ference) of these derivatives in the presence and absence of phosphate. This small influence indicates that phosphate is not directly interacting with Ni^{2+} in the inner coordination sphere but possibly with some positively charged residues in the proximity of the Ni^{2+} binding site. This result is similar to the studies of native SOD in which the Cu^{2+} site is not influenced by phosphate as observed by electronic absorption and EPR spectroscopies.[14,15] The influence of phosphate on the copper site of the derivative Cu_2Co_2SOD is also very small as shown by ^1H NMR spectroscopy.[45] However, this observation is completely different from the results observed for some Co^{2+}-substituted derivatives with Co^{2+} bound in the copper site, such as Co_2Zn_2SOD and Co_2Co_2SOD, for which phosphate causes dramatic changes in the electronic and NMR spectra, indicating that phosphate binds directly to Co^{2+} and causes changes in binding geometry.[13] The similar chemical shifts of the isotropically shifted signals of these two new derivatives at neutral and high pH indicate that the Ni^{2+} binding site in these derivatives is not perturbed significantly under different pH conditions. The similarity of the chemical shifts of the isotropically shifted signals at high pH in the presence of phosphate to those at pH 7.5 in the absence of phosphate indicates that phosphate does not interact with the derivatives significantly at high pH. The decrease of the phosphate interaction under highly alkaline conditions may be due to the deprotonation of a certain amino acid residue(s) in the active-site cavity (forming a less positively, or even a negatively, charged channel of the active site), which may result in decrease of the interaction of the anionic phosphate with the protein similar to that reported for native SOD[16] and Co^{2+}-substituted SOD.[46]

Conclusion

The configuration of the ligands about Ni^{2+} in these new derivatives Ni_2Zn_2SOD and Ni_2Co_2SOD is very similar to that of Cu^{2+} in native SOD, i.e., coordinated to one histidine through the $N_{\delta1}$ nitrogen and to another two histidines through the $N_{\epsilon2}$ nitrogen as well as to the bridging imidazolate of the His-61 residue (also through the $N_{\epsilon2}$ nitrogen). Both azide and cyanide bind Ni^{2+} in these two derivatives leaving the bridging histidine intact as revealed by electronic spectroscopy. NMR studies further suggest that the geometric changes that occurred upon anion binding to the Ni^{2+} binding site are similar to those observed for the native protein studied by different spectroscopies; i.e., a rearrangement from a distorted 5-coordination with water and four histidines bound to an axially symmetric 4- or 5-coordination with the anion and three or four histidines bound. The phosphate binding properties of these derivatives, i.e., no direct binding to the metal in the copper site, is also similar to that of the native enzyme. The similarities of the metal binding environment of these two new Ni^{2+}-substituted SODs to those of native SOD in the presence and absence of anions suggest that these derivatives can serve as good structural models for copper-zinc superoxide dismutase.

The change in the electron spin state of Ni^{2+} from high spin to low spin in the presence of strong ligand fields, such as cyanide in this study, represents one of the classical properties of simple Ni^{2+} complexes[16] and can be well applied to studies of metalloproteins. The preference of Ni^{2+} to form square-planar coordination is relevant to that of Cu^{2+}, since Cu^{2+} normally also prefers a square-planar ligand field.[16] The similar geometric preferences of these two metal ions allow the use of Ni^{2+} as a good substitute for Cu^{2+} for studies of structural properties of copper proteins. As shown in this study, isotropically shifted ^1H NMR spectroscopy can be used successfully in the study of Ni^{2+}-substituted metalloproteins to determine the identity and configuration of the ligands, especially histidines coordinated through the $N_{\delta1}$ or the $N_{\epsilon2}$ nitrogen, in the metal binding site.

Acknowledgment. Financial support from the USPHS (Grant GM 28222) is gratefully acknowledged. The use of the Bruker CX90 spectrometer at the University of Florence is also highly appreciated.

Registry No. Ni, 7440-02-0; Cu, 7440-50-8; Co, 7440-48-4; azide, 14343-69-2; cyanide, 57-12-5; phosphate, 14265-44-2; histidine, 71-00-1.

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Communications to the Editor

Relationship between Amidic Distortion and Ease of Hydrolysis in Base. If Amidic Resonance Does Not Exist, Then What Accounts for the Accelerated Hydrolysis of Distorted Amides?

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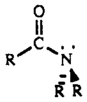
Chemists have invoked resonance theory[1] for amides ($1 \leftrightarrow 2$) to explain the short N-C(O) bond length,[2] planar geometry,[2] high N-C(O) rotational barrier,[3] infrared C=O stretching frequencies,[4] and kinetic stability toward nucleophilic attack/hydrolysis.[5] Wiberg and Laidig[6] have reported high-level ab initio calculations of planar **1a** and orthogonal **3a** along with Bader's[7] atomic population analyses for the various atoms in each conformer. In

1a R=H

2



3a R=H

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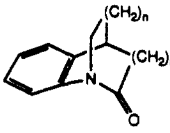
Table I. Structural Parameters for Amides **1a**, **3a**, **4b–d**, and **5a**

amide	r(N—C(O)), Å	r(C=O), Å	Dunitz parameters[a]			twist angle[b]	tilt angle[b]
			χ_C	χ_N	τ'		
1a[c]	1.349	1.193	0.0	0.0	0.0	0.0	0.0
3a[c]	1.423	1.179	0.0	63.4	180	90.0	19.5
4b[d]	1.401 (2)	1.216 (2)	9.0	57.2	71.2	30.7	15.2
4c[e,f]	1.413 (10)	1.225 (7)	11.0	52.8	75.6	33.2	16.0
	1.419 (11)	1.233 (10)	6.7	55.1	82.4	38.9	16.8
4d[f]	1.370 (6)	1.233 (6)	4.3	38.6	34.4	15.3	10.5
	1.374 (6)	1.241 (6)	3.8	38.3	37.8	17.1	10.6
5a	1.338 (7)	1.235 (6)	−1.5	3.7	1.3	1.5	1.0

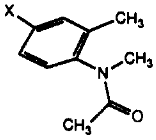
[a] Reference 11. [b] Defined as in ref 12. [c] Reference 6. [d] Reference 13a. [e] Reference 13b. [f] Two crystallographically independent molecules in unit cell.

contrast to the resonance model, the computed population at N in **1a** is larger than in **3a**, while the population at each O is similar. The C–N bond lengthens in passing from **1a** to **3a**; however, the C=O bond length is scarcely affected. The computed barrier to rotation closely approximates the experimental value.[8] Wiberg and Laidig[6] and Bader et al.[9] conclude that amidic resonance as is customarily invoked does not exist and that the properties stem naturally from N rehybridization (sp^2 (**1a**) → sp^3 (**3a**)) that accompanies rotation about the N–C(O) bond.

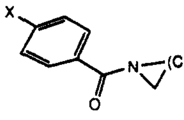
Experimental support for this intriguing theoretical analysis is conspicuously sparse due to the paucity of relevant physicochemical data on twisted amides.[10] We now provide X-ray diffraction structural data for the series of anilides **4b–d** and **5a** and rate constants for hydrolysis of these and other distorted amides in base.



4a n=m=1
b n=1, m=2
c n=2, m=1
d n=m=2



5a X=Br
b X=H



6a X=Br,H; n=1
b X=CH$_3$; n=2

In Table I are the structural parameters (r(C=O), r(N—C(O)), Dunitz parameters,[11] twist and tilt angles[12]) for formamides **1a** and **3a** (computed), **4b–d**, and **5a**.[13] The N—C(O) bond length increases by ~0.06–0.08 Å in passing from **5a** to **4b**,**c**, while the C=O bond length is scarcely affected, the overall decrease being ~0.02 Å. As well, in passing from **5a** through the series, there is an increase in molecular distortion of the amidic unit, characterized by N pyramidalization (χ_N,[11] tilt angle[12]) and rotation about N–C(O) (τ',[11] twist angle[12]). Although we have been unable to crystallize **4a**, its rigidity demands it to be the most orthogonal amide of the series.

Table II. Second-Order Rate Constants for Base Hydrolysis of Various Amides **4–6**, T = 25 °C, μ = 1.0 (KCl)

amide	k_{OH^-},[a] M^{-1} s^{-1}
4a	260 (20)[b]
4b	60 (3)[b]
4c	17.2 (1.7)[c]
4d	5.52 (0.06) × 10^{-4} [d]
5b	≪1 × 10^{-6} [d,e]
6a (X = H)	1.1[f]
6b	4.01 (0.05) × 10^{-5} [d]
N,*N*-dimethylbenzamide	6 × 10^{-6} [f]

[a] Bracketed number represents error. [b] Reference 12b. [c] Reference 13b. [d] This work. [e] No observable reaction after 50 h at 100 °C in 0.2 N NaOD/D$_2$O. [f] Reference 15.

We are concerned with how molecular deformation leads to accelerated hydrolysis and acyl transfer of amides.[12–15] In Table II are the rate constants for hydrolysis of various amides in base, μ = 1.0 (KCl), T = 25 °C. These indicate that the more heavily distorted the amide is, the faster it hydrolyzes relative to an appropriate comparison amide (**5b** for **4a–d**; *N*,*N*-dimethylbenzamide for **6a** (X = H) and **6b** (X = CH$_3$)).

These observations are grossly consistent with a resonance model, but not uniquely so, and there are indications of shortcomings. For example, although the amidic unit in **4a** must be more orthogonal than its counterpart in **4b** or **4c**, the former hydrolyzes in base only 4- and 15-fold faster than the latter, respectively.

According to Wiberg, Bader, and co-workers,[6,9] the stability of planar **1a** relative to orthogonal **3a** results not from resonance involving N → O charge transfer, but from a hybridization change at N (sp^2) which shortens its bonds and lowers the attractive potential energy more than it raises the e$^-$–e$^-$ and nuclear–nuclear repulsive energy. Thus, if the energy required for N pyramidalization and bond lengthening appears as part of the activation energy for rotation about the N–C(O) bond, it stands to reason that an amide such as **6a**[16] with an already pyramidalized N should exhibit a reduced rotational barrier. The experimental barrier for **6a** (X = H, n = 1) is <6 kcal/mol,[17] and we have determined that for toluoylazetidine (**6b**, X = CH$_3$, n = 2) to be 15.5 kcal/mol.[18]

In accepting the analysis that amide resonance does not exist,[6,9] one must ask whether an acceptable alternative explanation other than removal of resonance exists to explain the accelerated hydrolysis caused by distortion. Nucleophilic attack of OH$^-$ on an amide produces an anionic tetrahedral intermediate (To$^-$, RC(O$^-$)OHNR$_2$) in which both the RC(O$^-$)OH and N are pyramidalized[19,20] and the C–N bond length is longer than in the starting amide.[20] By calculation,[20a] attack of OH$^-$ on formamide (gas phase) proceeds without barrier to give To$^-$ which is stabilized relative to reactants. The transition state (TS) is early, resembling reactants, and distortion of the amide cannot accelerate an already barrierless process. However, in solution, To$^-$ is expected to have a similar geometry to the computed one, but it is a high-energy intermediate with a sizable barrier to formation.[21] The difference

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(8) For microwave structural studies of formamide, see: (a) Hirota, E.; Sugisaki, R.; Nielsen, C. J.; Sorensen, G. O. *J. Mol. Spectrosc.* **1974**, *49*, 251. (b) Costain, C. C.; Dowling, J. M. *J. Chem. Phys.* **1960**, *32*, 158.

(9) Bader, R. F. W.; Cheeseman, J. R.; Laidig, K. E.; Wiberg, K. B.; Breneman, C. M. *J. Am. Chem. Soc.*, in press. We thank Professor Bader for a preprint.

(10) For a compendium of extant data on twisted amides, see: Greenberg, A. Twisted Bridgehead Bicyclic Lactams. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers, Inc.: New York, 1988; Vol. 7, pp 139–178.

(11) Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr.* **1975**, *B31*, 251.

(12) (a) For a planar amide in the x–z plane with N—C lying on the x axis, the twist and tilt angles are respectively defined as the rotation angle of the N lone pair out of optimum conjugation with the C=O π-system, e.g., rotation about the x axis, and the tilt of the N lone pair away from the y axis. Lone pair position defined by a perpendicular drawn through N, normal to the plane defined by the three attached C's. (b) Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676. (c) Slebocka-Tilk, H.; Brown, R. S. *Ibid.* **1987**, *52*, 805.

(13) (a) **4b**: Somayaji, V.; Skorey, K. I.; Brown, R. S.; Ball, R. G. *J. Org. Chem.* **1986**, *51*, 4866. (b) **4c**: Wang, Q.-P.; Bennet, A. J.; Brown, R. S.; Santarsiero, B. D. *Can. J. Chem.*, in press. (c) **4d**, **5e**, this work. Full crystallographic details will be published.

(14) (a) Somayaji, V.; Skorey, K. I.; Brown, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 5205. (b) Skorey, K. I.; Somayaji, V.; Brown, R. S. *Ibid.* **1989**, *111*, 1445. (c) Somayaji, V.; Keillor, J.; Brown, R. S. *Ibid.* **1988**, *110*, 2625.

(15) Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1987**, *52*, 805.

(16) Shibaeva et al. (Shibaeva, R. P.; Atovmyan, L. O.; Kostyanovskii, R. G. *Sov. Phys.—Dokl.* (*Engl. Transl.*) **1968**, *12*, 669) have determined the X-ray structure of **6a** (X = Br).

(17) (a) Fong, C. W.; Grant, H. G. *Aust. J. Chem.* **1981**, *34*, 2307. (b) Boggs, G. R.; Gerig, J. T. *J. Org. Chem.* **1969**, *34*, 1484. (c) Anet, F. A.; Osyany, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 352. (d) In ref 17a–c, the low rotational barriers in **6a** are explained by invoking the customary resonance arguments.

(18) Determined by ^{1}H NMR (200 MHz) in CDCl$_3$ by observing coalescence of the azetidine 2′- and 4′-protons (decoupled from the 3′-proton); T_c = 37 °C (±1 °C), $\Delta\nu$ = 18.3 Hz at −30 °C.

(19) Schweizer, W. B.; Proctor, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783.

(20) (a) Alagona, G.; Scrocco, E.; Tomasi, J. *J. Am. Chem. Soc.* **1974**, *96*, 6976. (b) Lehn, J.-M.; Wipff, G. *Ibid.* **1980**, *102*, 1347.

between the gas-phase and solution processes is associated with solvent interactions on the TS and reactants. The solution TS structure, in accordance with the Hammond postulate,[22] now resembles To$^-$, and thus a share of the activation energy required for OH$^-$ attack on the amide is associated with structural changes accompanying rehybridization at N in much the same way as is responsible for the barrier to rotation in formamide.[6,9] Amides in which the structure predisposes the amidic unit toward a pyramidal N with attendant lengthening of the C-N bond are accordingly activated toward nucleophilic attack and exhibit an accelerated hydrolysis.[23]

This structural distortion amounts to destabilization of the ground state with concomitant reduction in the TS barrier for OH$^-$ attack. We[12-15] and others[24] have previously attributed the activation to a distortion that removes amidic resonance. However, structural distortion cannot remove resonance interactions if they are not present in the first place.[6,9] Our structural studies with **4** and **5** are consistent with the theoretical predictions.[6] Furthermore, the kinetic results suggest that there is no straightforward relationship between the degree of rotation about the N-C(O) bond and the kinetic reactivity toward OH$^-$. Rather, there is a direct relationship between (a) the extent of N pyramidalization and (b) N-C(O) lengthening and k_{OH^-}.[25]

Acknowledgment. We gratefully acknowledge the financial support of the University of Alberta and the Natural Sciences and Engineering Research Council of Canada.

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(21) (a) Guthrie, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 3608; (b) *Acc. Chem. Res.* **1983**, *16*, 1222.

(22) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 3608. (b) Farcasiu, D. *J. Chem. Educ.* **1975**, *52*, 76.

(23) Energetically, the accelerated hydrolysis of distorted amides appears as a reduction in the ΔG^* for OH$^-$ attack and thus depends on a reduction in ΔH^* and/or a less negative ΔS^*. Since the entropy term plays a large part in amide hydrolysis,[5,21] changes in this with increasing distortion may play a large role in the observed acceleration (work in progress).

(24) **4a** was originally prepared by Blackburn et al.: Blackburn, G. M.; Skaife, C. J.; Kay, I. T. *J. Chem. Res., Miniprint* **1980**, 3650.

(25) **Note Added in Proof.** It remains to be established whether the computed situation for formamide obtains for more heavily substituted amides. Work in progress in these laboratories addresses the adequacy of the resonance model in explaining the physicochemical properties of these and other amides.

Direct Approaches to Zinc Polychalcogenide Chemistry: ZnS_6(*N*-MeIm)$_2$ and $ZnSe_4$(*N*-MeIm)$_2$

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We describe new and efficient routes to zinc chalcogenides that involve the solution-phase reactions of zinc metal with sulfur, organic disulfides, and selenium.[1] Our findings further establish the remarkable reactivity of *N*-alkylimidazole solutions of chalcogen compounds toward metals[2] and as well as metal sulfides. Zinc sulfides (and selenides) are widely used as phosphors, semiconductors, long-wavelength windows, and catalysts.[3] Zinc mercapto imidazole complexes occur widely in biological systems.[4]

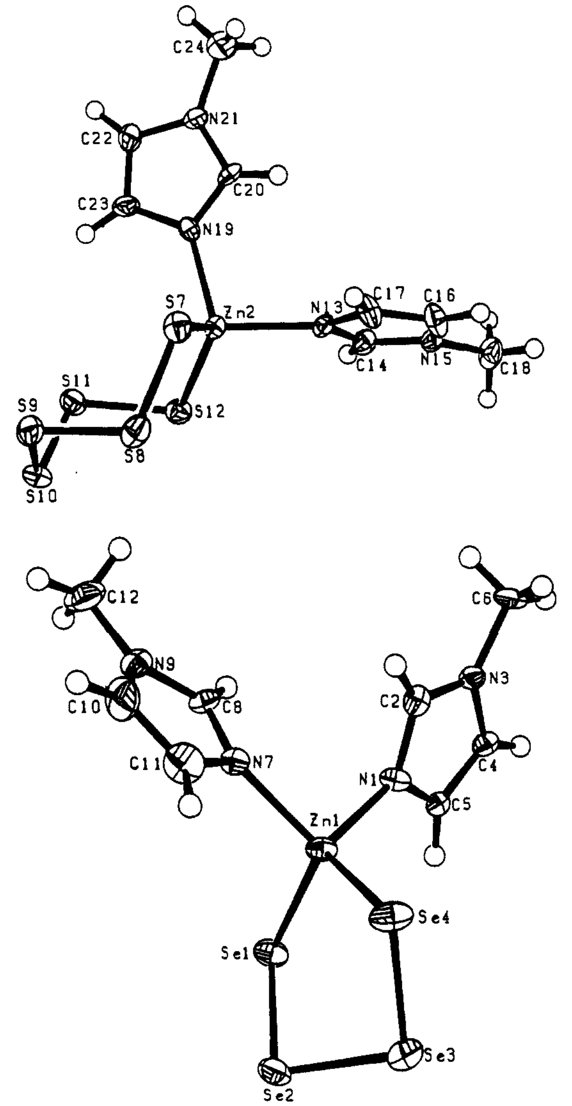

Figure 1. The structures of ZnS_6(*N*-MeIm)$_2$ (**1**) (top) and $ZnSe_4$(*N*-MeIm)$_2$ (**2**) (bottom) with thermal ellipsoids drawn at the 35% probability level. Selected bond distances (Å) and angles (deg) for **1**: Zn-S7, 2.312 (3); S7-S8, 2.048 (4); S8-S9, 2.043 (4); S9-S10, 2.058 (4); S10-S11, 2.047 (4); S11-S12, 2.044 (4); S12-Zn, 2.290 (3); N19-Zn, 2.014 (7); N13-Zn, 2.045 (7); N19-Zn-N13, 103.0 (3); S7-Zn-S12, 121.1 (1). Selected bond distances (Å) and angles (deg) for **2**: Zn-Se1, 2.431 (2); Se1-Se2, 2.330 (2); Se2-Se3, 2.333 (2); Se3-Se4, 2.345 (2); Se4-Zn, 2.430 (2); Zn-N1, 2.023 (10); Zn-N7, 2.021 (7); Se1-Zn-Se4, 111.56 (7); N1-Zn-N7, 101.0 (4).

Zinc dust (1.10 g, 16.83 mmol) was found to dissolve in a hot (100 °C) *N*-methylimidazole (*N*-MeIm, 20 mL) solution of elemental sulfur (3.25 g, 101.37 mmol). Over the course of 12 h, the reaction proceeded to give a clear, greenish-brown solution. The zinc dissolved *completely* in this reaction; we did not observe the formation of ZnS. The cooled, filtered solution was layered with toluene (40 mL), and after 24 h at 0 °C bright yellow crystals of ZnS_6(*N*-MeIm)$_2$ (**1**) were collected (3.69 g).[5] Yields ranged

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(1) Reviews of polychalcogenide complexes: Draganjac, M.; Rauchfuss, T. B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 742; *Angew. Chem.* **1985**, *97*, 745. Müller, A.; Diemann, E. *Adv. Inorg. Chem.* **1987**, *31*, 89. Ansari, M. A.; Ibers, J. A. *Coord. Chem. Rev.* **1990**, *100*, 223.

(2) Ramli, E.; Rauchfuss, T. B.; Stern, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 4043.

(3) A selection of recent references on the synthesis and applications of zinc sulfides: Osakada, K.; Yamamoto, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1117. Yao, G. Q.; Shen, H. S.; Honig, E. D.; Kershaw, R.; Dwight, K.; Wold, A. *Solid State Ionics* **1987**, *24*, 249. Yanagida, S.; Ishimaru, Y.; Miyake, Y.; Shiragami, T.; Pac, C.; Hashimoto, K.; Sakata, T. *J. Phys. Chem.* **1989**, *93*, 2576. Kortan, A. R.; Hull, R.; Opila, B.; Bawendi, M. G.; Steigerwald, M. L.; Carroll, P. J.; Brus, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 1327. Steigerwald, M. L.; Brus, L. E. *Annu. Rev. Mater. Sci.* **1989**, *19*, 431.

(4) Berg, J. M. *Prog. Inorg. Chem.* **1988**, *37*, 143.

(5) Anal. Calcd for $C_8H_{12}N_4S_6Zn$ (found): C, 22.80 (22.92); H, 2.87 (2.95); N, 13.27 (13.44); S, 45.59 (45.49); Zn, 15.49 (15.26). IR (KBr, cm^{-1}): 1111, 497, 459.