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論 文 要 旨 (博士)

論文題目	**Structural and Chemical Study of Metal Complexes that Specifically Recognize Nucleic Acid Bases** (核酸塩基を特異的に認識する金属錯体の構造化学的研究)

要旨

現在、核酸を構成する4種類の塩基（アデニン、グアニン、シトシン、ウラシル（またはチミン））のうちそれぞれの塩基を特異的に認識し得る金属錯体の開発に、その多方面での有用性が期待されることから、大きな注目が寄せられている。本研究はそのような金属錯体の開発と塩基特異的認識機構の解明を目的としている。

本論文は8章より構成されている。第1章は本研究の背景および目的を、第2章は基本的な実験手順を述べている。第3章は tetrakis(μ-carboxylato)dirhodium(II) 錯体と各種核酸塩基（アデニン、グアニン、シトシン、ウラシル）との反応を系統的に調査した結果、アデニン塩基とのみ特異的に反応することを観測し、その分子認識が〝金属イオン周りの立体配置に基づく分子内配位子間相互作用（立体障害、水素結合、静電気的（引力および斥力）相互作用）による〟ことを提案した。

第4章および第5章では、第3章で提案した分子認識機構の妥当性を確かめるために、水素結合の受容能のみをもつカルボキシラト配位子の替わりに、水素結合受容能および供与能をもつアミダト配位子を導入した bis(μ-carboxylato)bis(μ-amidato)dirhodium(II) 錯体（第4章）および tetrakis(μ-amidato)dirhodium(II) 錯体（第5章）と各種核酸塩基との反応を系統的に調査した結果、ウラシルを除くアデニン、グアニン、シトシンのいずれの塩基とも反応することを明かにした。これらの塩基との反応生成物の X線結晶構造解析により、アミダト配位子とアデニン、グアニン、シトシン各塩基の置換基との間の分子内配位子間水素結合の形成を確認し、上記提案の分子認識機構の妥当性を明かにした。

第6章および第7章はこの塩基特異的分子認識の原理に基づいて、アデニン塩基を特異的に認識する金属錯体システム（第6章）およびグアニン塩基を特異的に認識する金属錯体システム（第7章）を構築した。前者では（第6章）水素結合の受容能のみをもつ nitrilotriacetato (nta) 3脚配位子および八面体配位構造の Ni^{2+} イオンに注目して、各種核酸塩基との反応を系統的に調査した結果、アデニン塩基とのみ反応した。反応生成物のX線結晶構造解析により、nta 配位子のカルボキシラト酸素とアデニンの N(6) アミノ基との水素結合の形成を確認した。一方、後者では（第7章）水素結合供与能のみをもつ tris(2-aminoethyl)amine (tren) 配位子および Ni^{2+} イオンあるいは三方両錐体配位構造の Cu^{2+} イオンに注目して、各種核酸塩基との反応を系統的に調査した結果、グアニン塩基とのみ反応した。反応生成物のX線結晶構造解析により、tren 配位子のアミノ基とグアニンの O(6) カルボニル基との水素結合の形成を確認した。

最後に、結論を第8章に述べている。本研究はアデニン塩基を特異的に認識する $[Rh_2(carboxylato)_4]$ 錯体および $[Ni(nta)(H_2O)]^-$ 錯体、グアニン塩基を特異的に認識する $[Ni(tren)(H_2O)]^{2+}$ 錯体および $[Cu(tren)]^{2+}$ 錯体、を開発し、塩基特異的認識が〝配位子間相互作用〟に基づくことを明かにした。この〝配位子間相互作用〟の概念は、核酸の塩基特異的認識金属錯体の開発に作業原理として有効であるばかりではなく、より一般的に、核酸と金属イオンとの相互作用の理解に新たな視点を与えるものである。

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要旨

During more than four decades metal interactions with nucleic acids and their constituents have received much attention because of their biological importance in nucleic acid processes to result in a large body of data involving thermodynamic and kinetic properties, metal binding sites or modes, and structures formed. Currently, there has been much interest in the metal complexes that specifically recognize individual nucleobases (adenine, guanine, cytosine, thymine or uracil) because of their wide range of applications: as (i) probes for determining the sequence of nucleic acids by electron microscopic techniques, (ii) agents for isolating nucleic acids with the specific sequence, for example, polyadenylic acid chains in the 3′-end of messenger RNAs in the eukaryotic cell, (iii) reagents for preparing heavy-atom derivatives to determine nucleic acid structures like tRNAs and ribosomal RNAs by X-ray methods, (iv) artificial restriction enzymes by adding a nuclease function, (v) agents for controlling the expression of genetic information, and (vi) anticancer drugs. In spite of these usefulness, however, such metal complexes have still rarely been explored. This thesis aims at the development of base-specific metal complexes and elucidation of the mechanism of their molecular recognition.

This thesis consists of eight chapters. Chapter 1 is a general introduction. Chapter 2 gives a general experimental procedure. Chapter 3 describes reaction properties of tetrakis(μ-carboxylato)dirhodium(II) complexes, antitumor agents, toward nucleobases and their derivatives. A base-specific reactivity (adenine >> guanine, cytosine, and uracil) was observed and a mechanism for specific metal bonding to nucleobases is proposed: the octahedral metal ion ligated by the functional groups capable of acting as hydrogen-bonding donor or acceptor would differentiate between nucleobases due to differences in their steric, electrostatic, and hydrogen-bonding interactions toward the amino or keto substituents on individual nucleobases. The adenine-speific metal bonding observed here may be due to the formation of interligand hydrogen-bonding between the carboxylato oxygen and the amino N(6) substituent of adenine.

Chapters 4 and 5 deal with, in order to substantiate this hypothetical mechanism, reaction properties of bis(μ-carboxylato)bis(μ-amidato)dirhodium(II) and tetrakis(μ-

amidato)dirhodium(II) complexes toward nucleobases, respectively, where amidato ligand is introduced in place of carboxylato ligand because the amidato ligand is capable of functioning as both the hydrogen-bonding donor and acceptor. As expected, these dirhodium(II) complexes exhibit non-specific metal bonding to nucleobases, that is, they react with all of the nucleobases except uracil. X-ray structural analyses of the metal complexes formed have shown that the amidato oxygen forms an intramolecular interligand hydrogen bond with the amino $N(6)H_2$ of adenine in $[Rh_2(OAc)_2(CF_3CONH)_2(adeninium)_2]^{2+}$ and the amidato NH forms an interligand hydrogen bond with the keto O(6) of guanine in $[Rh_2(OAc)_2(CF_3CONH)_2(9\text{-ethylguanine})_2]$, while in $[Rh_2(CF_3CONH)_4(1\text{-methylcytosine})_2]$ the amidato ligand forms two kinds of hydrogen bonds with a cytosine molecule, one as a hydrogen-bonding donor with the keto O(2) and the other as a hydrogen-bonding acceptor with the amino $N(4)H_2$. These results are in accord with the recognition mechanism proposed in the chapter 3.

Chapters 6 and 7 present examples of the rationale design of the ligand systems for adenine-specific and guanine-specific metal bonding, respectively, based on the recognition mechanism established in the chapters 4 and 5. Reaction of $Ni(OAc)_2$ and nitrilotriacetic acid (H_3nta) with nucleobases, where the tripodal nta ligand could function as a hydrogen-bonding acceptor only, gave a metal complex only for adenine but no adduct for guanine, cytosine, and uracil, as expected. The crystal structure of $[Ni(nta)(H_2O)(adeninium)]$ involves the formation of interligand hydrogen bonds between carboxylato oxygens of the nta ligand and the amino $N(6)H_2$ of adenine, as a factor determining the adenine-specific metal bonding. Treatment of $Ni(ClO_4)_2$ or $Cu(ClO_4)_2$ and tris(2-aminoethyl)amine (tren) with nucleobases, where the tripodal tren ligand could function as a hydrogen-bonding donor only, gave a metal complex only for guanine but no adduct for N(9)-substituted adenine, cytosine, and uracil, as expected. The crystal structures of $[Ni(tren)(H_2O)(9\text{-ethylguanine})]^{2+}$ or $[Cu(tren)(9\text{-ethylguanine})]^{2+}$ include the formation of interligand hydrogen bonds between the amino NH_2 of the tren ligand and the keto O(6) of guanine, as a factor determining the guanine-specific metal bonding.

Finally, conclusion is given in chapter 8, which emphasizes the significance of a concept that interligand interactions involving steric, electrostatic, and hydrogen-bonding interactions are important factors determining specific metal bonding to nucleobases, that is, it might be valid not only for the development of base-specific metal complexes but also for, in general, our better understanding of metal interactions with nucleic acids.