Structure and metal binding of a 1H-1,5-benzodiazepine

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The X-ray crystal structure of 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine (L), which has medicinal effect on the central nervous system, has been determined. The solid state conformation of the seven-membered heterocyclic ring in L is found to be somewhat like an armchair. Its modes of binding to three metal ions — Ni²⁺, Cu²⁺ and Zn²⁺ — are identified. In cases of Ni²⁺ and Cu²⁺, the seven-membered heterocyclic ring in L opens up following a hydrolysis of the imino bond promoted by these two metal ions. Zn²⁺ cannot effect such ring opening.

Benzodiazepines have played a very significant role in medicinal chemistry over the last four decades.¹⁻⁵ These are widely used clinically for relief of anxiety and for sedation. Recently, their mode of action on the central nervous system has been elucidated in more detail.⁶ These are of various types depending on the relative positions of the two nitrogen atoms and presence of unsaturation(s) in the seven-membered ring fused to the benzene nucleus. While the medicinal and synthetic aspects of these heterocyclic compounds continue to draw an unabated interest, their transition metal chemistry has not been explored properly.⁷⁻¹² Herein we report the modes of interactions of a representative of 1H-1,5-benzodiazepines, which have behavioural and anticonvulsant effects, with some metal ions together with its structure.

Materials and Methods

Hexane (65 – 70°C) was purchased from S D Fine Chem. Ltd. (Bombay, India) and was used as such. Analytical reagent grade dimethylformamide from a freshly opened bottle (S D Fine Chem. Ltd., Bombay, India) was found to serve the purpose of a dry variety. Other solvents were dehydrated as per standard procedures. 2,3-Dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepinium perchlorate (LHClO₄), the perchloric acid salt of 2,3-dihydro-2,2,4-trimethyl-1H-1,5-benzodiazepine (L) was prepared by the action of acetone on the mono perchloric acid salt of o-phenylenediamine as described elsewhere.¹⁴ All the manipulations involving L were done in dimmed light since L is photosensitive. Our photophysical studies on L have been reported elsewhere.¹⁵ The ligand L' and its metal complexes were stored in dark. The melting point of L was determined by a melting point apparatus procured from CBC Power System (Calcutta, India) and is uncorrected. C, H and N analyses were performed using a Perkin-Elmer 2400 analyzer. IR spectra (KBr disc) were recorded on a Perkin-Elmer 783 spectrophotometer and UV-Vis spectra on a Shimadzu UV-160A spectrophotometer. Solution conductivity was measured by a Systronic (India) direct reading conductivity meter (model 304). Magnetic susceptibility was determined at room temperature by a PAR 155 vibrating sample magnetometer. The magnetometer was calibrated with Hg[Co(SCN)₄] and the susceptibility data were corrected for diamagnetism using Pascal’s constants.

Synthesis

2,3-Dihydro-2, 2, 4-trimethyl-1H-1, 5-benzodiazepine (L)—A reported procedure was modified in the following manner. Pulverised crude LHClO₄ (3.34 g, 11.6 mmol) was suspended in 25 cm³ of water. To this suspension, 1 g (9.4 mmol) of anhydrous Na₂CO₃ was added in small portions over a period of 2 h with constant stirring. Stirring was continued for another 1 h. The yellowish colour of the mixture gradually faded and a dirty-white compound appeared which was filtered, washed thoroughly with water and dried in vacuo over fused CaCl₂. The compound was
recrystallised from hexane as small white cubes (0.9 g, ~ 40%); m.p. 120-122 °C (lit.16, 127 °C). This compound can be further purified by vacuum sublimation. On prolonged exposition to light, L turns yellow.

ML₂(CIO₄)₂·4H₂O—L (2.18 mmol) was dissolved in 50 cm³ of warm hexane and then 1 mmol of solid M(ClO₄)₂·2H₂O was added to it. The mixture was stirred at room temperature for 6 h with a CaCl₂ (fused) guard tube fitted to the reaction vessel. The compound so obtained was filtered, washed thoroughly with hexane and dried in vacuo over fused CaCl₂; yield: 80-90 %. Caution! Care should be taken in handling these compounds as perchlorate salts are potentially explosive. These should not be prepared and stored in larger amounts.

**Characterisation**

ZnL₂(CIO₄)₂·4H₂O—Colour: yellow. Elemental analyses were consistent with the stoichiometry C₂₄H₄₀N₄O₁₂Cl₂Zn [Found: C, 40.15; H, 5.47; N, 8.06. Calc.: C, 40.41; H, 5.66; N, 7.86%]. IR data (cm⁻¹): 3600 (w), 3510 (m), 3360 (m, b), 3200 (w), 3100 (w, b), 2980 (w), 2920 (w), 1610 (s), 1490 (m), 1470 (m), 1450 (w), 1380 (s, splitted), 1325 (s), 1270 (m), 1240 (m, splitted), 1200-1000 (vs, b), 940 (m), 900 (m), 850 (w), 815 (w), 760 (vs), 640 (vs, splitted), 560 (w), 480 (w, b). Diamagnetic. Aₘ/μ₀ cm² mol⁻¹ (MeCN) = 297 (1:2 electrolyte).

**Table 1** — Fractional atomic coordinates (10⁴ Å) and the equivalent isotropic displacement parameters (10¹ Å²) for the non-hydrogen atoms in L with their standard deviations in parentheses. Ueq is given as one third of the trace of the orthogonalised Ueq tensor.

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UV/VIS (nujol): λ/μm = 415. UV/VIS (MeCN, concentration c, 0.534 mmol dm⁻³): λ/μm(ε/μmol⁻¹ cm⁻¹): 385(4520).

CuL₂(CIO₄)_2·4H₂O—Colour: dirty green. Elemental analyses were consistent with the stoichiometry Cu₂H₄O₄Cl₂Cu [Found: C, 40.60; H, 5.44; N, 8.01. Calc.: C, 40.51; H, 5.67; N, 7.88%].

**Table 2** — Selected bond distances (Å) and angles (°) for L

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**X-ray crystallographic analysis**

Single crystals of L were grown by slow aerial evaporation of a hexane solution. All measurements were performed on a PC-controlled Enraf-Niomon CAD4 automatic diffractometer with graphite
Fig. 1 — 50% probability displacement ellipsoid plot of \( L \) showing the labelling of the nonhydrogen atoms.

![Diagram](image1)

Fig. 2 — The “ball and stick” representation of the solid state conformation of the seven-membered heterocyclic ring in \( L \).

![Diagram](image2)

monochromated Mo-K\( \alpha \) radiation (\( \lambda = 0.70930 \, \text{\AA} \), \( \mu = 0.070 \, \text{mm}^{-1} \) on a single crystal of dimensions 0.45 \( \times \) 0.3 \( \times \) 0.6 mm. A total number of unique 830 reflections were measured in the range 3.25 < \( \theta < 23.49 \)° in the \( \omega-2\theta \) scan mode at 293 K. The \( hkl \) ranges were: \( 0 < h < 8, \ 0 < k < 13, \ 0 < l < 13 \). The structure was solved by direct method (MULTAN-80) using NRCVAX (PC version).\(^{17}\) Anisotropic refinement was carried out by full matrix least squares on \( F^2 \) for all nonhydrogen atoms. The hydrogen atoms, located from difference Fourier map, were used in the structure factor calculation, but were not refined and the convergence reached was \( R = 0.054, \ wR^2 = 0.1397 \) for all data. The extinction correction was done during the refinement and the final value of the coefficient was 0.84(7). Goodness of fit on \( F^2 = 1.078 \), maximum/minimum residual electron densities 0.199-0.242 e \( \text{\AA}^{-3} \). All calculations were done using SHELXL-93 program.\(^{18}\) For a displacement ellipsoid plot, ZORTEP was used.\(^{19}\) The positional parameters along with equivalent isotropic thermal parameters for the non-hydrogen atoms in \( L \) are given in Table 1.

**Crystal data**

The cell constants and crystallographic data for \( L \) are: mol. formula \( \text{C}_{12}\text{H}_{16}\text{N}_{2} \); mol. wt. 188.27;
orthorhombic $Pc2_1/n$; $a = 7.294(2)\text{Å}$; $b = 11.962(2)\text{Å}$; $c = 12.220(2)\text{Å}$; $V = 10066.1(4)\text{Å}^3$; $Z = 4$; $F(000) = 408$; $D_\text{s} = 1.173 \text{g cm}^{-3}$.

Results and Discussion

In the past, there have been some NMR studies on the conformations of some derivatives of $1H-1,5$-benzodiazepine in solution.$^{20}$ However, the crystal structure of the basic fragment is not yet known. We have now determined the X-ray crystal structure of 2,3-dihydro-2,2,4-trimethyl derivative of $1H-1,5$-benzodiazepine (L), which itself is medicinally potential.$^{13}$ An ORTEP diagram of the X-ray crystal structure of L is shown in Fig. 1. Some selected bond lengths and bond angles are given in Table 2. The N1-C6 bond (1.400 Å) is slightly shorter than the C1-N2 bond (1.427 Å). This is because of the resonance structure B for L. It is also evident from B that amino nitrogen (N1) bears a small amount of positive charge and there is a corresponding build up of negative charge at the imino nitrogen (N2). The solid state conformation of the seven-membered heterocyclic ring in L can be visualised better from Fig. 2; it is somewhat like an armchair.

Reaction of L with the perchlorates of Zn$^{2+}$, Cu$^{2+}$ and Ni$^{2+}$ in a nonpolar medium under a dry atmosphere yields complexes of general formula $ML_2(ClO_4)_2$·4H$_2$O — reaction (I). It may be noted that the use of a nonpolar medium for metal perchlorates

$$\text{ML}_2(ClO_4)_2\times \text{H}_2\text{O} + 2\text{L} \rightarrow \text{ML}_2(ClO_4)_2\times \text{H}_2\text{O} \ldots \ldots (I)$$

in the synthetic procedure is very novel. This was prompted by our observation that the perchlorates of Zn$^{2+}$, Cu$^{2+}$ and Ni$^{2+}$ react with L in the solid state to give slightly impure varieties of $ML_2(ClO_4)_2$·4H$_2$O. So far, we have not been able to grow single crystals of any of the three complexes. However, from their IR spectra (the most informative portion of which are reproduced in Fig. 3), the identified modes of the interactions of L with the metals can be summarised by Scheme I. When M = Zn(II), L remains intact and binds the metal through the imino N (situation I in Scheme 1); the C=N stretching frequency of L is lowered by 40 cm$^{-1}$ to 1600 cm$^{-1}$ on binding Zn(II). The binding of Zn$^{2+}$ ion through the imino nitrogen is in accord with the resonance structure B for L. In cases of copper and nickel, the C=N bond in L is hydrolysed; the generated keto group remains free in the Cu(II) complex [v(C=O): 1700 cm$^{-1}$; situation II in Scheme 1] but binds Ni(II) [v(C=O): 1660 cm$^{-1}$; situation III in Scheme 1]. Thus, our copper(II) and nickel(II) complexes of L are best described as Cu(ClO$_4$)$_2$(O$_2$)$_2$·2H$_2$O and Ni(ClO$_4$)$_2$(O$_2$)$_2$·2H$_2$O where OLH$_2$ indicates the hydrolysed product of L. Such metal promoted hydrolysis of a C=N bond is known for Schiff bases (for example, see ref. 21). The species OLH$_2$ may exist in solution.$^{22}$ Our experiments show that it can be isolated by complexation with a copper(II) or a nickel(II) centre.
Incidentally, with the tetrafluoro-borates of Cu(II) and Ni(II), no reproducible compounds of L could be obtained by following a similar synthetic procedure. So far, coordination of a keto oxygen to a copper(II) centre is not known. On the other hand, in the chemistry of nickel(II), keto oxygen is not a rare ligand. A known nickel(II) complex, structurally related to Ni(OLH)2(ClO4)2·2H2O is T2. Reaction of 1 with neat pyridine yields 2, a Ni(II) complex of Curtis' macrocycle.22 But reaction of pyridine with our nickel(II) complex leads to an intractable gummy material; it does not yield the cyclised product 3. 

The synthesised Zn(II), Cu(II) and Ni(II) complexes of L cannot be digested fully by the mineral acids even in hot condition — a small amount of white insoluble residue always remains. These complexes are indefinitely stable in dry atmosphere but are quite sensitive to moisture (all the solution studies reported here have been made in dehydrated solvents with freshly prepared complexes). It seems that their tolerance to water is optimally balanced in the solid state formulations. Interaction of these complexes with underhydrated nonaqueous polar solvents precipitates the corresponding metal hydroxides. The formation of metal hydroxides is, however, not quantitative and from the supernatant liquid bis a-phenylendiamine complexes are obtained indicating that L loses two molecules of acetone in such conditions. In dehydrated solvents, these complexes do not follow the Beer's law which means that the ligated moiety partially dissociates from the metal in solution. 

Earlier, Szeverenyl and coworkers have studied the reactions of L with some Co(II) and Mn(III) complexes of tetra(4-chlorophenyl)porphyrin; these complexes promote the aeral oxidation of 4-methyl group of L to a formyl one.10,12 They have isolated a Mn(II) complex of 4 from the reaction of MnCl2 with L in air.12 In our studies, we have not encountered such oxidations of L.

Supplementary Material
Tables containing listings of positional parameters, thermal parameters, all distances and angles for L are available from the authors.

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