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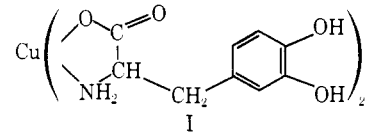
Copper Complexes of Dopa. Control of the Bonding Mode

Sir:

Catecholamines and catecholamino acids are important intermediates in many neurological and other biochemical reactions.[1] The coordination chemistry of these compounds is complicated by their ability to act as ambidentate or bridging ligands.[2,3] Thus, for example, L-dopa (3,4-dihydroxyphenylalanine), used in the treatment of Parkinson's disease, can coordinate as a bidentate ligand through either the catecholate (O, O) or the amino acid (O, N) end of the molecule. Furthermore, it is known that divalent transition metal ions such as Mn,[4] Cu,[5] and possibly Ni[6] also have biologically significant roles which in part involve interactions with the catechol amines. It thus seemed appropriate to investigate in greater detail the nature of the coordination compounds formed between these ligands and metal ions. In this paper we report what we believe to be the first isolated complexes of dopa with the transition metal ion Cu and discuss those conditions which lead to the different modes of binding observed.

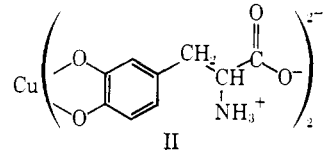
When Cu^{2+} and dopa in 1:2 mole ratio are placed in water and aqueous ammonia is added to bring the pH to 5.0, a blue-purple complex can be isolated from the solution.[7] This complex is sparingly soluble in water and methanol but quite soluble in DMF and DMSO. In DMF its electronic spectrum exhibits a peak at 16,130 cm^{-1} (ϵ = 97). The complex in DMSO can be reduced in two reversible one-electron steps by cyclic voltametric techniques at potentials of −0.04 and −0.53 V *vs.* sce.[8] These results can be compared with the known complex Cu(tryptophan)$_2$[9] wherein a peak at 16,130 cm^{-1} (ϵ = 85) and potentials of −0.04 and −0.53 V are found. Since the tryptophan complex almost certainly binds through its amino acid end, we conclude that this blue-purple complex involves bonding of dopa through the amine carboxylate linkage. The infrared spectrum further substantiates this, showing the absorptions characteristic of free catechol OH's. These data taken together with elemental analysis[7] lead us to formulate the isolated complex as Cu(O,N-dopa)$_2\cdot H_2O$, containing I, wherein the electronic spectrum and epr properties[10] are consistent with a trans square planar coordination geometry



I

When the pH of the solution is further raised by addition of ammonia (still under nitrogen), complex I redissolves and the solution color changes to olive green. If a cold 1:1 mixture of ethyl acetate and isopropyl alcohol is added to the 1:2 Cu–dopa solution at pH 9.5 an olive green solid can be obtained.[11] This solid is extremely soluble in water but insoluble in methanol. In water it displays absorption bands at 15,800 (ϵ = 62) and 23,000 cm^{-1} (ϵ = 100), and reversible voltametric waves at −0.15 and −0.30 V. It lacks the infrared bands characteristic of free catechol. The data are to be compared with the Cu(catecholate)$_2^{2-}$ complex[12] which absorbs at 14,900 (ϵ = 70) and 24,800 cm^{-1} (ϵ = 210) and shows voltametric waves at −0.15 and −0.39 V.[8] These comparisons together with elemental analysis[11] lead us to formulate this complex as $(NH_4)_2Cu(O,O\text{-dopa})_2\cdot 4H_2O$, with a square planar CuO_4 coordination sphere, II.

When II is dissolved in neutral unbuffered water the pH is found to be 6.4 and the spectrum indicates the presence of exclusively the complex II. This indicates that even below the nominal physiological pH range the O,O-bound form is a viable species (at least kinetically inert over the period of a few hours). On the other hand simply mixing 2:1, dopa–Cu^{2+} at pH 7.3 does not give 100% formation of the O,O complex



II

(1) J. H. Biel and L. G. Abood, Ed., "Biological Amines and Physiological Membranes in Drug Therapy," Marcel Dekker, New York, N. Y., 1971.
(2) J. E. Gorton and R. F. Jameson, *J. Chem. Soc. A*, 2615 (1968).
(3) J. E. Gorton and R. F. Jameson, *J. Chem. Soc. A*, 304 (1972).
(4) U. Meiri and R. Rahamimoff, *Science*, **176**, 308 (1972).
(5) M. Goldstein in "The Biochemistry of Copper," J. Peisach, P. Aisen, and W. E. Blumberg Ed., Academic Press, New York, N. Y., 1966, p 43.
(6) V. R. Soroka, V. Y. Arsentev, and M. S. Mukhaey, *Zh. Neuropatol. Psikhiat. im. S. S. Korsakova*, 72, 69 (1972).
(7) All operations are carried out under nitrogen. $CuCl_2\cdot 2H_2O$ (0.26 g) is dissolved in 2 ml of H_2O, and *d,l*-dopa (0.55 g) suspended in 3 ml of H_2O is added to the solution. The pH is brought up to 5 by slowly adding dilute ammonia over 45 min. The mixture is stirred for an additional 30 min and the blue-purple solid is collected by filtration, washed with water, methanol, and *n*-pentane, and dried under vacuum, decomposition point 220–223°. *Anal.* Calcd for $Cu(C_9H_{10}NO_4)_2\cdot H_2O$: C, 45.57; H, 4.64; N, 5.90. Found: C, 46.08, H, 4.39; N, 5.66.
(8) Voltametric methods utilized a dropping Hg electrode with Pt as counter and sce as reference electrodes. Tetraethylammonium perchlorate (0.1 *M*) was supporting electrolyte in DMSO while KCl was used in water. Complex concentration was roughly 10^{-3} *M*.
(9) C. J. Hawkins and C. L. Wong, *Aust. J. Chem.*, **23**, 2237 (1970).
(10) E. R. Purdy, W. L. Kwik, and E. I. Stiefel, to be submitted for publication.
(11) All operations are carried out under nitrogen. A solution of $CuCl_2\cdot 2H_2O$ (0.26 g) in 0.4 ml of H_2O plus 0.73 ml of aqueous NH_3 is added to a suspension of 0.55 g of *d,l*-dopa in 0.5 ml of H_2O and stirred for 30 min whereupon the pH is 9.5. A small amount of unreacted dopa is filtered off and the olive green filtrate is cooled in ice. Ice cold 1:1 ethyl acetate–isopropyl alcohol is added slowly and the solution is then decanted from the resulting olive green oil. The oil is washed with 1:1 ethyl acetate–isopropyl alcohol and then vigorously scratched in the presence of the ice cold liquid. The resultant solid is filtered, washed with 1:1 ethyl acetate–isopropyl alcohol, isopropyl alcohol, and ether and dried under vacuum, decomposition point 124°. *Anal.* Calcd for $(NH_4)_2Cu(C_9H_9NO_4)_2\cdot 4H_2O$: C, 38.47; H, 6.10; N, 9.97. Found: C, 38.97; H, 5.93; N, 9.88.
(12) F. Röhrscheid, A. L. Balch, and R. H. Holm, *Inorg. Chem.*, **5**, 1542 (1966).

although there is evidence from the electronic spectrum for its presence. Thus, at nominal physiological pH some mixed mode of bonding may be present as neither the O,O or the N,O complex forms exclusively when metal and ligand are mixed.

We have found that two distinct bis complexes are isolated at opposite sides of pH 7. The amino acid type of complex is isolated at a lower pH presumably because only one proton need be removed to produce the unprotonated ligand donor atoms while for the catecholate binding two protons must be removed. Thus, in gross agreement with the predictions of solution studies,[2] the pH is a sensitive determinant of the binding mode of Cu and dopa, and at physiological pH both modes of bonding are possible.

Another potential determinant of the bonding mode is the nature of other ligands in the coordination sphere of Cu. Thus, Sigel and coworkers[13] have shown that certain ternary complexes of Cu^{2+} have unexpected stability. In particular, if one of the ligands in the ternary complex is 2,2′-bipyridine (bipy) then the stable ternary complexes are formed when the second ligand is of the O,O-bidentate type such as oxalate, pyrophosphate, or *catecholate*. Thus, a ternary complex of Cu^{2+}, bipy, and dopa might be expected to favor formation of the complex containing the O,O-dopa ligand. To test this idea we carried out solution studies by monitoring the appearance of the 23,000-cm^{-1} absorption band as the pH was raised. This band has been assigned to ligand-to-metal charge transfer[11,13] and is thus a clear diagnostic of the formation of the Cu–O,O-dopa linkage. We find, however, that in this case no substantial difference occurs in the pH at which this band first appears in the presence or absence of bipyridyl.

The two factors which we have discussed above, pH and other ligands in the coordination sphere, may finely tune the way in which Cu binds to dopa. In the present case the pH seems to be the dominant factor. These same considerations apply to metal complexes of adrenaline, noradrenaline, and other biogenic amines which are under investigation in our laboratory. Copper containing enzymes are known to be strongly involved in the metabolism of these molecules. Our discussion here thus points to two ways in which an enzyme (or perhaps a membrane receptor) could control the mode of binding of these ambidentate ligands.

(13) H. Sigel, D. B. McCormick, and F. A. Walker, *Inorg. Chem.*, **11**, 2756 (1972).
(14) Recipient of Camille and Henry Dreyfus Foundation Teacher-Scholar Award.

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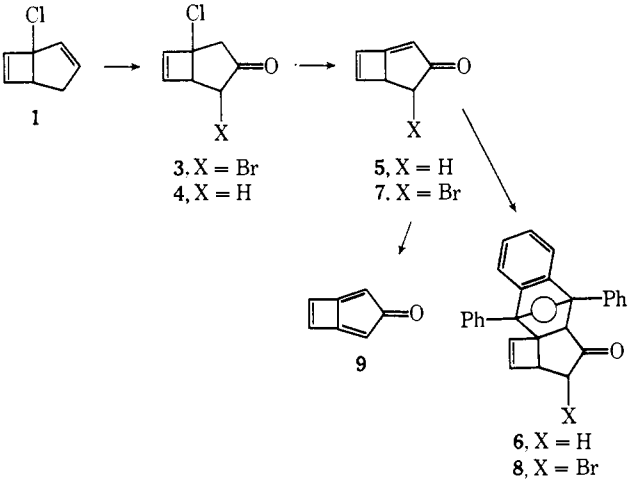
Bicyclotropones

Sir:

Among the most interesting fused-ring compounds are those in which two systems with $4n$ π-electrons are fused to give a composite with $4n + 2$ π-electrons. Such systems as octalene,[1] cyclooctatetraenocyclopentadienone,[2] cyclooctatetraenocyclobutadiene,[3] and the fleetingly transient butalene[4] (cyclobutadienocyclobutadiene) are examples. We now wish to report the detection of another member of this class, cyclobutadienocyclopentadienone (**9**), and some evidence contrasting the properties of **9** with those of an isomer **12**. Both compounds are formally derived from tropone (cycloheptatrienone) by bridging it in alternate ways.

The syntheses started with 1-chlorobicyclo[3.2.0]-hepta-3,6-diene (**1**).[5] Reaction of this compound with *N*-bromosuccinimide in aqueous 90% dimethyl sulfoxide afforded the trans bromohydrin[6] **2** which could be oxidized with Jones' reagent to the bromo ketone **3**.[6] For model spectroscopic studies, this was converted with sodium iodide and boron trifluoride etherate to the chloro ketone **4**.[6] On treatment with triethylamine in chloroform, this was converted to a solution of dienone **5**, with nmr signals at δ 7.48, 6.75, 5.56, and 3.84 for the vinyl and methine hydrogens, and a two-proton multiplet at δ 2.35 for the methylene group. In the uv, dienone **5** showed λ_{max} at 273 nm (THF solution). When the conversion of **4** to **5** was carried out in the presence of diphenylisobenzofuran, the adduct[6] **6**, mp 170–171°, was obtained in 91% yield.

Treatment of the bromochloro ketone **3** with triethylamine first led to bromodienone **7** in solution. This could be trapped if it were generated in the presence of diphenylisobenzofuran to afford adduct[6] **8**, mp 203–206°. Solutions of **7** showed uv absorption with λ_{max} 278 nm, but, on standing in solution with base, **7** was converted to a new species which we identify as the bicyclotropone **9**. This has in the uv a



λ_{max} at 284 nm, and in the nmr it shows two vinyl absorptions of equal intensity at δ 6.85 and 6.56. The same uv spectrum could be produced from **3** using KO-*t*-Bu. The spectral shift is comparable to the 7-nm difference between tropone and 2,3-dihydrotropone.

(1) R. Breslow, W. Horspool, H. Sugiyama, and W. Vitale, *J. Amer. Chem. Soc.*, 88, 3677 (1966).
(2) Ronald Breslow, William Vitale, and Kurt Wendel, *Tetrahedron Lett.*, 6, 365 (1965).
(3) G. Schröder and H. Röttele, *Angew. Chem., Int. Ed. Engl.*, 7, 635 (1968).
(4) R. R. Jones and R. G. Bergman, *J. Amer. Chem. Soc.*, **94**, 660 (1972); J. Napierski, Ph.D. Thesis, Columbia University, 1972.
(5) R. Breslow, W. Washburn, and R. G. Bergman, *J. Amer. Chem. Soc.*, **91**, 196 (1969).
(6) The structure is supported by mass and nmr spectra.