Solution Structural Study of the CuII Complexes of Quinazolone Type Ligands

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CuL_NCl_2 complexes where L = pyridine; 2,6 dimethylpyridine; 2-carboxy-6-methyl pyridine; aniline; N,N diethyl-2,6-dimethylaniline; 2-methyl-3(H)-4-quinazolone and methaqualone have been studied in solution by carbon-13 NMR. Model complexes indicate from ^{13}C relaxation data that steric considerations are important when considering the CuII binding site. Evidence is provided that supports steric hindrance toward CuII coordination at the N_3 position, forcing the CuII to coordinate to the N1 of methaqualone.

Introduction

In the 1950's and 1960's Umezana and his coworkers found several water soluble antibiotic compounds. Of these compounds, phleomycin and bleomycin (BLM) were unique due to their blue color [1]. Bleomycin was obtained as an equimolar complex with CuII which accounted for the blue color. The CuII could be removed from the complex and reinserted to form the same coordinate bonds even though many other potential coordination sites exist in the molecule. Both the metal-free and Cu-chelated BLMs inhibited growth of microorganisms. In 1978, Iitaka *et al.* [2], published the X-ray crystallographic analysis of a P-3A Cu complex, a biosynthetic intermediate of BLM. The CuII was found to be in a square pyramid geometry with an N5 ligand field. Since these early finds of naturally occurring CuII drug complexes, reports have appeared dealing with transition metal complexes of certain types of drugs. Preti and Tosi [3–5] have examined the Pd, Pt, Co, Ni, Cu complexes with some carcinostatic 1,4-benzodiazepines and a seditive-hypnotic, diazepam. The complexes are of the general formula ML_2X_2. In 1980, Mosset *et al.* [6], established the geometry of the complex CuII $(diazepam)_2Cl_2$. The metal ion was in a square planar environment coordinated to two nitrogens (N4) from the ligand and two chloride ions in a trans geometry. In the paper, the authors monitored the ^{13}C NMR of diazepan as a function of CuII concentration. They found that increasing quantities of CuII induced a systematic perturbation of the resonance conditions for the carbons of the ligand. This technique of paramagnetic nuclear relaxation [7, 8] aided the authors in confirming that the solution geometry was like that found in the solid state. In this paper, findings are presented on the perturbation of the ^{13}C resonance of certain model pyridine and aniline derivatives by CuII and these results are compared to the perturbations produced by the addition of CuII to methaqualone, a seditive-hypnotic [9] and its precursor, 2-methyl-3(H)-4-quinazolone. Binding sites for CuII to the drug molecules are deduced from the data.

Experimental

Materials

All pyridine and aniline derivatives were distilled under vacuum and stored under N_2 prior to use. Pyridine was obtained from Matheson, Coleman, Bell. 2,6-dimethyl pyridine was obtained from J. T. Baker. 2-carboxypyridine; 2-carboxy-6-methyl pyridine; 2,6 diacetyl pyridine and 2-methyl-3(H)-4-quinazolone were obtained from Aldrich Chemical Company. N,N-diethyl-2,5-dimethylaniline was obtained from Eastman. 2-Methyl-3-orthotolyl-4-quinazolone (methaqualone) was kindly provided by Professor J. F. Wolfe, Virginia Polytechnic Institute and State University.

NMR Study

The ^{13}NMR study was carried out on 10^{-3} moles of ligand (L) dissolved in 1.8 ml DMSO-d_6 with a variable metal ion (CuII) concentration. The CuII solutions were made in deionized water at 340 ng/μl CuII. Aliquots of 2.5 μl of the CuII solution were added to the ligand, L, in DMSO-d_6 solution in the NMR tube. The NMR spectra were recorded on a Varian FT80A Spectrometer equipped with a broad band frequency synthesizer and probe. The samples were run at 30 °C in 10 mm tubes

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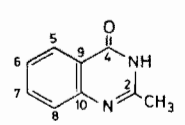
using DMSO-d_6 as an internal lock and tetramethylsilane (TMS) as a reference contained in a coaxial inner cell. The conditions for measurements were as follows: pulse width 18μ; repetition time 1.65; spectral width 4000 Hz, data points 8k. All chemical shifts are expressed in ppm deshielded from TMS.

Results and Discussion

Copper(II) acetylacetonate has been used effectively as a T_2 (line broadening) reagent for the ^{13}C spectral assignments in certain amines [10]. The amine coordinates to the CuII and subsequently perturbs the relaxation properties of the carbons bound to the amine. The structures of the two molecules of interest in this case are presented in Fig. 1. The predominate features of these molecules are the presence of two types of nitrogen atoms, each with a lone pair of electrons, and a carbonyl group. Both of these groups have the capacity to serve as donor atoms in a transition metal complex. The nitrogen donor atoms of these compounds should behave toward CuII like those examined by Doddrell *et al.* [10], and yield coordination site information. Behavior like that observed by Preti and Tosi [3–5] and Mosset *et al.* [6], should also be expected.

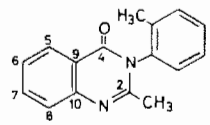
The ^{13}C NMR of methaqualone was published in 1978 by Singh *et al.* [11]. In addition to having repeated their NMR experiment, the ^{13}C NMR of 2-methyl-3(H)-4-quinazolone is now reported. This compound differs from methaqualone in that the ortho tolyl derivative has been removed from N_3 and replaced with an H (Fig. 1). The ^{13}C chemical shifts found here agree very well (±1 ppm) with those reported for methaqualone [11].

Since nitrogen #1 (N1) of L1, 2-methyl-3(H)-4-quinazolone, and L2, methaqualone, has the chemical characteristics of the nitrogen contained in pyridine, a study to illucidate the effect of added CuII to a DMSO solution of pyridine and pyridine derivatives was undertaken. The results are listed in Table I. Carbons 3 and 5 are the nuclei whose signal is consistently broadened upon addition of CuII. This affect has also been demonstrated by Morishima *et al.* [12], with NiII (acetylacetonate)$_2$ and pyridine. Apparently, the methyl groups in



2-methyl-3(H)-4quinazolone

L_1

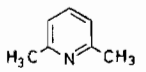
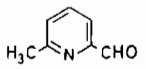
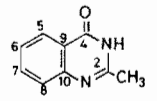
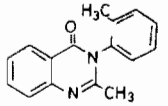
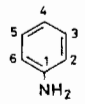
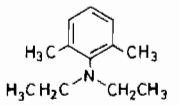


methaqualone

L_2

Fig. 1. Structures of 2-methyl-3(H)-4-quinazolone and methaqualone.

TABLE I. Effect of CuII on the ^{13}C NMR of Selected Amines.

Compound	Carbons signals broadened by Cu^{II} addition
	3,5
	3,5
	3,5
	2,8,10,6
	8,10,6
	2,4,6
	No effect

positions 2 and 6 of 2,6-dimethyl pyridine do not provide sufficient steric inhibition to CuII coordination, hence steric considerations should not interfere with CuII coordination to N1 of L1 and L2. With 2-carboxy-6-methyl pyridine, the carbonyl group apparently does not coordinate to the CuII because its ^{13}C NMR signal is not affected by CuII addition. Consequently extending this information to L1 and L2, the prediction is that carbons 8, 10 and possibly 6 should be significantly broadened upon addition of CuII. The data in Table I support this prediction and imply CuII coordination at N1 of both L1 and L2, Figs. 2 and 3. This pattern was also demonstrated in the CuII complex of diazepan in DMSO solution when carbons 12 and 11 of diazepan were broadened due to CuII coordination to N_4 [6]. However, the ^{13}C NMR signal of carbon #2 of L1 is also affected whereas it is not broadened in L2, implicating coordination to N3 of L1. Aniline was used to model this nitrogen (N_3), a secondary nitrogen. When the ^{13}C NMR of aniline was obtained in the presence of CuII, carbons 2 and 6 were broadened. Based on this, the prediction is that carbon 2 of L1 and L2 should be broadened if that

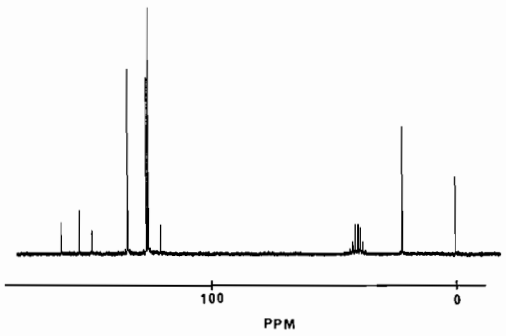


Fig. 2. C13 NMR of 2-methyl-3(H)-4-quinazolone in DMSO-d_6 conditions: see Experimental.

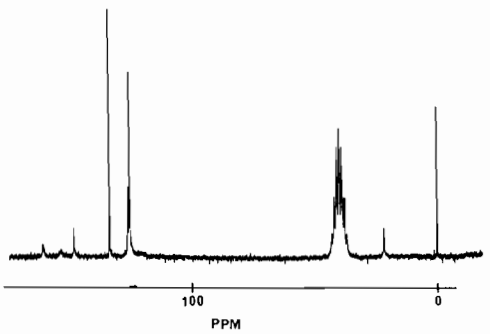


Fig. 3. C13 NMR of 2-methyl-3(H)-4-quinazolone in DMSO-d_6 + CuII.

nitrogen (N3) is coordinated to CuII. Coordination apparently occurs in L1, whereas it apparently does not with L2. Molecular models reveal that approach of a CuII ion to N3 of L2 is sterically hindered. To model this postulated steric affect, the ^{13}C NMR of N,N-diethyl-2,5-dimethyl aniline was examined in the presence of CuII. Little or no effect was observed on the ^{13}C signals when the mole ratio of CuII to L was identical to that when affects were clearly evident in the other cases. In addition, the carbons of the phenyl group attached to N3 are not affected by the addition of CuII. This model information further suggests that N3 does not coordinate to CuII in methaqualone. Consequently, it appears that N3 of L2 is sufficiently sterically hindered to prevent any significant amount of CuII coordination.

In summary, ^{13}C NMR results indicate that the seditive-hypnotic methaqualone and its precursor 2-methyl-3(H)-4-quinazolone bind CuII in DMSO solution. Selective resonance perturbations further indicate that the CuII binds to both nitrogens in the quinazolone, whereas, with methaqualone, CuII binding is restricted to N1 due to steric influences imposed on N3 by the tolyl group directly attacked. At the present time, attempts are underway to isolate the complexes in the solid state.

Acknowledgement

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