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Full Paper

Salicylaldehyde Hydrazones: Buttressing of Outer-Sphere Hydrogen-Bonding and Copper Extraction Properties

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Salicylaldehyde hydrazones are weaker copper extractants than their oxime derivatives, which are used in hydrometallurgical processes to recover ~20 % of the world's copper. Their strength, based on the extraction equilibrium constant K_e , can be increased by nearly three orders of magnitude by incorporating electron-withdrawing or hydrogen-bond acceptor groups (X) *ortho* to the phenolic OH group of the salicylaldehyde unit. Density functional theory calculations suggest that the effects of the 3-X substituents arise from a combination of their influence on the acidity of the phenol in the pH-dependent equilibrium, $Cu^{2+} + 2L_{org} \rightleftharpoons [Cu(L-H)_2]_{org} + 2H^+$, and on their ability to 'buttress' interligand hydrogen bonding by interacting with the hydrazone N–H donor group. X-ray crystal structure determination and computed structures indicate that in both the solid state and the gas phase, coordinated hydrazone groups are less planar than coordinated oximes and this has an adverse effect on intramolecular hydrogen-bond formation to the neighbouring phenolate oxygen atoms.

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Introduction

Approximately 20% of the world's copper is produced hydrometallurgically using phenolic oxime solvent $extractants^{[1,2]}$ of the types^[3,4] shown in Fig. 1. The acidity of the phenol allows metal uptake and release to be controlled by varying the pH of the aqueous phase (see Fig. 1).

The high selectivity for Cu^{II} over other first transition series metal cations has been assumed to be due, at least in part, to the goodness-of-fit^[5] for the cavity in these pseudomacrocyclic ligands. The head-to-tail hydrogen bonding in the complexes is also often found in the proligands.^[5]

In principle, variation of R, R' or R" groups in the structure in Fig. 1 can be used to tune the extractant strength, which is usually defined for these systems by the pH_{0.5} values (the pH at which 50 % of the theoretical loading is observed). Variation of the nature of an alkyl group *para* to the phenol (R in Fig. 1) does not change pH_{0.5} values greatly, ^[3,6,7] but more highly branched alkyl groups impart higher solubility in the hydrocarbon diluents used in industrial applications.

In general, salicylaldoximes with R' = H are stronger extractants than ketoximes or benzophenone oximes where R' groups are alkyl or aromatic groups.^[3] Groups present in the 3-position, *ortho-* to the phenolic oxygen atom (R" in Fig. 1), have very significant effects on extractant strength.^[3,6–8] Electronwithdrawing substituents such as halide and nitro groups make the proligands more acidic, favouring the extraction equilibrium shown in Eqn 2, whereas electron-donating substituents such as alkyl and methoxy groups have the opposite effect.^[3,8] Although proligands with higher phenol acidity form conjugate phenolate ions with lower basicity, which are poorer σ -donors^[9] and will



Fig. 1. The pH-dependent complexation of copper(II) by phenolic oxime extractants.

give a smaller overall formation constant β_2 , the square dependence of K_e on K_a :

$$K_{\rm e} \rightleftharpoons \beta_2 K_{\rm a}^2 \tag{1}$$

where $K_{\rm e}$ is the equilibrium constant for the formation of the neutral complex in a single phase,

$$Cu^{2+} + 2L \rightleftharpoons [Cu(L-H)_2] + 2H^+$$
 (2)

 β_2 represents the overall formation constant for the 2:1 (ligand: Cu^{II}) complex,

$$\operatorname{Cu}^{2+} + 2(\mathrm{L}-\mathrm{H})^{-} \rightleftharpoons [\operatorname{Cu}(\mathrm{L}-\mathrm{H})_{2}]$$
 (3)

and $K_{\rm a}$ represents the acid dissociation constant of the proligand LH,

$$L \rightleftharpoons [L-H]^- + H^+ \tag{4}$$

indicates that the phenol acidity has a greater effect on $K_{\rm e}$ than the phenolate basicity.

Substituents in the 3-position also influence the interligand hydrogen bonding shown in Fig. 1. Bulky *t*-butyl groups disrupt this stabilizing motif, whereas hydrogen-bond acceptors such as halide, nitro, and methoxy groups favour formation of bifurcated hydrogen bonds,^[10] 'buttressing' the stabilizing motif,^[6,7] and thus increasing extractant strength.

The combination of electronic, steric, and hydrogen-bond buttressing effects underpins the observed variation by more than two orders of magnitudes of the distribution coefficients for copper in the series of 3-substituted 3-*tert*-butylsalicylaldoxime extractants: $Br > NO_2 > Cl > OMe > Me \ge H > {}^{t}Bu.$ ^[6,7]

Salicylaldehyde hydrazones (Fig. 2) could also form N–H \cdots O hydrogen bonds to generate dimers with an R_4^4 (10) graph set



L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 NO_2 Br Х н Me NO₂ Br OMe н Me OMe R Me Me Ph Ph Ph Ph Ph Me Me Me ^tBu ^tBu ^tBu R ^tBu ^tBu ^tBu ^tBu ^tBu ^tBu ^tBu



Fig. 2. The 3- and *N*-substituted salicylaldehyde hydrazones L1-L10 and their pseudomacrocyclic copper complexes [Cu(L-H)₂], and related salicylaldoxime extractants **O1–O5** discussed in this paper.

descriptor^[11] and thus yield pseudomacrocyclic complexes similar to those formed by the analogous oximes. In the present paper, we consider whether 3-substitution of the phenol ring or *N*-substitution of the hydrazone group can be used to tune extractant strength to meet the requirements of commercial operations. It has been reported that both the unsubstituted ligand with R = R' = X = H (Fig. 2) and its *N*-phenyl analogue $(R = X = H, R' = C_6H_5)$ form neutral complexes of the type $[Cu(L-H)_2]$.^[12–16]

No work has been reported on the use of salicylaldehyde hydrazones as copper extractants, but other types of hydrazones have been used as spectrophotometric and gravimetric reagents for the detection and analysis of transition metals, including copper, nickel, and iron.^[12,13,17] Some show unusual magnetic^[18,19] and electronic^[20] properties, or are non-linearly optically active^[21–23] or fluorescent^[24,25] materials. They can also be used as optical chemosensors for analytical purposes.^[26,27] Salicylaldehyde benzoylhydrazone and analogous aroyl hydrazones have been studied as chelating agents to mobilize iron for iron-overload therapy,^[28,29] and their transition metal complexes possess antitumour properties.^[30–33] Many hydrazones and their transition metal complexes are used as antibacterial, antiviral, antitubercular,^[34] antimycobacterial,^[35] and antifungal agents,^[36,37] and in industry, they are employed as plasticizers^[38] and catalysts.^[39–41]

N-acyl and *N*-aroyl hydrazones of salicylaldehyde^[42–46] (Fig. 3) can form 2:2 copper(II) complexes as tridentate ligands with the phenolate oxygen, azomethine nitrogen, and enolimide oxygen atoms defining the binding site.^[42–46] In the *N*-aroylhydrazones shown in Fig. 3, it is understood^[42–46] that the phenolate oxygen atoms act as the bridges between the two copper atoms and, in some cases, a solvent molecule acts as a fifth ligand for each copper atom.

The 2Cu:2L stoichiometry and 3Cu:2L stoichiometry of related systems have been exploited to enhance the mass-transport efficiency of copper extraction over that associated with the 1Cu:2L system currently used (Fig. 1) in commercial processes.^[47,48]

Results and Discussion

L1–L10 were readily obtained in high yields (see Supplementary Material) by reaction of methyl or phenyl hydrazine with the substituted salicylaldehydes 1–5, which were prepared by formylation and 3-substitution of 4-*tert*-butylphenol (Scheme 1). A stock of 5-*tert*-butyl-2-hydroxybenzaldehyde (1) was synthesized by the Levin method,^[49] and the nitro-substituted



Fig. 3. Dinuclear complexes formed by *N*-acyl or *N*-aroyl hydrazones of salicylaldehyde derivatives.^[42–48]

(3) and bromo-substituted (4) salicylaldehydes were produced by optimizing literature conditions for electrophilic substitution.^[50] The methoxy-substituted salicylaldehyde (5) was prepared from its bromo analogue 4 by a modification of the literature method.^[51] In the case of 3-methyl-salicylaldehyde (2), the synthesis exploited the modified Duff reaction^[52] starting with 4-*tert*-butyl-2-methylphenol, because it was commercially available and it would be difficult to methylate 1 by Friedel–Crafts or related reactions.

X-ray structure determinations of **L6** and **L10** (Fig. 4) reveal that, as expected, the phenolic group acts as an intramolecular bond donor, $O-H\cdots N$, to the imine nitrogen atom and as an intermolecular hydrogen-bond acceptor from a hydrazone NH



Scheme 1. Synthetic routes to salicylaldehyde hydrazones L1–L10: (i) $(CH_2O)_n/[Mg(OMe)_2]/MeOH;$ (ii) hexamethylenetetramine/CF₃CO₂H; (iii) HNO₃/CH₃CO₂H; (iv) Br₂/CH₃CO₂H; (v) NaOMe/MeOH; (vi) MeNHNH₂ or PhNHNH₂/EtOH.

group in a neighbouring molecule. In both structures, the hydrogen bonding involving the NH groups leads to the formation of linear polymers rather than pseudomacrocyclic dimers of the type commonly found^[5] in the structures of phenolic oximes (see Fig. 1), which are preorganized for metal binding. In the case of **L10**, the formation of the linear polymer is clearly favoured by the hydrazone group being able to make an additional bonding contact with the 3-methoxy group.

NMR methods were used to probe how tautomerism, phenol acidity, hydrogen bonding, and intermolecular association in solution (Fig. 2) are affected by the substituents on the nitrogen atom or *ortho* to the phenol (Y or X respectively in Fig. 5) because these are likely to have a significant influence on strength as metal extractants. The ¹H NMR spectra confirm (see Supplementary Material) that the proligands exist in solution as the imino-enol tautomer (Fig. 5) as expected from the substantial advantage of aromaticity.^[53,54]

All the resonances in the ¹H NMR spectra of the *N*-methylhydrazones **L1–L5**, and the *N*-phenylhydrazones **L6–L10**, can be unambiguously assigned. In the spectra of the *N*-methylhydrazones, the hydrazone proton is coupled with the NCH₃ protons and appears as a quartet at δ 7–8 ppm (Supplementary Material). For the *N*-phenylhydrazones **L6–L10**, both the phenol and hydrazone protons appear as singlets at $\delta > 10$ ppm. These can be distinguished by examining the COSY (correlation spectroscopy) spectra, which indicate a weak coupling between the azomethine proton and one of the very-low-field protons (Fig. S1, Supplementary Material), which was therefore assigned as the hydrazone.

For the oximes **O1–O5**, the COSY spectra did not show spin– spin coupling between the azomethine and oxime protons, which suggests that the oxime oxygen, in contrast with the methyl hydrazone NH group, is not much involved in the conjugation of the molecule. Heteronuclear multiple-bond connectivity



Fig. 5. Imino-enol and amino-keto tautomers of the structurally related salicylaldoximes (O1–O5), *N*-methylhydrazones (L1–L5), and *N*-phenylhydrazones (L6–L10).



Fig. 4. X-ray crystal structures of the free ligands L6 and L10 with hydrogen-bond distances (Å).

(HMBC, also known as long-range ${}^{1}H^{-13}C$ COSY) experiments were carried out to distinguish the phenol and oxime protons. The HMBC spectrum of the unsubstituted oxime **O1** in DMSO-d₆ (Fig. S2, Supplementary Material) reveals correlation between the azomethine ${}^{13}C$ at 148.95 ppm and the proton at 11.25 ppm, which confirms the latter to be the oxime proton.

An order of electron-withdrawing effect, oxime > phenylhydrazone > methylhydrazone, is supported by the comparison of ¹H NMR spectra of the unsubstituted proligands L1, L6, and O1 with 4-*tert*-butylphenol, and those of their 3-methylsubstituted analogues L2, L7, and O2 with 4-*tert*-butyl-2methyl-phenol (see Supplementary Material). It has been

 Table 1.
 Chemical shifts (ppm) of the phenolic hydrazone and oxime protons of L1–L10 and O1–O5 in DMSO-d₆

3-Substituent	Methylhydrazones		Phenylhydrazones		Oximes	
Н	L1	11.19	L6	10.40	01	9.88
Me	L2	11.57	L7	11.09	02	10.12
NO ₂	L3	12.94	L8	11.76	03	11.13
Br	L4	12.26	L9	11.64	04	10.69
MeO	L5	11.08	L10	9.99	05	9.48



Fig. 6. The *E* and *Z* isomers of the 3-nitrosubstituted ligands L3, L8, and O3 in which ZH = MeNH, PhNH, and OH.

shown^[55,56] that there is a linear correlation between the pK_a values of phenols in aqueous solution and the chemical shift of the phenolic protons at infinite dilution in DMSO. On this basis, the chemical shift data for L1–L10 and O1–O5 in DMSO-d₆ (Table 1) suggest that the acidity of the phenolic proton follows the electron-withdrawing properties of the imine component with oxime > phenylhydrazone > methylhydrazone. The magnitude of the 3-substituent effects on acidity: NO₂ > Br > Me > H > OMe also follows that expected from their electron-withdrawing properties.

Hydrogen bonding between proligands in solution, to form cyclic dimers or linear oligomers, is of great relevance to their preassembly and strength as metal extractants. The temperature and concentration dependence of ¹H NMR experiments (Fig. S3, Supplementary Material) shows that, in contrast to the CH protons, the shifts for the phenolic and oximic protons are markedly temperature-dependent. As temperature is increased, the larger shift of the hydrazone signal to high field compared with that of the phenol is consistent with the former forming inter- and the latter intramolecular hydrogen bonds.^[57-61] The preference for the phenolic proton to form an intramolecular hydrogen bond to the imino nitrogen accords with solid-state structures (see Fig. 4). An exception is the 3-nitro-substituted proligands where the nitro group competes effectively for the phenolic proton to give structures such as those shown in Fig. 6 (see also computational results below).

The conformation and aggregation of the methylhydrazones **L1–L5** were investigated by nuclear Overhauser effect spectroscopy (NOESY). The spectrum of **L2** in CDCl₃ (Fig. 7) demonstrates that the azomethine proton is close to both the *N*-substituted methyl group and the benzene C6 proton. This is consistent with the presence of a phenol OH to imino N intramolecular hydrogen bond in the *E* conformation (see Fig. 8).

The *E* conformation implied by the NOESY spectrum allows the pseudomacrocyclic dimer to be formed as shown in Fig. 8.



Fig. 7. NOESY spectrum of L2 in CDCl₃.



Fig. 8. Formation of cyclic dimers from the *E* conformers of the salicy-laldehyde methylhydrazones showing possible hydrogen-bond buttressing by the 3-X groups.



Fig. 9. The solid-state structures of $[Cu(L1-H)_2]$ (top); and $[Cu(L5-H)_2]$ (below).

The NMR results suggest that in solution, the hydrazone proligands L1–L10 show a similar facility for aggregation and preorganization to their much more studied oxime analogues. Consequently, their abilities to function as extractants for Cu^{II} are of interest.

All the hydrazone proligands were found to form 1:2 Cu: L complexes [Cu(L–H)₂] on reaction with copper(II) acetate in methanol. X-ray structure determinations of [Cu(L1–H)₂] and [Cu(L5–H)₂] confirm that the methylhydrazones yield planar Cu^{II} complexes with pseudomacrocyclic structures similar to their oxime analogues (Fig. 9). The intramolecular contacts between terminal hydrazone nitrogen atoms and the phenolate oxygen atoms Y¹···O² in the hydrazone complexes are slightly longer than those defining the intramolecular hydrogen bond in the oxime complex [Cu(O1–H)₂] (see Table 2).

The Cu–N and Cu–O bond lengths in the hydrazone complexes (Table 2) fall in a similar range to those found in

the related oxime complexes.^[5] As the structures all have the copper atom on a crystallographic inversion centre, the bonding cavity radius^[5] defined by the N₂O₂ donor set is the mean of the Cu–O and Cu–N lengths. The smaller value for the oxime complex [Cu(O1–H)₂] implies tighter binding than in the hydrazone complexes but caution needs to be exercized in using cavity radii determined from solid-state structures to compare the equatorial planar fields defined by the N₂O₂ donor sets because axial contacts vary considerably between structures;^[5] for example, the phenolate oxygen atoms of adjacent complexes make close contacts (2.670 (2) Å) in the structure of [Cu(L1–H)₂] (see Fig. 9) but not in [Cu(L5–H)₂].

An interesting feature of the structures of $[Cu(L1-H)_2]$ and $[Cu(L5-H)_2]$ is that the hydrazone N–N bonds bend away from the central CuN₂O₂ unit to a greater extent than the N–O bonds in the related oxime complexes. This is manifest (Table 2) by larger deviations of the terminal hydrazone nitrogen atoms from the least-squares planes defined by the copper atom and the donor set (CuN₂O₂) than the oximic oxygen atoms and by the related torsion angles. The implications of this are that interligand hydrogen bonding is weaker in the hydrazones and will reduce complex stability and extractant strength. This and the effects on the hydrogen bonding by the 3-X substituents are considered further in density functional theory (DFT) calculations (see below).

A preliminary investigation of the strength of the hydrazones as solvent extractants by studying the pH-dependence of the reaction

$$\operatorname{CuSO}_4 + 2L_{(\operatorname{CHCl}_3)} \rightleftharpoons \left[\operatorname{Cu}(L-H)_2\right]_{(\operatorname{CHCl}_3)} + H_2\operatorname{SO}_4 \quad (5)$$

indicated that they are intrinsically weaker extractants than their oxime analogues. Two problems were encountered in obtaining solvent-extraction data. For some of the weaker extractants, loading is only observed at pH values at which precipitation of copper(II) hydroxide occurs and several of the ligands and their Cu^{II} complexes were insufficiently soluble in chloroform to allow extraction experiments to be conducted. To circumvent these problems, strength data were obtained by determining the pH values for 50% loading of copper from stripping experiments in which chloroform solutions of preformed [Cu(L–H)₂] were put in contact with aqueous solutions having different acidities but a constant sulfate (0.01 M) concentration. The pH-dependence of copper loading curves and pH_{0.5} values are shown in Fig. 10.

Clearly, 3-substitution significantly affects the extraction strength, and the distribution coefficient for copper transfer varies by more than three orders of magnitude across the series: $NO_2 > Br > H \ge OMe \ge Me$. It is apparent that the hydrazones are intrinsically weaker extractants than their oxime analogues $(pH_{0.5} data^{[6]} for the latter, O1-O5$, are included for comparison in the table inset in Fig. 10). The unsubstituted hydrazone (L1) and its 3-methyl and 3-methoxy derivatives (L2 and L5) show distribution coefficients for Cu^{II} approximately three orders of magnitude smaller than their oxime analogues (O1, O2, and O5). The differences in strength between the 3-nitro- and 3-bromo-substituted hydrazones L3 and L4 and their oxime analogues (O1-O5) is much smaller.

In an attempt to define to what extent the electronic, steric, and hydrogen-bond buttressing properties of the 3-X substituents determine the relative strengths of the extractants, DFT

X = R $H = Y_2$	Compound	Х	Y	R
	[Cu(L1 –H) ₂]	Н	Ν	Me
\mathbb{N}_1 \mathbb{O}_2 \mathbb{N}_1 \mathbb{O}_2	[Cu(L5 –H) ₂]	OMe	Ν	Me
R X	[Cu(01 –H) ₂]	н	0	-

Table 2. Bond lengths and angles in the inner coordination spheres of the [Cu(L1-H)₂] and [Cu(L5-H)₂] compared with those in [Cu(O1-H)₂]

Bond lengths (Å) and angles (°) ^A	$[Cu(L1-H)_2]^A$	$[Cu(\textbf{L5-H})_2]^{A,B}$	$[Cu(\mathbf{O1}\text{-H})_2]^{A,C}$			
Cu–O ₁	1.9244(11)	1.8658(10)	1.905(2)	1.900(2)	1.907(2)	
Cu–N ₁	1.9986(13)	2.0020(13)	1.941(2)	1.945(2)	1.943(2)	
O ₁ -Cu-O ₂	180.0	180.0	180.0	180.0	180.0	
N ₁ -Cu-N ₂	180.0	180.0	180.0	180.0	180.0	
O ₁ -Cu-N ₁	91.03(5)	92.24(5)	92.26(8)	92.13(8)	91.76(8)	
O ₂ -Cu-N ₁	88.97(5)	87.76(5)	87.74(8)	87.87(8)	88.24(8)	
$Y_1 \cdots O_2$	2.7005(18)	$2.604(4) 2.614(4)^{B}$	2.581(2)	2.583(5)	2.584(3)	
Cavity radius ^D	1.962(2)	1.934(2)	1.923(3)	1.923(3)	1.925(3)	
O ₁ -Cu-N ₁ -Y ₁	160.55(10)	$168.7(2), 162.8(2)^{B}$	173.8(2)	177.9(2)	175.5(2)	
O_2 -Cu-N ₁ -Y ₁	19.45(10)	$11.3(2), 17.2(2)^{B}$	6.20(16)	2.12(16)	4.54(16)	
Distance of Y from CuN2O2 plane	0.418(1)	$0.247(2), 0.380(4)^{\mathrm{B}}$	0.135(2)	0.046(2)	0.099(2)	

^AIn all complexes, the Cu^{II} atom lies on an inversion centre.

^BSeparate values are given for the two molecules having differently disordered hydrazone groups.

^CSee Forgan et al.^[6]

^DThe mean distance of the N and O donor atoms from their centroid.



Fig. 10. Copper loading of L1–L5 after placing 0.005 M chloroform solutions of $[Cu(L-H)_2]$ in contact with an equal volume 0.01 M Na₂SO₄ aqueous solutions of various acidities. The pH_{0.5} values of the oxime analogues O1–O5 are also listed. ^AFor [Cu(L3–H)₂], 0.0005 M chloroform solutions were used owing to the limited solubility. ^BThe 5-*t*-octyl-substituted analogue as O4 and its copper complex have insufficient solubility to allow the experiment to be conducted.

calculations were carried out to determine the enthalpies of the reactions

$$2L_{(g)} + Cu^{2+}{}_{(g)} \to \left[Cu(L-H)_2\right]_{(g)} + 2H^{+}{}_{(g)}$$
(6)

and

$$[L]_{2(g)} + Cu^{2+}{}_{(g)} \to [Cu(L-H)_2]_{(g)} + 2H^+{}_{(g)}$$
(7)

(see Table 3)

The energy-minimized structures of the copper complexes (see Supplementary Material) compare closely with those determined by X-ray crystallography (see Fig. 11). As for the X-ray structures (Table 2), the DFT calculations indicate that the N–N bonds in the hydrazone complexes are bent away from the coordination plane. In contrast, the N–O bonds in the oxime [Cu(O1–H)₂] lie very close to the CuN₂O₂ plane (see O–Cu–N–Y torsion angles in Table 3). This is consistent with the interligand O–H···O_{phenolate} hydrogen bonds being shorter and stronger than the N–H···O_{phenolate} hydrogen bonds in the hydrazone complexes. The greater strength of the hydrogen bonds to the phenolate oxygen atoms in [Cu(O1–H)₂] is consistent with the oxime complex having slightly weaker Cu–O bonds than those in the hydrazone complexes (see natural bond orbital (NBO) values in Table 3).

The buttressing of interligand hydrogen bonding by the nitro-, bromo-, and methoxy-groups in [Cu(L3–H)₂], [Cu(L4–H)₂],



Fig. 11. The calculated structure of $[Cu(L1-H)_2]$ showing the displacement of the N–NHMe units from the coordination plane.

Table 3. DFT calculated gas-phase deprotonation enthalpies $(E_{depr}, L \rightarrow [L-H]^- + H^+)$, ligand dimerization energies $(E_{dimer}, 2L \rightarrow [L]_2)$, Cu complex formation energies, natural bond orbital (NBO) values, and geometric data for energy-minimized structures of Cu complexes

	L1	L3	L4	L5	01
	X = H	$X = NO_2$	X = Br	X = OMe	X = H
$E_{\text{depr}} [\text{kcal mol}^{-1}]^{\text{C}} \text{ for } L \rightarrow [L-H]^{-} + H^{+A}$	364.48	347.32	357.19	364.84	356.42
$E_{\text{dimer}} [\text{kcal mol}^{-1}] [L]_2^{\text{A}}$	-8.46	-17.08	-11.98	-10.92	-10.63
$E_{\text{form}} \text{ [kcal mol}^{-1} \text{] [Cu(L-H)_2] from [L]}_2^A$	34.57	30.44	33.08	32.80	27.43
$E_{\text{form}} \text{ [kcal mol^{-1}] [Cu(L-H)_2] from 2L^A}$	26.11	13.36	21.10	21.88	16.80
NBO for Cu–O [kcal mol ⁻¹] ^B	51.23	52.01	52.69	54.70	50.10
NBO for Cu–N [kcal mol ⁻¹] ^B	36.71	37.07	36.05	37.26	47.37
Torsion angle O–Cu–N–Y [°] ^B	170.5	172.5	174.2	171.9	180.0
Torsion angle O'-Cu-N-Y [°] ^B	9.5	7.5	5.8	8.1	0.0
NBO for Y–HO [kcal mol ⁻¹] ^B	9.13	5.77	5.98	6.08	11.50
Y-HO contact distance [Å] ^B	1.86	1.91	1.88	1.86	1.78
Y–HX contact distance [Å] ^B	2.91	2.02	2.81	2.72	2.99
Distance of Y from the least-squares mean plane $\text{CuN}_2\text{O}_2\left[\mathring{A} ight]^A$	0.21	0.16	0.13	0.18	0.00

^AEnergies and Cartesian coordinates for energy-minimized structures are provided in the Supplementary Material, Sections 4.1 and 4.2 respectively. ^BMean of the two calculated values (no symmetry constraints were imposed during energy minimization).

 $^{\rm C}$ 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹.

and $[Cu(L3-H)_2]$ (see the Y-H···X contact distances, Table 3) is, as might be expected, accompanied by a weakening of the other interligand hydrogen bond (Y-H···O_{phenolate}).

The non-planar disposition of bonds about the coordinated nitrogen atoms in the hydrazone complexes suggests that they have sp³ character to a greater extent than those in their oxime analogue. This is associated with them forming significantly weaker Cu–N bonds than those in the oxime complex [Cu(**O1**–H)₂] and mirrors the relative Cu–N bond lengths found in the solid-state structures (see Table 2).

The extent to which the 3-X substituents can buttress the interligand hydrogen bonds is also revealed by the enthalpies of formation of the proligand dimers (E_{dimer} in Table 3). Incorporation of the hydrogen-bond accepting groups, NO₂, Br, and OMe, leads to more favourable enthalpies of dimerization than that for the unsubstituted compound.

As discussed above, the NO_2 , Br, and OMe groups all show bonding interactions in the outer coordination sphere with the hydrazone hydrogen. Although the nitro-substituent forms a particularly strong interaction with the hydrazone N–H group, the dimerization enthalpy of L3 is only slightly more favourable than that of the unsubstituted ligand L1. This is a consequence of the monomer adopting a very favourable conformation that allows the phenolic OH group to hydrogen bond to the adjacent nitro substituent and the hydrazone N–H group to the phenolic oxygen atom.

The calculated gas-phase formation energies for the copper complexes $([L]_{2(g)} + Cu^{2+}_{(g)} \rightarrow [Cu(L-H)_2]_{(g)} + 2H^+_{(g)}, Table 3)$ are more favourable for those having the hydrogen-bond acceptor groups NO₂, Br and OMe. This trend is not so marked for the methoxy-substituted ligand, mainly a consequence of its less favourable deprotonation enthalpy. Although the predicted order of extractant strength, NO₂ > Br > OMe > H, appears to correlate reasonably well with that observed experimentally, NO₂ > Br > H \geq OMe, the calculated values are based on the assumption that the reagents are exclusively in the cyclic dimeric form before copper uptake, and this is known not to be the case for the nitro ligand L3 (see above). If the monomeric proligands are taken as the starting forms, the nitro-substituted extractant still shows the most favourable formation energy.

For L5, the electron-donating properties of the methoxy substituent lead to a higher deprotonation enthalpy term than

for the unsubstituted ligand L1, but this appears to be more than compensated for by the more favourable strengths of bonds to copper and the buttressed hydrogen bonding to the hydrazone NH.

At first sight, the correlation between calculated energies of formation in the gas phase and the relative strength of extractants in a two-phase liquid system is quite remarkable. As discussed recently for other systems where this occurs,^[62] this correlation will only be observed when the process occurring in the aqueous phase is the same, in this case two protons replacing one copper dication, for the series of extractions. Consequently, as in the current work, hydration energies of species do not contribute to differences in the formation energies of metal complexes. The solvation energies of the proligands and their copper complexes in the organic phase will obviously show some dependence on the nature of the 3-X substituent. However, the differences in solvation energies of the preorganized dimers and their copper complexes are likely to be fairly small and, consequently, it is the effect of the 3-X substituents on the deprotonation energies of the proligands and the binding energies of the conjugate anions to copper that largely determine the energies of formation of the complexes.

Conclusions

The approach of using the cavity size in macrocyclic proligands to tune the strength of binding of base metal ions, established by Lindoy and coworkers,^[63] can be extended to much simpler reagents such as the salicylaldehyde hydrazones described in the present work, which assemble in pseudomacrocyclic structures via interligand hydrogen bonding.

The *N*-methyl hydrazone derivatives (**L1–L5**) are analogues of the commercial phenolic oxime reagents but are significantly weaker copper extractants. On the basis of the DFT calculations and X-ray structure determinations, it appears that this arises from a combination of the weaker Cu–N bonds and the less favourable interligand hydrogen bonds formed by the hydrazones (OH groups are generally better hydrogen bond donors than NH groups^[64,65]) and from their higher deprotonation enthalpies. The *N*-phenyl hydrazones (**L6–L10**) are too weak to allow solvent extraction to be carried out under conventional conditions.

The results confirm the importance of understanding outersphere coordination chemistry in designing metal solvent extractants and, in particular, the efficacy of interligand hydrogen bonding in extracted species. As for the oximes,^[6,7] the introduction of substituents adjacent to the phenolic hydroxyl group with electron-withdrawing and hydrogen-bond acceptor properties significantly increases the strength as copper extractants. For the *N*-methyl hydrazones, the distribution coefficient for copper extraction is increased by three orders of magnitude on introducing a 3-bromo or 3-nitro-substituent. The resulting extractants have strengths comparable with the commercial oximes, but their lower solubilities in water-immiscible solvents and the higher costs of synthesis arising from introduction of the substituent make them poor candidates to replace the tried and tested commercial reagents.

Experimental

Chemicals and Equipment

Unless otherwise specified, reagents or solvents were used as obtained from Aldrich, Fisher or Acros. Standards for inductively coupled plasma optical emission spectroscopy (ICP-OES) were purchased from Alfa Aesar. ¹H and ¹³C NMR spectra recorded in the experimental section were run on a Bruker ARX250 at ambient temperature. ¹H NMR NOESY spectra were recorded on a Bruker DPX360 spectrometer at 298 K (unless stated otherwise), and chemical shifts (δ) are reported in parts per million (ppm) relative to TMS. CHN analytical data were obtained by the University of St Andrews Microanalytical Service. Mass spectrometry was performed on a Micromass ZMD instrument with a z-spray electrospray ionisation (ESI) source. Melting points were measured on a Gallenkamp melting point apparatus. ICP-OES analysis was performed on a Perkin Elmer Optima 5300DV spectrometer. The measurement of pH was carried out using a Sartorius PP-50 pH meter.

X-Ray Crystal Structures

These were obtained by measuring suitably sized crystals on either a Bruker D8 with a Smart Apex or Apex II charge coupled device (CCD) or an Oxford Diffraction SuperNova with an Atlas CCD. Data were collected at 150 K unless otherwise specified and reduced with the relevant manufacturer's software. All structures were solved by direct methods and refined with *ShelXL*. Refer to the Supplementary Material for the details for each structure. In the crystal structure of [Cu(L5–H)₂], there was some disorder in the position of the hydrazone N–H group. This was modelled as two components, with each fixed at 50 % occupancy, determined from approximate values gleaned through refinement. This approach was used as a consequence of minor instability of the refinement and unreasonable, unequal atomic displacement parameters when occupancies were refined with linked occupancies summing to 100 % occupancy.

NMR Studies

Samples were generally prepared by dissolving 10 mg of the ligand in 0.6 mL CDCl₃ or DMSO-d₆. Samples for NOESY and 1D NOE difference spectra required more concentrated solutions, and 40 mg of the ligand in 0.6 mL CDCl₃ was used. The concentration-dependence NMR study was carried out by diluting an NMR sample containing 40 mg of the ligand in 0.6 mL DMSO-d₆ to 1.2, 1.6, and 2.4 mL in the same NMR tube.

Solvent Extraction

Preliminary loading experiments were carried out by placing a chloroform solution of the ligand (5.00 mL, 0.010 M) in contact with an aqueous solution of copper(II) sulfate (5.00 mL, 0.010 M) at different pH values in a tightly sealed, screw-top glass jar. The aqueous solution was prepared by adding an H₂SO₄ solution (0.10 M for pH 1.5 and above, 1.00 M for lower pH) or a NaOH solution (0.10 M) to a CuSO₄ solution (3.00 mL, 0.0167 M) and adding water to make up to 5.00 mL. The two-phase system was stirred at 900 rpm at room temperature for 18 h. A 1.00 mL aliquot was taken from the organic phase, dried under vacuum, and redissolved in butan-1-ol (10.00 mL). The residues from L3 and L4 solutions were dissolved in nitrobenzene. The copper was then analysed by ICP-OES. The pH of the aqueous phase was measured using a pH meter. The calculated percentage of the copper(II) taken into the organic phase was plotted against the measured equilibrium pH to give the S-curve.

The data presented in Fig. 10 were obtained by taking a chloroform solution of the copper(π) complex (5.00 ml, 0.005 M) and an aqueous solution of sodium sulfate (5.00 mL, 0.010 M) with varying H₂SO₄ content. In some cases, the low

solubility of the complex required slight modifications of the procedure (Section 3 in the Supplementary Material).

Computational Work

For the determination of energies of formation (rows 1–4 in Table 3), DFT calculations employed the B3LYP hybrid exchange-correlation functional^[66,67] and the 6–31+G(d,p) basis set,^[68–71] and were performed using the *Gaussian 09 Revision E.01* program.^[72] The energy-minimized structures used to compare bond lengths and angles and to provide NBO data (rows 5–12 in Table 3) were generated using *Gaussian 03*^[73] with the B3LYP functional and 6–31G+(d,p) basis set. More information, including Cartesian coordinates for atom positions, are provided in Tables S4.1 and S4.2 in the Supplementary Material.

Synthesis

The preparation and characterization of all proligands and copper complexes are described in detail in the Supplementary Material (Section 5). L6: CCDC deposition number: 1517105; L10: CCDC deposition number: 1517104; [Cu(L1–H)2]: YUPBAO, CCDC deposition number: 1410136; [Cu(L5–H)2]: YUNZUE, CCDC deposition number: 1410135.

Supplementary Material

Additional NMR data for the proligands, experimental conditions for solvent extraction experiments, positional parameters for all DFT energy minimized proligand and copper complex structures, and full experimental details for the synthesis and characterization of proligands and complexes are available on the Journal's website.

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