- **Tell me about Quinine .**

Quinine is a natural alkaloid, mainly extracted from the bark of cinchona trees. It was first isolated by Pelletier and Caventou in 1820, marking the beginning of its research and medicinal use.

1. Chemical and physical properties
   ① Molecular formula/molar mass: $C_{20}H_{24}N_2O_2$, 324.4 g/mol
   ② Structure: An alkaloid containing a quinoline ring.
   ③ Properties: White crystalline powder; extremely bitter (threshold ≈ 1 ppm); slightly soluble in water; easily soluble in ethanol and chloroform, and is usually prepared as a stock solution dissolved in ethanol; exhibits bright blue fluorescence under ultraviolet light; the naturally occurring stereoisomer is levorotatory; four chiral centers result in 16 possible stereoisomers (quinine, quinidine, cinchonine, and cinchonidine are the main natural isomers).

2. Medical uses
   ① Malaria treatment: Quinine was the first effective drug for treating malaria, especially Plasmodium falciparum infections.
   ② Other uses: It is sometimes used to treat nighttime leg cramps and other muscle spasms, but this is less common due to potential side effects.

3. Mechanism of action
   The mechanism of action of quinine is mainly achieved by inhibiting the metabolism and growth of malaria parasites, and the specific process is as follows:
   ① It binds to the DNA of the malaria parasite to form a complex, thereby effectively inhibiting the replication of the parasite's DNA and the transcription of RNA, blocking the protein synthesis of the parasite, and ultimately killing the parasite.
   ② It interferes with the parasite's ability to digest hemoglobin in red blood cells, leading to the accumulation of toxic heme, which eventually kills the parasite.

4. Side effects and risks
   ① Common side effects: Nausea, headache, tinnitus, blurred vision, vomiting, diarrhea, etc. Excessive intake may have adverse effects on health, such as thrombocytopenia, thrombotic microangiopathy, blindness, and acute kidney injury.
   ② Serious risks: High doses can cause "cinchonism" (a syndrome with symptoms such as hearing loss, confusion, and heart problems), and in rare cases, severe allergic reactions or blood diseases.
   ③ Contraindications: People with certain diseases (such as tinnitus, hemolytic anemia, or allergies to quinine) should avoid taking it. It can be used to treat severe malaria during pregnancy, but caution is required, and its benefits outweigh the risks. Quinine may also interact with other drugs, so guidance from medical professionals is

important.

5.   Other uses (non-medicinal)

Tonic water: Quinine has a unique bitter taste, making it a key ingredient in tonic water and contributing to the unique flavor of popular mixed drinks such as gin and tonic.

6.   Legal and safety considerations

Quinine is a controlled substance in many countries due to its potential for abuse and risks. Possession without a prescription may be illegal. Due to its potential toxicity, many countries have regulations on the allowable concentration of quinine in consumer products.

7.   Analytical methods

Many analytical techniques for quantifying quinine have been developed, including electrochemical methods, high-performance liquid chromatography (HPLC), colorimetry, fluorescence analysis, high-resolution mass spectrometry, and the recent innovative method - an electrochemical sensor developed using indicator displacement assay (IDA) technology. This sensor detects quinine by utilizing the host-guest interaction between β-cyclodextrin and methylene blue (MB), and has the advantages of simplicity, cost-effectiveness, and reusability. These methods usually involve host-guest chemistry, in which quinine interacts with cyclodextrins or other macrocyclic hosts to improve selectivity and sensitivity.

8.   Summary

Quinine is a historically significant compound for treating malaria, known for its unique bitter taste in tonic water. Although the role of quinine as an antimalarial drug has largely been replaced by new drugs, it remains important in selected clinical cases. Like any drug, it may have side effects, and medical guidance is essential if used for therapeutic purposes.

● What is an Indicator Displacement Assay?

Indicator Displacement Assay (IDA) is a supramolecular analytical technique used to detect and quantify analytes (target molecules) in solutions. It is based on competitive binding, followed by changes in color or fluorescence signals.

1. Key Components

①   Host molecule: A synthetic receptor with specific binding sites, such as cucurbiturils, β-cyclodextrins, or calixarenes. These molecules can form stable complexes by binding with indicators and analytes.

②   Indicator: A molecule whose optical properties (such as fluorescence or color) change when displaced from the host by the analyte, such as methylene blue, proflavine, etc.

③   Analyte: The target molecule to be detected, which competes with the

indicator for binding sites on the host molecule.

2. Working Mechanism

① Formation of complex: The receptor (usually a synthetic receptor, protein, or other binding entity) initially binds with a known indicator molecule (such as a dye or chromophore) to form a host-indicator complex. The optical signal (color or fluorescence) of this complex is significantly different from that of the free indicator.

② Addition of analyte: When the target analyte (substance to be detected) is added, it competes with the indicator for binding to the receptor.

③ Release of indicator: Due to higher affinity or favorable interactions, the analyte displaces the indicator from the receptor.

④ Signal change: The release of the indicator leads to a measurable signal change (for example, a change in color or fluorescence intensity). This change is related to the concentration of the analyte, enabling quantitative analysis.

3. Advantages

① No need for covalent labeling of the analyte, simple and economical, and can be performed in aqueous solutions.

② High specificity and sensitivity due to selective host-guest interactions.

③ Versatility: Applicable to a variety of analytes (ions, small molecules, peptides, etc.).

④ Simple reading: Usually visible color changes or fluorescence, allowing simple, real-time, high-throughput, and even naked-eye detection.

⑤ Compatible with multiple detection platforms (colorimetry, fluorescence, etc.).

⑥ Potential for real-time monitoring and imaging in biological environments.

4. Limitations

① The performance of the assay largely depends on differences in binding affinity. Insufficient selectivity or affinity differences can lead to poor sensitivity or false positives.

② In complex matrices, potential interference from other molecules that may bind to the host or indicator must be considered.

5. Applications

This method can develop highly selective sensors for various analytes, with applications covering environmental monitoring (such as metal ions, pollutants), clinical diagnosis, biosensing (e.g., detection of sugars, amino acids, drugs), and chemical analysis, etc.

● What techniques are used to analyze Quinine?

Quinine is a natural alkaloid that is typically analyzed in pharmaceuticals, beverages (such as tonic water), and biological samples. Several analytical techniques are used to identify, quantify, and characterize quinine. The main techniques are as follows:

1. Spectroscopic techniques

① UV-Vis spectrophotometry: Quinine has a unique UV-Vis absorption spectrum due to its conjugated aromatic system, which can be used for qualitative and quantitative analysis.

② Fluorometry (fluorescence spectroscopy): Quinine is highly fluorescent (emitting at ~450 nm when excited at ~350 nm).

③ Infrared (IR) spectroscopy: Helps identify characteristic functional groups through vibrational modes, such as quinoline rings and hydroxyl groups.

④ Nuclear magnetic resonance (NMR) spectroscopy: ^{1}H and ^{13}C NMR can provide detailed information about the molecular skeleton, functional groups, and stereochemistry of quinine.

⑤ Circular dichroism (CD) spectroscopy: Can be used to analyze chiral host-guest complexes, providing information on stereochemistry and conformation.

2. Chromatographic techniques

① High-performance liquid chromatography (HPLC): HPLC is widely used for quantitative analysis, capable of separating quinine from impurities and degradation products. It is usually combined with UV detection or mass spectrometry to improve specificity.

② Gas chromatography (GC): Less common due to the non-volatility of quinine, but can be used after derivatization.

③ Thin-layer chromatography (TLC): Can be used for qualitative analysis, purity checking, and preliminary identification of quinine.

3. Mass spectrometry (MS): Provides molecular weight confirmation and fragmentation patterns, aiding in purity evaluation and structural verification.

4. Electrochemical analysis techniques

Differential pulse voltammetry (DPV) and cyclic voltammetry: These methods utilize the redox activity of quinine for sensitive quantification.

5. Titration: Classical methods include titration with reagents such as potassium permanganate or other oxidizing agents to determine quinine content.

6. Other analytical methods

① X-ray crystallography: When suitable crystals are available, X-ray diffraction provides definitive three-dimensional structural information, including stereochemistry and molecular packing, which is relevant to understanding

supramolecular host-guest interactions involving quinine.

② Thermal analysis: Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) can assess purity and stability.

③ Polarimetry: Quinine is optically active; measuring optical rotation helps in purity evaluation.

● What are the components of an Indicator Displacement Assay?

Indicator Displacement Assay (IDA) is a powerful analytical technique widely used in supramolecular chemistry for the selective and sensitive detection of various analytes. Its operation relies on competitive, non-covalent interactions and specific host-guest binding.

1. Main Components

① Host molecule (receptor)

The host is a molecular receptor, usually a macrocyclic or supramolecular structure such as cyclodextrin, cucurbituril, or pillararene, with well-defined binding sites or cavities. This host is designed to selectively bind guest molecules through non-covalent interactions, including hydrogen bonding, π-π stacking, hydrophobic effects, electrostatic interactions, and van der Waals forces. The selectivity and affinity of the host are determined by its size, shape, and structure, which are tailored to recognize specific structural or electronic features of potential guests.

② Indicator

Indicators are usually chromogenic or fluorescent molecules that can bind to the host to produce different optical signals—typically changes in absorbance or fluorescence. The binding of the indicator to the host usually alters the photophysical properties of the indicator due to changes in the microenvironment or specific host-guest interactions. A suitable indicator is selected such that its binding to the host is reversible and its signal is sensitive to displacement.

③ Target analyte

The analyte is the target molecule to be detected or quantified. It can be a small organic molecule, ion, drug, or biomolecule (such as methylated amino acids). The analyte must have a higher affinity for the host than the indicator. When introduced, the analyte competes with the indicator for the binding sites of the host, and if it has a stronger binding force, it will displace the indicator from the host.

④ Solvent and buffer system

The medium in which the host, indicator, and analyte interact. The choice of solvent and pH significantly affects the binding equilibrium, stability, and overall assay performance. Appropriate pH and ionic strength are maintained to ensure host-guest interactions, stability of components, and signal transduction.

⑤ Signal reading system

The release of the indicator by the target analyte results in a detectable signal change—fluorescence "on" or "off", or a change in absorbance. Techniques such as fluorescence spectroscopy, UV-visible spectroscopy, or electrochemical methods are used to measure changes in the properties of the indicator after displacement.

2. Mechanism of action

　　① Formation of complex: The receptor (usually a synthetic receptor, protein, or other binding entity) initially binds with a known indicator molecule (such as a dye or chromophore) to form a host-indicator complex, whose optical signal (color or fluorescence) is significantly different from that of the free indicator.

　　② Addition of analyte: When the target analyte (substance to be detected) is added, it competes with the indicator for binding to the receptor.

　　③ Release of indicator: Due to higher affinity or favorable interactions, the analyte displaces the indicator from the receptor.

　　④ Signal change: The release of the indicator leads to a measurable signal change (e.g., a change in color or fluorescence intensity), which is related to the concentration of the analyte, enabling quantitative analysis.

● Are there electrochemical sensors using Indicator Displacement Assay (IDA) to detect Quinine?

　　Yes, electrochemical sensors adopting the Indicator Displacement Assay (IDA) strategy have been developed for the detection of quinine.

1. Principle and Mechanism:

　　The core concept utilizes host-guest chemistry. A macrocyclic host, such as β-cyclodextrin (β-CD), is immobilized on the electrode surface to form a supramolecular receptor. The cavity of β-CD serves as a binding site for indicator molecules (e.g., methylene blue, MB). Upon the introduction of quinine, which has a strong affinity for the β-CD cavity, competitive binding leads to the displacement of MB. This displacement manifests as a measurable change in the electrochemical signal, particularly a decrease in the reduction peak current of MB, enabling the quantitative analysis of quinine.

2. Materials and Design:

　　① Electrode modification: A functionalized glassy carbon electrode is modified with graphene (to enhance electron transfer), poly(N-acetyl aniline) (to inhibit non-specific adsorption of methylene blue, MB), and β-CD (to achieve selective host-guest recognition) on the electrode surface.

　　② Detection mechanism: The sensor is sequentially exposed to MB and quinine. When quinine competitively displaces MB from β-CD, the decrease in the peak current of MB upon its displacement from the host cavity by quinine is monitored via differential pulse voltammetry (DPV). This decreasing trend is proportional to the concentration of quinine.

　　③ Analytical performance: The sensor has a linear detection range of 10-125 μM with a lower detection limit of 1.32 μM. It exhibits high selectivity, good reusability, stability for at least 21 days, and reproducibility.

3. Main Advantages:

① Selectivity: The host-guest recognition of β-CD endows high selectivity for quinine over common interfering substances.

② Reusability: The indicator (MB) can be reloaded onto the sensor, enabling multiple measurement cycles.

③ Applications: This sensor is suitable for the detection of actual samples such as beverages, and due to its strong robustness and simple operation, it shows promising application prospects in clinical fields (e.g., monitoring of blood drug concentrations) and environmental analysis (e.g., screening of water pollutants).

● Which host molecules use host-guest recognition in electrochemical assays?

"Host-guest recognition" is a powerful concept in supramolecular chemistry, which is widely applied in electrochemical analysis for selective sensing and detection. In these systems, host molecules selectively bind to guest molecules and then convert this interaction into an electrochemical signal. Common host molecules used in electrochemical host-guest analysis are as follows:

1. Cyclodextrins (CDs)

Structure: Cyclic oligosaccharides with hydrophobic cavities, such as α-, β- and γ-cyclodextrins.

Characteristics: The hydrophobic cavity can bind to hydrophobic or size-matched guest molecules, such as organic molecules, drugs, aromatic compounds, etc.

Applications: Used in electrochemical sensors to enhance the selectivity and sensitivity for the recognition of guests (e.g., dopamine, cholesterol, pesticides).

2. Calixarenes

Structure: Cup-shaped macrocycles with adjustable cavities, such as calix[4]arene, calix[6]arene, calix[8]arene and their derivatives.

Characteristics: They can bind to cations, amino acids and organic molecules through size/shape complementarity and functional group interactions.

Applications: Used for sensing metal ions, amino acids, neurotransmitters, etc.

3. Cucurbiturils

Structure: Pumpkin-shaped macrocycles with hydrophobic cavities and carbonyl-lined portals, such as cucurbit[6]uril, cucurbit[7]uril, cucurbit[8]uril, etc.

Characteristics: They bind positively charged and neutral guests to form highly stable host-guest complexes, with guests including drugs, peptides, and dyes.

Applications: Used for the detection of drugs, amino acids, or metal ions.

4. Crown Ethers and Cryptands

Structure: Cyclic ether compounds. - Characteristics: Selectively bind alkali and

alkaline earth metal cations (e.g., K^+, Na^+, Ca^{2+}).

Applications: Used in ion-selective electrodes and sensors for metal ions.

5. Pillarenes

Structure: Rigid columnar macrocycles with electron-rich cavities.

Characteristics: Used for recognizing cations or neutral guests.

Applications: Used in the electrochemical detection of certain ions and small molecules.

6. Molecularly Imprinted Polymers (MIPs)

Structure: A type of synthetic polymer whose molecular recognition sites are complementary to the target molecule in terms of shape, size, and functional group orientation.

Recognition: Synthetic host molecules with cavities complementary to the target molecule (template).

Applications: Used for the selective recognition of drugs, proteins, pesticides, etc., in electrochemical sensors.

7. Porphyrins and Phthalocyanines

Structure: Aromatic macrocyclic compounds.

Recognition: Bind metal ions and small molecules through coordination and π-π interactions.

Applications: Used for the detection of gases, metal ions, and organic molecules.

8. Other Supramolecular Hosts

Examples: Supramolecular polymers, dendrimers, etc.

Applications: Used for the selective recognition of various guests in electrochemical sensing.

● **How stable and reproducible is the electrochemical sensor that uses an Indicator Displacement Assay (IDA) for detecting Quinine?**

The stability and reproducibility of electrochemical sensors for detecting quinine using the Indicator Displacement Assay (IDA) depend on several factors, including sensor design, selection of indicators and receptors, electrode materials, and experimental conditions. The following is a summary based on literature:

1. Stability

When stored at 4°C, the differential pulse voltammetry (DPV) signal of the sensor shows a negligible decrease within the first seven days, indicating its strong short-term stability. Even after 21 days, the sensor retains 86.47% of its original signal, confirming its long-term performance. This sustained performance is attributed to the use of a nanocomposite platform, which provides a chemically inert and physically stable environment for the supramolecular host-guest interactions in the IDA mechanism. The moderate decrease in peak current over three weeks is within the acceptable range for most analytical protocols, indicating that the recognition elements and transduction interface of the sensor are not prone to rapid degradation or fouling.

2. Reproducibility
   ① Inter-electrode reproducibility: Repeatability is a hallmark of well-designed supramolecular sensors. When tested in quinine solutions, multiple independently fabricated MB@β-CD/pNAANI/rGO/GC electrodes show highly consistent DPV responses, with a relative standard deviation (RSD) of 2.06% for seven identical sensors. This low RSD indicates excellent reproducibility in sensor fabrication and measurement.
   ② Batch-to-batch repeatability: For practical validation, five independently produced electrodes were used to detect 30 μM quinine solution, yielding comparable responses with a relative standard deviation of 0.5%, further enhancing the batch-to-batch reproducibility.
   This high degree of reproducibility is a direct result of the controlled assembly of the host-guest system on the electrode surface and the uniformity of the nanocomposite matrix, which minimizes batch-to-batch variations and ensures reliable molecular recognition events.
   ③ Regeneration: IDA-based sensors can be regenerated by removing the bound analytes through washing or applying an electric potential, but repeated regeneration cycles may degrade performance over time.

● **How is the electrochemical sensor that uses an Indicator Displacement Assay (IDA) for detecting Quinine verified?**

Verifying an electrochemical sensor using the Indicator Displacement Assay (IDA) for quinine detection involves several key steps to demonstrate that the sensor functions as intended, with selectivity, sensitivity, and reliability. Here are the typical validation methods for such a sensor:

1. Sensor fabrication and baseline characteristics

Electrode preparation: Electrodes (usually glassy carbon, gold, etc.) are modified with host molecules (such as macrocycles or receptors) and electroactive indicators. Surface analysis techniques like Scanning Electron Microscopy (SEM) and Fourier Transform Infrared Spectroscopy (FTIR) are used to verify the physical and chemical modification of the electrode surface.

Baseline measurement: The electrochemical response of the sensor (e.g., cyclic voltammetry, differential pulse voltammetry, or amperometry) is recorded in the absence of quinine to establish a baseline.

2. Verification of the Indicator Displacement Assay (IDA) principle

Formation of host-indicator complex: The host molecule binds to the indicator, altering its electrochemical signal (usually suppressing or shifting the peak).

Addition of quinine: Upon the addition of quinine, it competes with the host and displaces the indicator. The electrochemical signal of the free indicator is restored or changed.

Signal change: Changes in current or potential are monitored.

3. Calibration and sensitivity

A series of quinine solutions with known concentrations are prepared to generate a calibration curve. The electrochemical response (e.g., current, potential shift) of each standard is recorded. - Linearity is confirmed, and the sensitivity, limit of detection (LOD), and limit of quantitation (LOQ) of the sensor are determined.

4. Comparison with reference methods

The same samples are analyzed using the IDA-based sensor and standard methods such as HPLC to confirm the detection reliability.

5. Selectivity and interference studies

Selectivity test: The sensor is exposed to structurally similar compounds or common interferents (such as caffeine, other alkaloids, ions) to ensure that the response to quinine is specific.

Interference study: The impact of potential interfering factors on the quinine signal is evaluated.

6. Reproducibility, stability, and reusability

Reproducibility: Multiple measurements are performed using the same sensor and different sensors to assess reproducibility (usually reported as a percentage of RSD).

Stability: The response of the sensor is monitored over time to check for signal drift or degradation.

Reusability: The sensor is immersed in a buffer solution for incubation, and MB re-competes to bind to β-CD. Multiple usage cycles are tested to demonstrate the robustness of the sensor.

7. Real sample analysis

Spiked samples: The sensor is tested in real matrices (such as tonic water, pharmaceutical preparations) spiked with known amounts of quinine.

Recovery study: The percentage recovery of quinine is calculated. A recovery rate close to 100% indicates that the sensor reliably measures quinine without significant matrix effects.

● **In the electrochemical sensor that uses an Indicator Displacement Assay (IDA) for detecting Quinine, how does Quinine displace Methylene Blue from beta-Cyclodextrin?**

1. System Composition

① Host: β-cyclodextrin (β-CD) — a cyclic oligosaccharide with a hydrophobic cavity, capable of encapsulating small molecules through non-covalent interactions such as van der Waals forces, hydrophobic effects, and hydrogen bonds.

② Indicator: Methylene blue (MB) — a cationic dye that can be detected electrochemically.

③ Analyte: Quinine — an alkaloid with aromatic and hydrophobic regions.

2. Step-by-Step Mechanism

① Formation of initial complex

Methylene blue (MB) is a cationic dye, forms a non-covalent complex with β-cyclodextrin (β-CD). The hydrophobic inner cavity of β-CD encapsulates MB, stabilizing it within the host and generating a measurable electrochemical signal.

② Addition of quinine

Quinine is introduced into the system. Due to its hydrophobic and aromatic structure, it also has a high affinity for the β-CD cavity, usually stronger than that of MB.

③ Competitive binding (displacement)

Quinine competes with MB for the β-CD cavity. Because of its stronger affinity, quinine displaces MB from the β-CD cavity.

④ Release of MB

As quinine binds to β-CD, MB is squeezed out of the cavity and becomes free in the solution.

⑤ Change in electrochemical signal

The loss of MB from the electrode surface leads to a decrease in its characteristic DPV peak current. The degree of this decrease is proportional to the concentration of quinine, thereby enabling the quantitative analysis of quinine.

3. Displacement Mechanism

Based on the competitive host-guest interactions within the cavity of β-cyclodextrin (β-CD), the binding strength of β-CD to quinine is two to three orders of magnitude stronger than that to methylene blue. This higher affinity stems from:

① The strong hydrophobic quinoline ring of quinine matches better with the hydrophobic inner wall of the β-CD cavity.

② Additional hydrogen bonding between the secondary hydroxyl groups on the edge of cyclodextrin (CD) and the tertiary amino/tertiary nitrogen atoms in the quinine guest molecule.

③ Favorable size/shape complementarity. The structure of quinine can fit more tightly into the hydrophobic cavity of β-CD, while the planar phenothiazine structure of MB only partially enters the β-CD cavity and cannot be completely contained within β-CD, resulting in weaker binding.

- **What does Graphene do in the electrochemical sensor that uses an Indicator Displacement Assay (IDA) for detecting Quinine?**

In electrochemical sensors for detecting quinine using Indicator Displacement Assay (IDA), graphene plays several key roles:

1. High electrical conductivity

Graphene's excellent electrical conductivity facilitates efficient electron transfer between electroactive substances (quinine and indicators) and the electrode surface. This enhances signal sensitivity and lowers the limit of detection.

2. Large surface area

The two-dimensional structure of graphene provides a vast surface area, allowing the immobilization of a higher density of recognition elements (such as host molecules or indicators). This increases the sensor's ability to interact with quinine molecules, minimizes interference from other substances, and improves selectivity and sensitivity.

3. Enhanced electron transfer kinetics

Graphene accelerates the electron transfer process, thereby generating clearer and more distinguishable electrochemical signals. This improves the resolution of quinine detection and enables more accurate quantification.

4. Facilitation of the IDA process

In IDA-based sensors, the indicator initially binds to the host molecule. When

quinine is present, it displaces the indicator due to its higher affinity, resulting in measurable electrochemical changes. The surface of graphene provides a favorable platform for such interactions, stabilizes the host-guest complex, and promotes effective displacement.

5. Chemical stability and biocompatibility

Graphene exhibits chemical stability and biocompatibility, which ensure the durability of the sensor and consistent performance across multiple uses.

6. Signal amplification

Graphene can amplify electrochemical signals in the following ways: enhancing the redox reactions of the indicator or the quinine-indicator complex; reducing background noise due to its high purity and low capacitive current.

7. Stabilizing substrate

Graphene serves as a stable substrate for the poly(N-acetylaniline) film, which is electropolymerized on the electrode surface. This film prevents non-specific adsorption of the indicator molecule methylene blue (MB), ensuring the selective interaction between β-cyclodextrin (β-CD) and MB.

● What is a cryptand?

1. Definition

"Cryptand" is an important class of synthetic macrocyclic molecules in supramolecular chemistry, designed to bind specific ions or molecules within their structure. The term derives from "crypt" (meaning hidden) and "and" (from "andros," signifying "man," analogous to how "crown" in "crown ether" comes from "corona"), reflecting their ability to "hide" ions within their structure. Cryptands are a type of macrocyclic ligand, but unlike simple cyclic structures (such as crown ethers), they possess a three-dimensional, branched, or cage-like architecture.

2. Structure

Cryptands are typically composed of multiple interconnected polyether chains (often based on $-OCH_2CH_2O-$ units), amine $(-NH-)$ bridges, or sulfur bonds, which form a cavity or "crypt" capable of encapsulating guest ions (such as metal cations or organic cations). The most familiar series is denoted as [m.n.p] cryptands, e.g., [2.2.2] cryptand, [2.2.1] cryptand, etc., where m, n, and p represent the number of heteroatom-containing linkages in the three bridging chains.

3. Function

Cryptands are highly efficient chelating agents—their ion-binding ability and selectivity far surpass those of similar compounds like crown ethers, with binding constants that can be several orders of magnitude higher. This is because they encapsulate guest ions from all three dimensions in space, rather than merely binding them through monocyclic coordination. Their unique three-dimensional structure exhibits higher selectivity and stability in complexation; they can bind guests through non-covalent interactions such as hydrogen bonding, van der Waals forces, or ion-dipole interactions.

Cryptands are particularly renowned for their remarkable selectivity toward various cations, achieved through a combination of size/shape complementarity and the precise positioning of donor atoms (e.g., nitrogen and oxygen) within the cavity. A key feature of cryptands is their ability to facilitate the transport, separation, and detection of specific ions. Additionally, they have strong binding affinity for ammonium cations, alkali metals, and alkaline earth metals, and are often used in conjunction with functional groups (such as dye moieties) in chemical sensors.

4. Applications

The ability of cryptands to form highly stable and selective complexes has solidified their utility in a range of applications, including chemical sensing, ion transport and separation, analytical and preparative chemistry, supramolecular chemistry, phase-transfer catalysis, and stabilizing unconventional oxidation states of metals.

5. Example

[2.2.2] cryptand, which consists of three ethyleneoxy bridges connecting two nitrogen atoms, forms a cavity well-suited for encapsulating alkali metal cations (e.g., K^+ or Na^+).

● **Is pyrrole considered an aromatic system?**

Yes, pyrrole is considered an aromatic system, which can be judged mainly from the following points:

① Cyclic and planar structure: Pyrrole is a five-membered heterocycle with the molecular formula C_4H_5N. It is a cyclic molecule and has a planar cyclic structure.

② Conjugated system: All atoms in the ring (4 C atoms and 1 N atom) are sp^2 hybridized, so each atom has an unhybridized p orbital. These p orbitals can overlap around the ring to form a continuous conjugated large π bond, and the π electrons can delocalize freely over the entire ring.

③ Aromatic electron counting: The delocalized system of pyrrole contains 6 π electrons — 4 from the double bonds and 2 from the lone pair of electrons on the

nitrogen atom, which satisfies Hückel's rule ($4n + 2$ π electrons, where $n = 1$).

Conclusion: Pyrrole meets all the criteria for aromaticity, so it is regarded as an aromatic system.

● What types of molecules typically act as guests for supramolecular hosts?

In supramolecular chemistry, a "guest" is a molecule or ion that binds to the interior or surface of a "host" molecule through non-covalent bonds, and together they form a host-guest complex. The types of molecules that usually act as guests for supramolecular hosts include:

1. Cations
   ① Alkali metal ions (e.g., Na^+, K^+, Li^+)
   ② Alkaline earth metal ions (e.g., Ca^{2+}, Mg^{2+})
   ③ Transition metal ions (e.g., Cu^{2+}, Fe^{2+}, Zn^{2+})
   ④ Organic cations (e.g., quaternary ammonium cations, primary amines, protonated amines)
   ⑤ Inorganic cations (e.g., NH_4^+)

2. Anions
   ① Halide ions (e.g., Cl^-, Br^-, I^-)
   ② Oxyanions (e.g., NO_3^-, SO_4^{2-}, $H_2PO_4^-$)

3. Neutral organic molecules
   ① Aromatic compounds (e.g., benzene, naphthalene)
   ② Alkanes, alkenes, alcohols, ketones, etc.
   ③ Fullerenes (e.g., C_{60})

4. Biomolecules
   Amino acids, peptides, nucleotides, carbohydrates

5. Drugs and pharmaceuticals
   Ibuprofen, paracetamol

6. Gases
   ① Noble gases (e.g., Xe, Kr)
   ② Small molecules (e.g., CO_2, O_2, N_2)

7. Other guests
   ① Dyes
   ② Ionic liquids

③　Polymers (as segments or chains)

Summary: A "guest" can be an ion, small molecule, biomolecule, or even a gas — essentially any species that can fit into the host's cavity and interact through non-covalent forces (hydrogen bonds, van der Waals forces, π-π stacking, electrostatic forces, etc.). The choice of guest depends on the host's size, shape, hydrophobicity, charge, functional groups, and binding properties. The nature of these guest molecules is determined by the structure and binding preferences of the specific host.

● **What are some specific types of macrocycles?**

　　Macrocyclic compounds are a class of compounds with cyclic structures and a relatively large number of atoms in the ring (usually ≥ 12). Here are some specific types of macrocyclic compounds and their examples:

1.　Macrocyclic Ethers
(1)　Crown Ethers
　　①　Structure: Cyclic polyethers with repeating ethyleneoxy ($-O-CH_2-CH_2-$) units.
　　②　Example: 18-crown-6 (an 18-membered ring containing 6 oxygen atoms).
　　③　Uses: Cation complexation (such as binding potassium ions), phase transfer catalysts, ion recognition, ion transport, chemical sensing, and aiding in the detection and recognition of peptides and amino groups.
(2)　Lariat Ethers
　　①　Structure: Crown ether skeletons with attached side arms (containing additional coordinating atoms like N, O), which can enhance binding with guests.
　　②　Uses: Cation recognition (with more stable binding than crown ethers).

2.　Cyclodextrins
　　①　Structure: Cyclic oligosaccharides derived from starch (D-glucose units linked by α-1,4 bonds), forming a conical cavity composed of glucose units, with a hydrophobic inner cavity and hydrophilic outer edge.
　　②　Types: α-cyclodextrin (6 units), β-cyclodextrin (7 units), γ-cyclodextrin (8 units).
　　③　Uses: Drug delivery, molecular encapsulation, catalysis, molecular recognition, and as scaffolds for supramolecular assembly.

3.　Macrocyclic Aromatics
(1)　Calixarenes
　　①　Structure: Cyclic oligomers of phenol units linked by methylene bridges, forming cup-shaped macrocycles. The upper and lower rims of calixarenes can be functionalized to enhance their binding properties.
　　②　Examples: Calix[4]arene (4 phenol units), calix[6]arene, calix[8]arene,

resorcinarenes, p-sulfonatocalix[n]arenes.

    ③   Uses: Host-guest chemistry, molecular recognition, sensors.

(2) Pillar[n]arenes

    ①   Structure: Symmetric macrocyclic compounds formed by para-phenylene units linked at the para positions via methylene bridges, creating a rigid columnar structure with an electron-rich cavity.

    ②   Examples: Pillar[n]arenes, with variable cavity sizes (n = 4, 6, 8 units).

    ③   Uses: Molecular recognition, materials science, and stimuli-responsive systems.

(3) Cyclophanes

    ①   Structure: Macrocycles formed by aromatic rings bridged by aliphatic chains at non-adjacent ring positions, creating cavities suitable for π-π and hydrophobic host-guest interactions, with "basket-like" or "cage-like" structures.

    ②   Examples: [2.2]paracyclophane, basketane derivatives.

    ③   Uses: Biorecognition and molecular sensing.

(4) Annulenes

    ①   Structure: Monocyclic polyolefins with alternating single and double bonds, containing ≥ 10 atoms in the ring.

    ②   Example: [18]annulene.

    ③   Uses: Aromaticity research, materials chemistry (conjugated systems can conduct electricity).

(5) Cyclotriveratrylenes

    ①   Structure: Cage-like structures.

    ②   Uses: Molecular recognition.

4.   Cucurbiturils

    ①   Structure: Barrel-shaped macrocyclic compounds composed of glycoluril units ($-C_4H_2N_4O_2-$) linked by methylene bridges, with a cavity of variable polarity (hydrophobic core + polar ports).

    ②   Examples: Cucurbit[5]uril, cucurbit[6]uril, cucurbit[7]uril.

    ③   Uses: Their rigid hydrophobic cavities and carbonyl-arranged ports make them excellent hosts for various cations and neutral guests (including amino acids and peptides). They are highly valuable in sensing, molecular encapsulation, enzyme mimicking, and even protective roles in biological systems.

5.   Pyrrole / Porphyrin Macrocycles

(1) Porphyrins

    ①   Structure: Tetrapyrrolic macrocycles (four pyrrole rings linked by methine (–CH=) bridges).

    ②   Examples: Heme (iron-porphyrin complex), chlorophyll (magnesium-porphyrin complex).

    ③   Uses: Biological pigments, catalysis.

(2) Calixpyrroles

    ①   Structure: Macrocycles of pyrrole units linked by sp³-hybridized carbon

bridges, with inward NH groups that can form hydrogen bonds with anions (such as F^-, Cl^-).

 ②   Examples: Calix[4]pyrrole (4 pyrrole units), calix[6]pyrrole.

 Uses: Anion recognition, environmental monitoring (such as detecting halide ions).

(3) Phthalocyanines

 ①   Structure: Similar to porphyrins but containing isoindole units.

 ②   Uses: Dyes, pigments, photodynamic therapy.

6.   Bioactive Macrocycles Containing Acyl / Ester Groups

(1) Cyclopeptides and Cyclic Peptides

 ①   Structure: Peptides with a cyclic backbone.

 ②   Examples: Cyclosporin A (immunosuppressant), gramicidin S (antibiotic), vancomycin.

 ③   Uses: Drugs, antibiotics.

(2) Siderophores

 ①   Structure: Macrocyclic molecules produced by microorganisms for chelating iron.

 ②   Examples: Enterobactin, desferrioxamine B.

(3) Macrolides

 ①   Structure: Macrocyclic compounds containing lactone bonds.

 ②   Examples: Many natural products belong to this class, such as erythromycin, azithromycin, midecamycin.

 ③   Uses: Possess biological activities such as antibacterial and antitumor effects, and their cyclic structure is key to exerting pharmacological effects.

(4) Macrocyclic Lactams

 ①   Structure: Macrocycles containing lactam bonds, which enhance selective binding to targets through the cyclic lactam structure.

 ②   Examples: Actinomycin D, certain peptide antibiotics.

 ③   Uses: Antibacterial.

7.   Others

(1) Cryptands

 ①   Structure: Three-dimensional cage-like macrocycles with multiple binding sites, belonging to cryptate compounds.

 ②   Uses: Cation encapsulation, supramolecular chemistry.

(2) Cyclotris(p-quinomethane) Derivatives

 ①   Structure: Macrocyclic compounds derived from trimeric quinones.

 ②   Applications: Redox-active materials for energy storage.

● When a calixarene containing pyrrole groups binds an anion, what specific non-covalent interactions are typically involved?

When calixarenes containing pyrrole groups bind to anions, the specific non-covalent interactions involved usually include the following:

1. Hydrogen bonding (dominant role)

The pyrrole NH group is an excellent hydrogen bond donor. Its NH proton can form hydrogen bonds with anions, especially anions such as Cl^-, NO_3^-, and $H_2PO_4^-$. In most cases, this is the main interaction.

2. Anion-π interactions

The π system of the pyrrole ring (and possibly other aromatic rings of the calixarene) can interact with anions through anion-π interactions. This interaction is more significant for anions that can interact with the aromatic π system, such as NO_3^- and ClO_4^-.

3. Electrostatic (ion-dipole) interactions

The N-H bond of the pyrrole NH group is highly polar because the lone pair of electrons on the nitrogen atom participates in aromatic conjugation, which can interact electrostatically with negatively charged anions.

4. Hydrophobic interactions

Calixarenes themselves have a hydrophobic aromatic ring skeleton and relatively hydrophilic pyrrole groups. The hydrophobic microenvironment of their macrocyclic cavity can generate hydrophobic interactions with the hydrophobic parts of anions (such as long-chain alkyl-substituted anions), helping to stabilize the binding system.

5. Cavity/encapsulation effect (steric hindrance and shape matching)

The calixarene skeleton provides a preorganized cavity, and the pyrrole NH groups are oriented toward the cavity to maximize the synergistic binding effect. This cavity can encapsulate anions, and the binding is enhanced through shape complementarity and multi-point interactions.

6. Van der Waals forces

These weak, non-specific interactions result from close contact between the anion and the hydrophobic wall of the calixarene cavity. Although individual Van der Waals forces are weak, their combined effect helps stabilize the host-guest complex and can influence selectivity, especially for anions that fit closely into the cavity.

7. Secondary interactions

① Structural variations (such as large meso-substituents) can create additional hydrophobic pockets, stabilizing the encapsulated anion or affecting selectivity

through steric hindrance and Van der Waals forces.

② If the calixarene is further functionalized (e.g., with cationic substituents), anion-π interactions and other electrostatic interactions may also play a secondary auxiliary role.

Summary: The binding of anions by calixarenes with pyrrole groups is dominated by strong, directional hydrogen bonds, supported by electrostatic interactions, Van der Waals forces, anion-π interactions, and hydrophobic interactions. The preorganized macrocyclic structure of calixarenes and the strategic arrangement of pyrrole groups are key to achieving effective and selective anion recognition in supramolecular systems.

● Are there known supramolecular hosts that are derivatives of calixarenes and also feature pyrrole functional groups?

Yes, there are known supramolecular hosts that are derivatives of calixarenes and possess pyrrole functional groups. The following are representative examples:

1. Calix[4]arene-porphyrin conjugates
   ① Structure: The tetrapyrrolic porphyrin macrocycle is fused with calix[4]arene or immobilized above the calix[4]arene.
   ② Applications: They can be used for fullerene recognition, photoinduced electron transfer, anion sensing, etc.

2. Calixarene-pyrrole conjugates
   Researchers have synthesized calixarene derivatives with pyrrole units as substituents on the upper or lower rim.

● What are common applications for cage molecules compared to macrocycles, and do they have any overlapping uses?

1. Macrocyclic Compounds
   Macrocyclic compounds are large cyclic molecules, often planar or near-planar in structure, with sizes typically ranging from 12 to over 50 atoms. Examples include crown ethers, porphyrins, and cyclodextrins, with common applications as follows:
   ① Host-guest chemistry: Binding and transporting ions or small molecules

(e.g., ionophores, molecular recognition).

② Catalysis: Acting as ligands for metal ions, mimicking the active sites of enzymes to facilitate catalytic reactions.

③ Sensors: Detecting specific ions or molecules through selective binding.

④ Drug delivery: Encapsulating drugs for controlled release (e.g., cyclodextrins).

⑤ Supramolecular assemblies: Serving as building blocks for larger structures and as scaffolds for higher-order structures, materials, and functional systems.

⑥ Biomimicry: Mimicking the role of biological macrocycles (e.g., porphyrins) in oxygen transport or photosynthesis.

⑦ Biomedical applications: Being researched in bioimaging, targeted therapy, and diagnostic tools.

2. Cage-like Molecules

Cage-like molecules (including synthetic cryptates, metal-organic cages (MOCs), molecular capsules, etc.) are three-dimensional closed structures capable of binding guests within their internal cavities. Compared with macrocyclic compounds, common applications of cage-like molecules are as follows:

① Molecular encapsulation: Trapping guest molecules or ions inside the cage (e.g., stabilizing active species, isolating unstable intermediates) for storage or transport.

② Gas storage/separation: Their cavity size, shape, and inner wall functional groups can precisely match gas molecules (e.g., CO_2, CH_4), enabling efficient adsorption and separation through host-guest interactions (e.g., clathrate hydrates, MOCs for gas storage).

③ Host-guest chemistry: Forming inclusion complexes with small organic molecules, peptides, and ions for chelation, ion transport, and recognition, including drug molecules, hydrocarbons, and hard-to-analyze analytes.

④ Drug delivery: Encapsulating drugs to provide protection and controlled release.

⑤ Catalysis and reaction vessels: The three-dimensional cavity can act as a "molecular reactor," providing a confined microenvironment for reactions to regulate reaction pathways and selectivity.

⑥ Sensing and fluorescence applications: Cage-like molecules can serve as components of OFF/ON fluorescent sensors, functioning by regulating the optical properties of guests upon encapsulation.

⑦ Separation and purification: Selectively binding and separating specific molecules from mixtures based on size or shape.

⑧ Supramolecular assembly: Cage-like molecules self-assemble into porous frameworks (e.g., caged polymers) through non-covalent interactions, acting as scaffolds for higher-order structures, materials, and functional systems.

⑨ Biomedical applications: Being researched in bioimaging, targeted therapy, and diagnostic tools, and can be used as contrast agents in imaging.

⑩ Environmental remediation: Adsorbing pollutants (e.g., heavy metal ions,

persistent organic pollutants) from water or soil through their cavities.

3. Overlapping Uses

Both macrocyclic compounds and cage-like molecules utilize non-covalent interactions (hydrogen bonds, hydrophobic interactions, π-π interactions, and ion-dipole forces) to achieve selective molecular recognition. Their overlapping applications include:

①   Host-guest chemistry: Both can bind and transport ions or small molecules, although cage-like molecules typically provide more complete encapsulation.

②   Molecular recognition and sensing: Both platforms are used for the selective sensing and detection of ions, small molecules, and biomolecules. Structural design — cyclic for macrocyclic compounds and closed for cage-like molecules — determines the size and selectivity of targets.

③   Drug delivery: Both macrocyclic compounds and cage-like molecules can encapsulate pharmaceuticals to provide protection and controlled release — macrocyclic compounds are usually used for smaller guests, while cage-like molecules are used for larger or more complex payloads.

④   Catalysis: Both can act as enzyme mimics, providing a defined environment for reactions.

⑤   Supramolecular assembly: Both serve as scaffolds for higher-order structures, materials, and functional systems, including as building blocks for supramolecular polymers or nanomaterials.

⑥   Biomedical applications: Both are researched in bioimaging, targeted therapy, and diagnostic tools.

● What types of supramolecular hosts are known to bind anions primarily through anion-π interactions?

1. Electron-deficient aromatic receptors

Macrocyclic compounds with electron-deficient aromatic rings (such as perfluorinated aromatic systems) can participate in anion-π interactions. These molecules include:

1) Macrocyclic aromatic derivatives

①   Calixarene derivatives: Calixarenes can enhance π-acidity through chemical modification, thereby improving their ability to attract and bind anions via the π system. This modification increases their selectivity for specific anionic guests.

②   Cyclophanes: Cyclophanes, through electron-deficient modification (such as perfluorination), can form stacked π-acidic aromatic rings. Their adjustable cavity environment provides a suitable π-receptor surface platform for anion-π interactions.

③   Pillararenes: Columnar macrocycles formed by multiple hydroquinone units linked via methylene bridges. The anion-π interactions can be enhanced through fluorination or electron-deficient modification (such as trifluoromethyl groups).

2) Nitrogen-containing heterocyclic aromatics

Refers to aromatic systems containing nitrogen-containing electron-deficient heterocycles such as pyridine, pyrimidine, and triazine. The N-H on the ring can act as a hydrogen donor to form hydrogen bonds with anions, and at the same time, the π-acidic surface of the heterocycle enhances binding through anion-π interactions.

2. Receptors with built-in anion-π sites

Electron-deficient π-moieties (such as triazine, perfluorophenyl) are artificially designed to be embedded into the assembly structure, forming sites specifically adapted for anion-π interactions.

1) Metal-organic cages (MOCs)

Three-dimensional cage structures assembled from metal ions (such as Zn^{2+}, Cu^{2+}) and electron-deficient ligands (triazine, pyridine). Multiple π surfaces in the cavity synergistically bind anions.

2) Triarylboranes

The electron deficiency of boron atoms synergizes with the π-acidity of aromatic rings, binding anions through a dual mechanism of "anion-π interaction + Lewis acid coordination".

3. Foldamers and cleft-shaped hosts

1) Foldamers with π-acidic surfaces that can fold to encapsulate anions.
2) Cleft-shaped molecules (such as molecular tweezers) have two opposing π-acidic aromatic surfaces, forming an anion-binding pocket.

4. Other important types

1) Fullerene derivatives

The spherical π-electron cloud density of fullerenes such as C60 is low (electron-deficient), enabling them to bind large-volume anions (such as $ClO4^-$, $PF6^-$).

2) Porphyrin derivatives

After modification with axial electron-deficient ligands, the π surface of porphyrins can be transformed into anion-π interaction sites.

Summary: The core of such supramolecular hosts lies in utilizing the electrostatic attraction between the π surface of electron-deficient aromatic rings and anions. The strength and selectivity of the interaction are enhanced through structural design (such as macrocycles, cages, foldamers) and functional modification (such as electron-withdrawing groups, metal coordination).

● Why are supramolecular hosts containing pyrrole units generally effective at binding anions?

Supramolecular hosts containing pyrrole units are generally effective in binding anions, mainly for the following reasons:

1. Pyrrole NH as a hydrogen bond donor

Pyrrole is a five-membered aromatic heterocycle with a hydrogen atom attached to the nitrogen atom (NH). Its NH group has relatively strong acidity (for aromatic NH) and can act as a strong hydrogen bond donor. Anions (such as Cl^-, NO_3^-, $H_2PO_4^-$, etc.) are good hydrogen bond acceptors. When multiple pyrrole units are arranged in the host (such as calix[4]pyrrole, porphyrin, expanded porphyrin), their NH groups can converge to form multiple hydrogen bonds with an anion, thereby achieving strong and selective binding.

2. Preorganization and complementarity

Supramolecular hosts are usually preorganized so that the pyrrole NH groups face the central cavity. This geometric complementarity enables the host to encapsulate the anion, maximize hydrogen bond interactions, and reduce the entropy cost.

3. Aromatic stabilization and charge delocalization

The aromaticity of pyrrole helps delocalize charges and stabilize the host-anion complex. In some cases, the π system of the pyrrole ring may also participate in anion-π interactions (though this is less common than hydrogen bonding).

4. Solvent effect

Anion recognition is particularly challenging in aqueous environments because anions are strongly hydrated, and hydrogen bonds are weakened due to competition with solvent molecules. Pyrrole-containing hosts, especially when arranged in hydrophobic cavities (such as in macrocyclic compounds or cryptands), can isolate the binding interaction from water, partially desolvate the anion, and enhance hydrogen bond interactions.

5. Structural versatility

Pyrrole units can be incorporated into various macrocyclic or linear frameworks, making it possible to design hosts with customized cavity sizes and shapes suitable for specific anions, thereby improving binding specificity.

6. Charge transfer interactions

The electron-rich nature of pyrrole can lead to charge transfer with anions, especially when the anion is a strong electron acceptor (such as picrate, hexafluorophosphate).

7. Synergistic enhancement of metal coordination

 After metal ions coordinate with pyrrole nitrogen atoms, they will enhance the polarity of the N-H bond (electron-withdrawing effect), making it easier for NH to form hydrogen bonds; at the same time, the positive charge of metal ions attracts anions through electrostatic interaction, forming a "metal coordination - hydrogen bond - electrostatic" triple synergy.

Summary: The reason why pyrrole units in supramolecular hosts can effectively bind anions is that their NH groups are strong hydrogen bond donors, the aromaticity of the pyrrole ring can enhance charge stability, and when arranged in a preorganized manner, they can form multiple directional hydrogen bonds with anions, thus achieving strong and selective binding with anions.

● What is the role of non-covalent interactions like hydrogen bonds and anion-π interactions in the formation of supramolecular host-guest complexes?

 The role of non-covalent interactions in the formation of supramolecular host-guest complexes:

 Non-covalent interactions, especially hydrogen bonds and anion-π interactions, are the core driving forces behind the formation, stability, and selectivity of supramolecular host-guest complexes. These weak interactions, characterized by reversibility and dynamics, enable molecular recognition, structural assembly, and functional regulation without the need for covalent bonds, and are widely present in biological systems and synthetic materials.

1. Hydrogen bonds

 Hydrogen bonds are formed by electrostatic attraction between a hydrogen atom on an electronegative donor (such as O-H, N-H) and an electronegative acceptor (such as O, N, or groups with lone pairs of electrons). Their main roles include:

 ① Molecular recognition and selectivity: They have directionality and specificity, enabling precise binding through matching hydrogen bond sites between hosts and guests (e.g., donor-acceptor complementarity), similar to the "lock-and-key model" (such as the recognition between crown ethers and ammonium ions).

 ② Structural stability: Multiple hydrogen bonds act synergistically to form a network, significantly enhancing the stability of complexes (e.g., hydrogen bond interactions between the inner cavity of cyclodextrins and guests, and binding of urea-based receptors to anions).

 ③ Preorganization effect: Host molecules often optimize binding sites by prearranging hydrogen bond donor/acceptor groups, simulating the efficient

recognition mechanisms of biological systems (such as DNA base pairing).

④ Dynamic reversibility: With relatively weak bond energy (10–40 kJ/mol), they can break and recombine, allowing complexes to respond to external stimuli (such as pH and temperature), making them suitable for fields like molecular machines and self-healing materials.

2. Anion-π interactions

Anion-π interactions refer to non-covalent attraction between anions and electron-deficient aromatic π systems (such as perfluorobenzene, triazine derivatives). Their key functions are as follows:

① Anion recognition: Through electrostatic interactions between electron-deficient aromatic surfaces and anions, they achieve selective binding of negatively charged guests (such as halide ions, nitrate ions), complementing or surpassing the recognition ability of traditional hydrogen bonds.

② Stability enhancement: They synergize with hydrogen bonds, van der Waals forces, etc., to improve the binding affinity of host-guest systems (e.g., porphyrin-based hosts binding halide ions through anion-π interactions).

③ Functional innovation: They promote the design of new anion receptors, sensors, and catalysts, especially suitable for large-volume or highly charged anions that are difficult to recognize through hydrogen bonds.

3. Synergism and complementarity

① Synergy of multiple interactions: Hydrogen bonds and anion-π interactions often participate in binding together, enhancing the stability and selectivity of complexes through "multi-point contact" (such as chelation effect).

② Dynamic assembly: Both are reversible interactions, endowing supramolecular systems with dynamic properties of self-assembly/disassembly and supporting stimuli responsiveness (such as pH-regulated guest release).

③ Multifunctional integration: Combined with other non-covalent forces such as π-π stacking and hydrophobic interactions, they can construct complex structures (such as capsules, molecular cages), expanding applications in fields like drug delivery and molecular switches.

Summary

Hydrogen bonds and anion-π interactions, through specific recognition, structural stability, and dynamic reversibility, jointly regulate the formation and functions of supramolecular host-guest complexes. Their synergistic effect is the core foundation for designing intelligent materials, bionic systems, and efficient molecular devices, reflecting the essence of supramolecular chemistry: "weak interactions drive complex functions."

● What types of molecules can be detected by IDA?

IDA can detect any molecule that can competitively displace an indicator from a receptor. Selectivity is determined by receptor design (such as cavity size, charge, and functional groups) and binding affinity. This modular feature makes it widely applicable in analytical chemistry, biosensing, and diagnostic fields.

Types of molecules detectable by IDA: IDA (Indicator Displacement Assay) is a supramolecular sensing technique that enables molecular detection through the competitive binding of analytes and indicators to receptors. Its core advantage lies in the modular design of receptor-indicator pairs, allowing it to detect various types of molecules, specifically including:

1. Cations

Metal ions: alkali metals/alkaline earth metals (e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}), transition metals (e.g., Zn^{2+}, Cu^{2+}, Fe^{3+}), and heavy metals (e.g., Pb^{2+}, Hg^{2+}, Cd^{2+}). Such detection relies on the receptor's selective coordination ability for metal ions; for example, macrocyclic compounds like crown ethers and calixarenes are often used as receptors.

2. Anions

① Inorganic anions: halide ions (F^-, Cl^-, Br^-, I^-), oxyanions (NO_3^-, SO_4^{2-}, PO_4^{3-}), and toxic anions (CN^-, PF_6^-, ClO_4^-), etc.

② Organic anions: carboxylates, phosphates, sulfonates, and biologically relevant anions (such as pyrophosphate). Receptors achieve anion recognition through hydrogen bonding, electrostatic interactions, or Lewis acid sites.

3. Neutral small molecules
① Carbohydrates (e.g., glucose)
② small organic molecules (e.g., drugs, neurotransmitters, pesticides)
③ biological small molecules (e.g., amino acids, nucleotides, peptides, polyamines, etc.)
④ gas molecules.

4. Biological macromolecules
① Proteins/enzymes: Interactions with proteins are feasible, especially in cases of specific host-protein fragment binding or post-translational modifications (e.g., methylation detection).
② Nucleic acids: DNA/RNA with specific sequences.

● What types of host-guest interaction can be used to design IDA-based electrochemical sensors?

When designing IDA-based electrochemical sensors, various host-guest interactions can be utilized to achieve selective and sensitive detection of analytes. These interactions are mainly non-covalent, enabling the target analyte to displace the redox-active indicator, thereby generating a measurable electrochemical signal. The main types of host-guest interactions include:

1. Hydrogen bonding interactions

Host molecules with hydrogen bond donors (such as ureido, thioureido, amido, or pyrrolyl groups) interact with guests containing hydrogen bond acceptors (such as anions, polar functional groups). This directional interaction improves the selectivity for analytes such as carboxylates, phosphates, or amino acids. For example, calix[4]pyrrole binds anions through NH···anion hydrogen bonds, and molecularly imprinted polymers (MIPs) utilize hydrogen bonding during template polymerization.

2. Electrostatic (ionic) interactions

The attraction between oppositely charged host and guest species drives binding. Cationic hosts (such as quaternary ammonium-functionalized calixarenes) bind anionic guests (such as phosphate, sulfate), and anionic hosts (such as sulfonated calixarenes, cucurbiturils) interact with cations (such as alkali metals, protonated amines). Crown ethers and cryptate ligands are typical examples for cation recognition, achieving selective binding through electrostatic attraction.

3. Hydrophobic interactions

Non-polar guests are encapsulated in the hydrophobic cavities of hosts such as cyclodextrins, cucurbiturils, calixarenes, or pillararenes. The hydrophobic effect is driven by the entropy increase from water displacement, stabilizing the inclusion complex. For instance, β-cyclodextrin encapsulates hydrophobic redox indicators (such as methylene blue), and analytes like quinine displace the indicator through stronger hydrophobic binding.

4. π-π stacking interactions

Aromatic hosts (such as calixarenes, pillararenes, cyclodextrins with aromatic modifications) interact with aromatic guests through π-electron overlap. This interaction is crucial for detecting polycyclic aromatic hydrocarbons, dyes, or biomolecules containing aromatic residues (such as tryptophan, caffeine), enhancing the binding affinity and selectivity for planar conjugated guests.

5. Metal-ligand coordination interactions

Hosts containing metal centers (such as Zn^{2+}, Cu^{2+}, or lanthanides) coordinate with guests through Lewis basic sites (such as nitrogen, oxygen, sulfur atoms). For

example, metal-organic cages, porphyrins, or dipyridylamine complexes bind analytes like imidazole, pyridine, or metal ions. This interaction has high specificity and adjustable binding strength, often acting synergistically with other interactions.

6. Van der Waals forces

Weak non-specific van der Waals forces (London dispersion forces, dipole-induced dipole forces) contribute to binding, especially in shape-complementary host-guest systems. They synergize with other interactions such as hydrophobic or hydrogen bonding to stabilize complexes, particularly for guests that precisely match the size/shape of the host cavity.

7. Host-guest inclusion interactions

Macrocyclic hosts (cyclodextrins, cucurbiturils, calixarenes, pillararenes) encapsulate guests in their cavities, driven by a combination of hydrophobic effects, hydrogen bonding, and van der Waals forces. This "lock-and-key" mechanism achieves high selectivity based on the size, shape, and chemical compatibility of the guest. For example, cyclodextrins of different sizes (α-, β-, γ-) selectively bind guests of matching sizes.

8. Charge transfer interactions

Electron-rich hosts (such as tetrathiafulvalene, TTF) form complexes with electron-deficient guests (or vice versa), generating charge transfer states. This interaction is used to detect electron-accepting/donating analytes, though it is less common than other interactions.

9. Dynamic covalent interactions (rare)

Reversible covalent bonds (such as boronate ester, imine formation) are occasionally used for irreversible detection, but they are less typical in reversible IDA sensors due to stability reasons. For example, the binding strength of boronic acid-diol is regulated by solution pH (pH 7–9), and selectivity can be enhanced by optimizing buffer conditions.

Summary
IDA-based electrochemical sensors utilize a variety of host-guest interactions, among which hydrogen bonding, electrostatic attraction, hydrophobic effects, π-π stacking, and inclusion interactions are the most common. These interactions enable selective, sensitive, and reversible detection of analytes ranging from ions, small molecules to biomolecules and drugs:

① Synergistic interactions: Sensors often combine multiple interactions (such as hydrophobic + hydrogen bonding) to improve selectivity and affinity.

② Host selection: Cyclodextrins, calixarenes, cucurbiturils, and MIPs are widely used due to their adjustable cavities and functional groups.

③ Signal transduction: The displacement of the redox indicator changes the electrochemical signal (current/potential), which is directly related to the analyte

concentration.

● What types of host-guest interaction can be used to design IDA using optical detection?

Types of host-guest interactions used in designing optical detection-based IDAs:
Indicator Displacement Assays (IDAs) are detection methods based on supramolecular sensing strategies. Their core principle lies in the competitive binding among hosts, guests (analytes), and optical indicators, enabling detection through optical signals (such as colorimetric or fluorescent changes). The types of host-guest interactions that can be utilized when designing optical detection IDAs are as follows:

1. Hydrogen bonding interactions
  ① Description: Hosts (such as urea, thiourea, amide, or crown ether-based compounds) bind to guests (containing appropriate donor/acceptor groups) through hydrogen bonds.
  ② Example: Binding between urea-based hosts and carboxylate or phosphate guests.

2. Electrostatic (ionic) interactions
  ① Description: Attraction between oppositely charged species (e.g., cationic hosts with anionic guests, and vice versa).
  ② Example: Binding between quaternary ammonium hosts and anionic dyes or analytes.

3. π-π stacking interactions
  ① Description: Aromatic hosts (such as cyclodextrins, calixarenes, cucurbiturils) bind to aromatic guests or indicators through π-π stacking.
  ② Example: Interaction between calixarene hosts and aromatic dye indicators.

4. Hydrophobic interactions
  ① Description: Non-polar guests are encapsulated in the hydrophobic cavities of hosts (such as cyclodextrins, cucurbiturils).
  ② Example: Inclusion of hydrophobic dye indicators by cyclodextrin hosts.

5. Metal coordination interactions
  ① Description: Hosts containing metal centers (such as complexes of Zn^{2+}, Cu^{2+}, or lanthanides) coordinate with guests having suitable ligands (such as phosphate, carboxylate, amine).
  ② Example: Binding between Zn^{2+}-dipyridylamine complexes and phosphate-containing guests.

6. Van der Waals forces

① Description: Weak non-specific interactions, often synergizing with other forces to enhance overall binding affinity.

② Example: Present in all host-guest systems, frequently acting in synergy with other interactions (such as hydrophobic or π-π stacking).

7. Covalent (reversible) interactions

① Description: Reversible binding of guests through dynamic covalent bonds (such as boronic acid-diol interactions).

② Example: Binding between boronic acid hosts and diol-containing indicators or carbohydrate guests.

8. Conformational changes

Binding can induce conformational changes in host or guest molecules, affecting their optical properties, such as fluorescence quenching or enhancement.

Summary

The design of optical detection IDAs can utilize hydrogen bonding, electrostatic, π-π stacking, hydrophobic, metal coordination, van der Waals forces, and reversible covalent interactions. The selection depends on the properties of the analyte, the type of indicator, and the required selectivity and sensitivity. These interactions regulate the stability of the host-indicator complex, enabling optical signal changes after analyte displacement to complete the detection.

● What types of host-guest interaction can induce changes in optical signals?

Host-guest interactions can induce optical signal changes through various mechanisms, with specific types as follows:

1. Electron transfer-related mechanisms

① Photoinduced electron transfer (PET) The binding of a guest to the host promotes or inhibits electron transfer between the host and the fluorophore, resulting in fluorescence quenching or enhancement. For example, when a crown ether host with a fluorophore binds to a metal ion guest, the PET process is inhibited, turning on the fluorescence.

② Charge transfer (CT) interactions Hosts and guests form charge transfer complexes, generating new absorption bands or color changes. Such as interactions between aromatic hosts (cyclodextrins, calixarenes) and electron-rich or electron-deficient guests.

2. Structural and conformational changes

① Conformational changes

Guest binding induces conformational changes in the host, affecting the environment of the chromophore. For example, after a rotaxane host binds to a guest, a conformational twist occurs, leading to a blue shift in the absorption spectrum of the attached dye.

② Aggregation/disaggregation effects

Host-guest binding promotes or inhibits the aggregation of dye molecules, altering optical properties. For instance, cyclodextrins bind to hydrophobic cyanine dyes, disrupting H-aggregates and causing the absorption peak to redshift from 550 nm to 620 nm.

3. Energy and environmental regulation

① Energy transfer (FRET)

Binding brings the donor and acceptor luminophores close, enabling Förster resonance energy transfer, which is monitored through changes in the emission spectrum. For example, supramolecular assemblies where the host and guest are labeled with two different dyes.

② Polarity or microenvironment changes

Guest binding alters the polarity or hydrogen bonding environment around the chromophore, leading to shifts in absorption or emission spectra. Such as spectral changes when solvatochromic dyes are embedded in cyclodextrins.

③ Excimer/exciplex formation

Host-guest binding brings two aromatic units close, forming excimers or exciplexes that produce new emission bands. For example, pyrene-labeled host-guest systems.

4. Types of non-covalent interactions

① Metal coordination

Metal ion guests coordinate with the host, changing the optical properties (color change, luminescence) of the complex. For example, the binding of crown ethers or cryptands to transition metal ions; specifically, when a cryptand coordinates with Fe^{3+}, the solution changes from colorless to deep red.

② Hydrophobic interactions

Guests are embedded in the hydrophobic cavity of the host (such as cyclodextrins, cucurbiturils), resulting in fluorescence enhancement/quenching or absorption peak shifts, reducing solvent quenching effects.

③ Hydrogen bonding

Hydrogen bonds between the host and guest alter the electronic environment of the guest, affecting photophysical properties. For example, urea-based hosts bind to anionic guests through hydrogen bonds, leading to changes in optical signals; specifically, when a urea-based host binds to a phosphate guest via hydrogen bonds, the UV absorption peak of the guest redshifts from 260 nm to 280 nm.

④ Electrostatic and ion-dipole interactions

Electrostatic attraction between charged hosts and guests changes fluorescence

intensity. For example, cationic hosts binding to anionic fluorophores result in fluorescence enhancement or quenching.

⑤　π-π stacking interactions

π-π stacking between aromatic hosts and guests disturbs the electronic state, causing changes in absorption and emission spectra, commonly seen in interactions between pyrenyl hosts and aromatic guests.

5. Dynamic and stimulus-responsive mechanisms

①　Stimulus-responsive assembly/disassembly

Stimuli such as pH and ionic strength regulate host-guest binding, leading to fluorescence "on-off" effects. For example, competitive guest displacement of fluorescent dyes triggers signal changes.

②　Excited-state proton transfer (ESPT)

Guest binding promotes excited-state proton transfer, altering the fluorescence emission wavelength.

Summary：

The above mechanisms regulate optical signals such as absorption, fluorescence, and phosphorescence by changing electronic structures, conformations, or microenvironments, and are widely used in sensing, imaging, and molecular recognition fields.

● What types of host-guest interaction can induce changes in electrochemical signals?

Host-guest interactions can induce changes in electrochemical signals through various mechanisms, depending on the properties of the host and guest, as well as the type of electrochemical measurement. The main types of host-guest interactions that can regulate electrochemical signals are as follows:

1. Interactions based on redox activity

Core mechanism: Signal regulation is achieved by changing the electronic environment or transfer efficiency of redox centers.

①　Binding of redox-active guests

The host binds to electrochemically active guests (such as ferrocene derivatives, metal ions). Through steric hindrance, solvation effects, or electronic effects, it alters the redox potential of the guest (e.g., cucurbiturils cause a positive shift in the oxidation potential of ferrocene) or the current intensity (e.g., changes in peak current in cyclic voltammetry).

② Host-induced electron transfer

The host itself has redox activity (such as metal-organic frameworks, redox-modified cyclodextrins). After guest binding, the electron transfer kinetics of the host are changed through conformational adjustment or electronic coupling, which is manifested as a shift in peak potential or enhancement/inhibition of current response in the voltammogram.

2. Spatial regulation of electron transfer pathways

Core mechanism: Blocking/opening the electron transfer channel at the electrode-electrolyte interface through physical or chemical effects.

① Hindrance/promotion of interfacial electron transfer pathways

Host molecules (such as calixarenes, crown ethers) form an assembled layer on the electrode surface. After guest binding, through steric hindrance (e.g., inclusion of guests blocks active sites) or changes in hydrophobicity/hydrophilicity (e.g., exposure of the electrode surface), the Faraday current of probe molecules (such as $[Fe(CN)_6]^{3-/4-}$) decreases or increases, which is often used in sensor design.

② Proximity effect of catalytic centers

The host brings the catalytic center (such as metal porphyrins) close to the substrate (such as O_2, NO) through complexation, enhancing the efficiency of electrocatalytic reactions, which is manifested as an increase in catalytic current or a negative shift (reduction reaction)/positive shift (oxidation reaction) of the onset potential.

3. Molecular recognition effects of non-covalent interactions

Core mechanism: Changing the electrochemical microenvironment of the system (charge distribution, dielectric constant, etc.) through specific binding.

① Electrostatic and ionic bonding

Charged hosts (such as sulfonated calixarenes) bind to ionic guests (such as metal cations, organic ammonium salts) through Coulomb forces, changing the charge density on the electrode surface, leading to changes in double-layer capacitance or ionic conductivity, which can be detected by electrochemical impedance spectroscopy (EIS) or potentiometry.

② Hydrogen bonding and π interactions

Hosts (such as urea derivatives) stably bind to guests through hydrogen bonds, or aromatic hosts interact with guests through π-π stacking/cation-π interactions to change electron cloud distribution, causing a shift in redox potential (e.g., hydrogen bonds cause a negative shift in the reduction potential of quinone guests).

③ Hydrophobic inclusion and cavity effects

The hydrophobic cavity of macrocyclic hosts (such as cyclodextrins, cucurbiturils) encapsulates guests. By changing the solvation environment (e.g., reducing the hydration layer) or restricting molecular movement, it leads to a decrease in the diffusion coefficient of the guest (decrease in peak current) or enhancement of redox stability (e.g., the oxidized state of bipyridine derivatives has a longer lifespan after being encapsulated).

4. Dynamic binding and conformational regulation

Core mechanism: Realizing "on-off" signal responses through reversible binding or structural changes.

① Competitive displacement and indicator release

The host pre-binds an electroactive indicator (such as methylene blue). The target guest releases the indicator into the solution through competitive binding, resulting in a change in the concentration of the indicator on the electrode surface, which is manifested as a decrease in the reduction peak current (e.g., the β-cyclodextrin-quinine system displaces methylene blue).

② Conformational switching and mechanical movement

Flexible hosts (such as rotaxanes, foldamers) undergo conformational transitions (e.g., from "folded" to "extended") after guest binding, changing the distance between redox groups and the electrode, and regulating electron transfer efficiency (e.g., "on-off" states of current in molecular switches).

③ Stimulus-responsive assembly/disassembly

External stimuli (pH, light, ions) trigger the disintegration or reorganization of host-guest supramolecular assemblies, leading to abrupt changes in electrochemical signals (e.g., pH-induced deprotonation of carboxyl hosts, releasing guests to restore current).

5. Ion recognition and chemical environment modulation

Core mechanism: Changing local ion concentration or acid-base balance through selective binding.

① Ion-selective complexation

The selective binding of hosts (such as crown ethers, cryptands) to specific ions (such as K^+, Ca^{2+}) changes the ion activity on the electrode surface, leading to a potential response of ion-selective electrodes (e.g., valinomycin-K^+ complexation in potassium ion-selective electrodes produces a Nernst response).

② Proton coupling and pKa shift

Guest binding induces changes in the pKa of the host or guest (e.g., protonation of amino hosts after binding acidic guests). pH-responsive current or potential is achieved through pH-dependent redox reactions (e.g., quinone-hydroquinone conversion of phenols).

Summary:

Host-guest interactions ultimately manifest as quantitative changes in electrochemical signals (potential, current, impedance, capacitance) by regulating redox activity, electron transfer pathways, molecular recognition, dynamic conformation, and ionic environment. This is the core principle for constructing highly selective sensors, molecular switches, and electrocatalytic systems.

● What types of supramolecular hosts are known to bind to their guests primarily through cation-π interactions?

Supramolecular hosts that primarily bind to guests through cation-π interactions mainly include the following categories:

1. Calixarenes

macrocyclic compounds composed of phenol units linked by methylene bridges, with a bowl-shaped cavity. Their π-electron-rich cavity can encapsulate cations through cation-π interactions, especially alkali metal ions and ammonium ions. For example, p-tert-butylcalix[4]arene in a cone conformation can bind alkali metal cations.

2. Pillararenes

Rigid columnar macrocyclic compounds composed of hydroquinone units, with an electron-rich aromatic cavity. They can bind cations such as ammonium ions and alkali metal ions through cation-π interactions.

3. Cyclophanes

Macrocyclic compounds formed by two or more aromatic rings connected by aliphatic bridges. The space between the aromatic rings can accommodate cations, which are stabilized through cation-π interactions. Such as [2.2]paracyclophane.

4. Aromatic Cages

Including cryptophanes, cavitands, etc., which have cavities formed by aromatic walls. For example, deep-cavity cavitands based on resorcinarenes, whose cavities formed by aromatic panels can stabilize guest cations through cation-π interactions.

5. Molecular Tweezers and Clips

Open hosts with two parallel aromatic arms. Cations can be clamped between the aromatic arms and stabilized through cation-π interactions. For instance, Rebek's molecular tweezers can bind ammonium ions and alkali metal cations.

6. Other Types

① Fullerenes and carbon nanotubes: In some cases, their π-electron-rich carbon frameworks can bind cations on the surface or in the cavity through cation-π interactions, but this is less common in classical host-guest chemistry.

② Resorcinarenes and pyrogallolarenes: Formed by the condensation of resorcinol or pyrogallol with aldehydes, their bowl-shaped or vase-shaped cavities with exposed aromatic surfaces can stabilize cationic guests.

③ π-carbon-rich frameworks: Such as "bucky catchers", corannulene bowls, and belt-shaped macrocycles. Cages or bowls composed of sp²-hybridized carbon have highly polarized π surfaces and can bind alkali metals and ammonium ions

through cation-π interactions.

Summary：
The binding sites of these supramolecular hosts are mainly defined by converging electron-rich aromatic rings, with almost no classical donor atoms for ion-dipole coordination. Therefore, the complexation energy mainly comes from multiple cation-π contacts, and they have good binding effects especially on cationic guests such as alkali metal cations and ammonium ions.

● What are the main factors controlling host-guest interaction?

The main factors controlling host-guest interactions are as follows:

1. Structural complementarity
   ① Size and shape matching: The geometric size and contour of the host cavity must match those of the guest (such as the selective inclusion of hydrophobic guests by cyclodextrins) to avoid steric hindrance.
   ② Functional group arrangement: The spatial arrangement of binding sites (such as hydrogen bond donors/acceptors) must be complementary to the binding sites on the guest (chemical complementarity).
   ③ Surface complementarity: The chemical compatibility of the surfaces of the host and guest (hydrophobic/hydrophilic balance, charge distribution) directly affects the recognition efficiency.

2. Non-covalent interactions (core driving force)
   ① Hydrogen bonds: Highly directional, dominating specific recognition (such as N-H…O=C interactions between amide groups).
   ② Electrostatic and ionic interactions: Coulomb attraction between oppositely charged regions, regulated by pH and ionic strength.
   ③ Van der Waals forces and π-π stacking: Weak interactions that enhance binding through molecular surface contact or aromatic ring stacking.
   ④ Hydrophobic effect: In an aqueous environment, non-polar guests enter the hydrophobic cavity of the host, releasing high-entropy water and driving the formation of complexes (such as protein-ligand binding).

3. Electronic properties
   ① Polarity and hydrogen bond donor/acceptor sites — help ensure that attractive forces (rather than repulsive forces) dominate.
   ② Partial charge matching — aligning complementary regions of electron density on the host and guest can improve stability.

4. Thermodynamic and kinetic regulation
(1) Thermodynamic equilibrium

① Enthalpy change (ΔH): The strength of non-covalent bonds (such as strong hydrogen bonds providing negative ΔH).

② Entropy change (ΔS): Solvent molecule release or conformational freedom changes (such as less entropy loss when rigid hosts bind).

(2) Kinetic characteristics

The binding/dissociation rate affects complex stability (such as rapid exchange for sensors, slow exchange for drug delivery).

5. Environmental and medium influences

(1) Solvent effect

Polar solvents (such as water) may compete for hydrogen bonds, while non-polar solvents (such as chloroform) enhance hydrophobic interactions.

(2) External conditions

① pH and ionic strength: Change the ionization state of the host/guest (such as protonation of carboxyl groups under acidic conditions, weakening electrostatic interactions).

② Temperature: Affects the balance between ΔH and ΔS; high temperatures may disrupt weak interactions.

③ Light, redox events, or biomolecular triggers can be used in responsive host-guest assemblies, especially in the design of smart materials or targeted drug delivery systems.

6. Concentration and stoichiometry

① Concentration: Higher host/guest concentrations increase the possibility of complex formation.

② Stoichiometry: The composition ratio of the complex (1:1, 1:2, etc.) affects binding properties and potential functions (such as cooperativity).

7. Molecular properties of host and guest

① Host structure

Rigid hosts (such as calixarenes) have high selectivity, while flexible hosts (such as crown ethers) have strong adaptability but low specificity; functional group modification (such as introducing charged groups) can regulate binding sites.

② Guest properties

Flexible guests can optimize binding through conformational adjustment; substituents (such as long alkyl chains) enhance hydrophobic interactions and improve binding affinity.

Summary：

Host-guest interactions are jointly determined by structural matching, the combined force of non-covalent bonds, thermodynamic driving forces, and environmental regulation. The core lies in "complementarity" and "synergy of weak interactions".