ca\textsuperscript{2+}, 1.8; Cd\textsuperscript{2+}, 3.9; Co\textsuperscript{2+}, 3.7; Cu\textsuperscript{2+}, 5.7; H\textsuperscript{+}, 3.8; K\textsuperscript{+}, 0.8; La\textsuperscript{3+}, 4.4; Mg\textsuperscript{2+}, 1.9; Na\textsuperscript{+}, 0.7; Ni\textsuperscript{2+}, 3.8; Pb\textsuperscript{2+}, 3.6; Sc\textsuperscript{3+}, 5.9; Sr\textsuperscript{2+}, 1.8; Tb\textsuperscript{3+}, 4.3; Ti\textsuperscript{4+}, 3.6; and Zn\textsuperscript{2+}, 3.7. References to the computation of plasma membrane surface activities and toxicities are presented in previous reports \( [8,26,27] \). The toxicities of Al\textsuperscript{3+} and Sc\textsuperscript{3+} were greater in that study than in some others because of the attention given to speciation as described later.

It was noted previously that hard ions with \( Z < 3 \) are generally not toxic but that all ions with \( Z > 2 \) generally are toxic. Figures 5c and 5d present ion toxicity as a function of charge and activity.

Fig. 2. Some softness scales plotted one against the other. The smallest of the 45 correlations was for \( \sigma_z \) versus \( \sigma_p \), and the greatest was for \( \sigma_{\text{Part}} \) versus \( \sigma_M \).
Table 3. Linear correlations among various scales. The first number column presents the mean $R^2$ values for correlations of the indicated scale versus the nine other scales from the 10 scales $\sigma_k$ through $\sigma_p$. Subsequent columns present the $R^2$ values for the correlations between the two scales or parameters indicated. $F$ ratio refers to the analysis of variance for the indicated scale versus the hard-borderline-soft classification.

<table>
<thead>
<tr>
<th>All softness scales</th>
<th>$E^0$</th>
<th>$\sigma_{metal}$</th>
<th>$F$ ratio</th>
<th>$\sigma_{Con obs}$</th>
<th>$\sigma_{Con comp}$</th>
<th>$T_{Con obs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_K$</td>
<td>0.572</td>
<td>0.508</td>
<td>0.574</td>
<td>30.9</td>
<td>0.715</td>
<td>0.609</td>
</tr>
<tr>
<td>$\sigma_M$</td>
<td>0.553</td>
<td>0.627</td>
<td>0.821</td>
<td>14.9</td>
<td>0.862</td>
<td>0.716</td>
</tr>
<tr>
<td>$\sigma_A$</td>
<td>0.505</td>
<td>0.819</td>
<td>0.730</td>
<td>12.0</td>
<td>0.805</td>
<td>0.839</td>
</tr>
<tr>
<td>$\sigma_Z$</td>
<td>0.500</td>
<td>0.417</td>
<td>0.293</td>
<td>15.9</td>
<td>0.733</td>
<td>0.584</td>
</tr>
<tr>
<td>$\sigma_{SLS}$</td>
<td>0.467</td>
<td>0.380</td>
<td>0.260</td>
<td>9.1</td>
<td>0.728</td>
<td>0.495</td>
</tr>
<tr>
<td>$\sigma_{H}$</td>
<td>0.448</td>
<td>0.603</td>
<td>0.434</td>
<td>8.7</td>
<td>0.759</td>
<td>0.698</td>
</tr>
<tr>
<td>$\rho_{Ksp}$</td>
<td>0.442</td>
<td>0.628</td>
<td>0.411</td>
<td>14.8</td>
<td>0.715</td>
<td>0.694</td>
</tr>
<tr>
<td>$\sigma_{Ker}$</td>
<td>0.395</td>
<td>0.440</td>
<td>0.571</td>
<td>1.7</td>
<td>0.565</td>
<td>0.542</td>
</tr>
<tr>
<td>$\sigma_{P}$</td>
<td>0.377</td>
<td>0.286</td>
<td>0.412</td>
<td>4.9</td>
<td>0.508</td>
<td>0.504</td>
</tr>
<tr>
<td>$\sigma_{Con obs}$</td>
<td>0.332</td>
<td>0.451</td>
<td>0.420</td>
<td>1.8</td>
<td>0.500</td>
<td>0.498</td>
</tr>
<tr>
<td>$\sigma_{Con comp}$</td>
<td>0.689</td>
<td>0.780</td>
<td>0.755</td>
<td>23.0</td>
<td>1.000</td>
<td>0.867</td>
</tr>
<tr>
<td>$\sigma_{Con comp}$</td>
<td>0.598</td>
<td>0.873</td>
<td>0.636</td>
<td>25.3</td>
<td>0.867</td>
<td>1.000</td>
</tr>
</tbody>
</table>

$a$ Mean $R^2$ for correlation of $\sigma_{Con obs}$ versus the 10 scales $\sigma_k$ through $\sigma_p$ (mean of fifth number column, values 0.715–0.500).

$b$ Mean $R^2$ for correlations of $\sigma_{Con comp}$ versus the 10 scales $\sigma_k$ through $\sigma_p$ (mean of sixth number column, values 0.609–0.398).

for harder ions ($\sigma_{Con obs} < -0.1$) and for softer ions ($\sigma_{Con obs} \approx -0.1$). Therefore, $T_{Con obs}$ appears to be a function of softness and charge, and for the equation $T_{Con obs} = \sigma_{Con comp} + b\sigma_{Con comp}Z + cZ$, $R^2 = 0.923$, $a = 2.16$, $b = -0.521$, and $c = 0.0778$, with all coefficients statistically significant. This equation indicates an interaction between softness and charge, and this interaction is illustrated in Figure 6, where the slope of plots for $T_{Con obs}$ versus $\sigma_{Con comp}$ can be seen to decrease with increasing charge. The inset figure in Figure 6 presents the correlation for $T_{Con obs}$ versus $T_{Con comp}$, the latter as computed by the equation just given.

**DISCUSSION**

The objectives of the study appear to have been achieved. Hardness and softness scales were objectively ranked, and a consensus scale for softness ($\sigma_{Con obs}$) was devised that is superior to previously published scales. Superiority was determined on the basis of correlations among published scales for

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Fig. 3. The consensus scale for ion softness ($\sigma_{Con obs}$) plotted against physical parameters of the metals.
Improved scales for metal ion softness and toxicity

![Graph showing the consensus scale for ion binding to soft ligands (SLScale) plotted against \( \sigma_{\text{Con obs}} \) and against the consensus scale for ion binding to hard ligands (HLScale).]

sofness and other possible indicators of softness, such as \( E^0 \), \( \rho_{\text{Metal}X_n} \), conformity to the hard-borderline-soft classification, and so on. Because of the great disagreement among the scales, one must wonder how the 10 scales used in the construction of \( \sigma_{\text{Con obs}} \) were selected. Principally, scales were selected on the basis of their use (citation in the literature). No commonly used scale was deliberately omitted because of apparent incompatibility with other scales or presumed inaccuracy. Interestingly, the most widely used scale (\( \sigma_x \)) was the one ranked 10th among the 10 scales (Table 3). Certainly some other scales are available. Among them are three scales presented by Martin [24]. Two of those scales have a middling correlation with other scales, and one correlates poorly.

Eventually, any scale must conform to what I have referred to as chemical lore, and other authors appear to agree. Despite the statement of Parr and Pearson [20] that "there seem to be no other acceptable definitions [of hardness other than \( \eta = (\delta \mu /\delta N)_{2} \) or \( \eta = (I_s - A_s)/2 \)""] (p 7516), Pearson [23] later thought it "necessary to show that \( (I - A) \) indeed does correlate with earlier assignments of hardness and softness for various systems" (p 736). He also stated, "It can be seen that . . . the values of \( \eta \) calculated for these ions agree very well with their known chemical hardness." However, the scale \( \sigma_{\text{Parr}} \) based on \( 1/\eta = 2/(I_s - A_s) \), exhibits only a modest agreement with "earlier" or "known" assignments of chemical hardness or softness, as demonstrated in Table 3. Martin [24], in reference to his scales, stated, "These scales probably correspond to what most investigators imply when they use the terms hardness and softness." (p 27). However, his three scales agree poorly with one another (R's were 0.538, 0.127, and 0.125).

Thus, the present study has done what previous authors have attempted to do either theoretically or empirically: Incorporate into a quantitative scale the accumulated lore regarding chemical softness or hardness. This was done by deriving from 10 existing scales a consensus scale for softness. Then the consensus scale was evaluated against the scales used in its construction and against other measures of softness not used in the construction.

It is well known that soft, or class B, metal ions are often very toxic [8,28]. Thus, two of the objectives of the study were to evaluate various softness scales as predictors of metal ion toxicity and to relate concepts such as softness and toxicity to simpler physical properties such as \( E^0 \), \( \rho_{\text{Metal}X_n} \), \( I_n \), and \( Z \). The finding with regard to the first of these additional objectives is that only \( \sigma_s \) and \( pK_{\text{exp}} \) compare well with \( \sigma_{\text{Con obs}} \). and \( \sigma_{\text{Con comp}} \) as indicators of toxicity (\( R^2 = 0.874 \) for \( T_{\text{Con obs}} = a + bpK_{\text{exp}} + cpK_{\text{exp}} + dZ \) and \( R^2 = 0.832 \) for \( T_{\text{Con obs}} = a + bpK_{\text{exp}} + cpK_{\text{exp}} + dZ \)). The second of the additional objectives is met with equations that relate softness to \( E^0 \), \( \rho_{\text{Metal}} \), and \( I_n \), and relate toxicity to softness and \( Z \):

\[
\sigma_{\text{Con obs}} = aE^0I_n + bp_{\text{Metal}}
\]

\[
T_{\text{Con obs}} = a\sigma_{\text{Con comp}} + b\sigma_{\text{Con obs}}Z + cZ
\]

where \( R^2 = 0.867 \), \( a = 0.0607 \), and \( b = 0.0454 \) for Equation 1 and \( R^2 = 0.923 \), \( a = 2.16 \), \( b = -0.521 \), and \( c = 0.0778 \) for Equation 2.

Although Equation 2 predicts toxicity well, it is not certain that charge influences toxicity directly. Toxicity is also related to strength of binding to biomass (plasma membranes, cell walls, proteins, and so on [8]), and strength of binding is related to charge. Consider these facts: The strength of metal ion binding to biomass is similar to binding to hard ligands (HLScale) [8]. Some but not all ions of small HLScale are nontoxic, but all ions of large HLScale are toxic (Fig. 8a in Kinraide et al. [8] and read Fig. 4b in conjunction with Table 2). The binding strength of harder metal ions (\( \sigma_{\text{Con obs}} < -1 \)) to hard ligands is influenced by charge (\( R^2 = 0.916 \) for HLScale = \( a + bZ \)), the binding strength of harder metal ions to soft ligands is influenced by charge (\( R^2 = 0.854 \) for SLScale = \( a + bZ \)), the binding strength of softer metal ions (\( \sigma_{\text{Con obs}} \geq -1 \)) to hard ligands is modestly influenced by charge (\( R^2 = 0.585 \) for HLScale = \( a + bZ \)), but the binding strength of softer metal ions to soft ligands is not influenced by charge (\( R^2 = 0.004 \)). Charge appears to influence the toxicity of harder ions (Fig. 5c) but not softer ions (Fig. 5d), but, as just noted, these effects are not independent of binding strength.

Is there any evidence that charge is an independent determinant of toxicity? The rhizotoxicity of Al species provides
circumstantial but inconclusive evidence. Intoxicating effectiveness follows the order \( \text{AlO}_3\text{Al}_{12}\text{(OH)}_{36}(\text{H}_2\text{O})_{12}^{2+} > \text{AlF}^{2+} > \text{AlF}_2^+ > \text{AlF}_3^- \), but this may also be the order of binding strength to cell surfaces. (The tested hydroxo-, sulfato-, organo-, and phosphato-Al species are not rhizotoxic at achievable concentrations [29].) Other polyvalent cations, such as poly-L-lysine, are toxic [30]. The discovery of a highly charged, intoxicating cation that otherwise had the characteristics of nonintoxicating ions (hard and weakly binding) would be interesting because the only characteristic predisposing the ion to toxicity would be charge. I have not found such an ion among the metals. Similarly interesting is Ag because its only predisposition for toxicity is softness and not charge or strength of binding [8] (Fig. 4b).

How might softness determine toxicity? The biotic ligand model proposes that an intoxicating ion must first bind to a cell-surface ligand [27]. The actual intoxication need not occur at that site, but occupation of that site must be related to the intoxication that may occur intracellularly. The connection to softness may be that the biotic ligand is soft—perhaps a thiol- or sulfhydryl-bearing protein [28]. Perhaps we could name this extended model the soft biotic ligand model (SBLM). If the SBLM accounts for most metal ion toxicity, then we might expect SBLScale to predict toxicity better than softness itself. In fact, equations of the form 
\[
T_{\text{Con Obs}} = f(S\text{LScale}, Z) \]
predict toxicity fairly well but not as well as 
\[
T_{\text{Con Obs}} = a\sigma_{\text{Con Comp}} + b\sigma_{\text{Con Comp}}Z + cZ.
\]
I consider the SBLM to be a likely mechanism, but the data are presently inadequate to resolve the issue. Of course, an SBLM may apply to some of the metal ions but not all, and the mechanism will probably be determined only when some likely ligands have been identified and then altered by genetic modification from soft to hard. If such an alteration were not lethal and if the alteration reduced the sensitivity to soft metal ions, then the SBLM would be supported. A search for Ag-resistant mutants may be worthwhile because Ag binds weakly to hard ligands and to most biomass (Table 2) but is extremely toxic. Perhaps the unmutated ligand binds Ag strongly, but the mutated ligand binds Ag weakly, indicating a possible transformation from soft to hard.

In some toxicological studies the speciation of ions is difficult to determine and may have been neglected. This can lead to the misattribution of toxicity to one ion when another may be the toxicant. In the scale of Kinraide and Yermiyahu [8] and presented in the Results section as \( T_{\text{Kin}} > T_{\text{Yerm}} \), great care was taken to ensure that in the Al studies, for example, all species other than Al\(^{3+} \) were excluded or accounted for. Surely, the injection of AlCl\(_3\) solutions into the bloodstream, for example, would not allow the attribution of toxicity specifically to the Al\(^{3+} \) species, and in some cases, as with Fe, Cr, or Mn, for example, oxidation or reduction may lead to misattribution of toxicity. Thus, the injection of FeCl\(_3\) into the bloodstream could result in several Fe(III) and Fe(II) species but virtually no Fe\(^{3+} \).

In conclusion, improved scales for metal ion softness and toxicity have been constructed from previous scales. Softness can also be computed from three physical parameters (\( E^0 \), \( I_p \), and \( \rho_{\text{total}} \)) by a simple equation (Eqn. 1), and toxicity can be
computed from softness and charge (Eqn. 2). The mechanisms of toxicity are very poorly understood for most ions. The fact that ions are toxic if they are soft or highly positively charged may guide the search for possible cell-surface ligands whose occupancy may initiate intoxication.

REFERENCES