Inorganica Chimica Acta, 66 (1982) L29–L30

On the Metal Ion Coordinating Properties of the Cocaine-model N-Methylpiperidine and Related Ligands [1]

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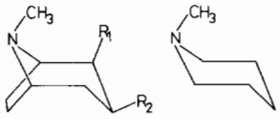
Received October 1, 1981

The knowledge on complexes of hallucinogenic drugs is scarce [2], although the significance of metal ions for the neuronal functions is accepted [3, 4]. The question [2] whether transition metal ions contribute to the hallucinogenic effect of certain drugs, and if so, to what extent, is clearly a fascinating one.

In this context a recent publication on the "copper(II) complexes and basic properties of cocaine" [5] has attracted our attention. In this study stability constants for the Cu^{2+} complexes of cocaine and its model ligand, N-methylpiperidine, were determined.



The equilibrium constants given for the two ligand systems are very similar; the values in 50% aqueous dioxane (v/v) at 30 °C ($I \rightarrow 0$) for the N-methylpiperidine system are $pK^{H}_{H(N\text{-}Mp)} = 8.34$, $\log K^{Cu}_{Cu(N\text{-}Mp)} = 17.90$ and $\log K^{Cu(N\text{-}Mp)}_{Cu(N\text{-}Mp)_2} = 16.68$. These values imply an extraordinary large stability of the corresponding complexes, but a comparison with the stability of the Cu^{2+} ammonia complexes [6] indicates that these values must be wrong.[c]

Since the question of the coordinating properties of the tertiary amino nitrogen in cocaine is important, we decided to prove our preceding conclusion and to study the stability of the complexes formed between Co^{2+}, Ni^{2+}, Cu^{2+} or Zn^{2+} and the model-ligand N-methylpiperidine, using also 50% aqueous dioxane as solvent. Obviously, one may expect that the coordination tendency of N-Mp is lower than that of ammonia for steric reasons; therefore ammonia as well as trimethylamine (Tma) were included in the present study for comparison.

Results and Discussion

Complex formation of the monodentate (hence relatively weakly-coordinating) ligands is expected to be hampered by the hydrolysis reactions of the metal ions. This problem may be overcome by using a *large* excess of ligand, which would be possible with ammonia but not with N-methylpiperidine. Another possibility is to reduce the tendency for hydrolysis of the metal ions. We have done the latter by studying[d] complex formation between metal ions already coordinated to nitrilotriacetate (Nta^{3-}), and N-Mp, Tma or NH_3 (= L) according to equilibrium (1):

$$M(Nta)^- + L \rightleftharpoons M(Nta)(L)^- \qquad K^{M(Nta)}_{M(Nta)(L)} = [M(Nta)(L)^-]/[M(Nta)^-][L] \qquad (1)$$

Indeed, the stability of the ternary $M(Nta)(NH_3)^-$ complexes could be determined without any problems. The corresponding constants are given in Table I, together with related data determined earlier in different connection for aqueous solutions [7]. The change in solvent from water to 50% aqueous dioxane has led to a slight decrease in the basicity of ammonia, but also to an increase in the stability of the complexes by about 0.4 log unit. It may be pointed out that in aqueous solution [7] the difference $\log K^{M}_{M(NH_3)} - \log K^{M(Nta)}_{M(Nta)(NH_3)}$ is relatively small, *i.e.* about 0.2 log unit for the complexes with Co^{2+},

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[c]Indeed, based on these values [5] one calculates for $[Cu^{2+}]_{tot} = [N\text{-}Mp]_{tot} = 10^{-3}$ *M*, that in 1 *M* acid, *i.e.* pH 0, already 67% of the total Cu^{2+} exists as $Cu(N\text{-}Mp)^{2+}$ and another 16.5% as $Cu(N\text{-}Mp)_2^{2+}$. This is clearly impossible. The sentence: "Titrations with up to approximately a 4.1 mol ratio of cocaine and N-methylpiperidine with copper(II) did not yield $\bar{n}$ values appreciable over 2" given in [5], indicates that the liberated protons were actually due to the hydrolysis of Cu^{2+}_{aq} because only two protons per Cu^{2+} were determined

[d]N-Methylpiperidine and trimethylamine hydrochloride were from Fluka AG, Buchs (Switzerland), and NH_4NO_3 was from Merck AG, Darmstadt (Fed. Rep. of Germany). All the other reagents were the same as used previously [7]. The potentiometric pH titrations were carried out by titrating 50 ml of a reaction solution with 1 ml of 0.1 *M* KOH exactly as described [7], including the concentrations of the reactants, but 50% aqueous dioxane (v/v) was used as solvent (I = 0.1, KNO_3, 25 °C). The stability constants $K^{M(Nta)}_{M(Nta)(L)}$ were calculated by considering the species H^+, $H(L)^+$, L, $M(Nta)^-$ and $M(Nta)(L)^-$. All constants given in Table I are the average of the results from four to eight independent titrations.

TABLE I. Comparison of the Stability Constants of Several Ternary M(Nitrilotriacetate) $(L)^-$ Complexes where L = Ammonia, Trimethylamine (Tma) or N-Metylpiperidine (N-Mp), together with the Acidity Constants of the Corresponding Monodentate Ligands (I = 0.1, KNO_3, 25 °C)[a]

L	pK_H^H (L)	$\log K_{Co(Nta)}^{Co(Nta)}$ (L)	$\log K_{Ni(Nta)}^{Ni(Nta)}$ (L)	$\log K_{Cu(Nta)}^{Cu(Nta)}$ (L)	$\log K_{Zn(Nta)}^{Zn(Nta)}$ (L)
NH_3 in water [7a][b]	9.36 ± 0.01	1.82 ± 0.03	2.54 ± 0.02	3.79 ± 0.08	~2.3
NH_3 in 50% aq. dioxane	9.18 ± 0.01	2.23 ± 0.02	2.85 ± 0.01	4.27 ± 0.03	2.88 ± 0.05
Tma in 50% aq. dioxane	9.40 ± 0.01	<1.3	<1.7	<3.8	<2.4 (~2.0)[c]
N-Mp in 50% aq. dioxane	9.53 ± 0.01	<1.3	<1.7	<3.9	<2.5 (~2.1)[c]

[a]The errors given are three times the standard error of the mean value or the sum of the probable systematic errors, whichever is the larger. [b]In this case $NaNO_3$ had been used as inert salt (I = 0.1; 25 °C). [c]The estimated error range is ±0.3 log unit.

Ni^{2+}, or Zn^{2+}, and about 0.4 log unit for the Cu^{2+} complexes; this difference is certainly eqully small in 50% aqueous dioxane.

Tma and N-Mp are more basic than ammonia, but their ternary complexes are less stable, as expected (Table I). In fact, with these ligands only the upper limits of the stability constants of the complexes could be determined with certainty, due to the interference of hydrolysis reactions of $M(Nta)_{aq}^-$. Only in the case of Zn(Nta) $(N\text{-}Mp)^-$ and Zn(Nta) $(Tma)^-$ was a rough estimation of the actual constants possible. The results indicate that the coordinating properties of N-Mp and Tma are rather similar; possible small differences are obviously due to the slightly different basicities of the two ligands.

To conclude, the coordinating properties of N-methylpiperidine are relatively small and the same may be surmised for cocaine. It is quite clear that neither ligand forms complexes with exceptionally high stability, as claimed earlier [5]. This fact should however not lead to the conclusion that any metal ion interaction is *a priori* unimportant during the action of cocaine as a drug, because weak interactions may still be relevant—and they can occur, as the example of Zn(Nta) $(N\text{-}Mp)^-$ indicates. In addition, due to the aromatic moiety and the aliphatic parts of cocaine, it appears possible that with a suitable second ligand intramolecular aromatic ring stacking or hydrophobic interactions occur within a ternary complex; such intramolecular ligand–ligand interactions have already been observed [8–10] in other mixed ligand complexes.

Acknowledgements

Part of the experiments have been carried out with the technical assistance of Ms. Madeleine Imhof. The computer was made available by the Rechnenzentrum der Universitat Basel. These supports and a research grant from the Swiss National Science Foundation are gratefully acknowledged.

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