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Abiotic guanidinium containing receptors for anionic species

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Contents

Abstract

In the field of molecular recognition, the guanidinium group has been established as a highly effective functional group in the binding of anionic guests. This moiety has been proven to form a strong interaction with anions through charge pairing and hydrogen bonding in competitive solvent systems. The group also features a high pK_a value, allowing for its utility over an expansive pH range. As a result of these qualities, the guanidinium group has become ubiquitous in literature involving the design and synthesis of receptor molecules for small target anions. An overview of the inclusion of the guanidinium group within synthetic receptor molecules is presented in this review article.

Keywords: Guanidinium; Anion; Receptor; Recognition; Sensing; Scaffold; Detection

1. Introduction

The guanidinium group has become an extremely advantageous functional group for the binding of anionic guest molecules in competitive media using synthetic host molecules. This moiety forms strong non-covalent interactions with anionic groups such as carboxylates, phosphates, sulfates and nitrates through hydrogen bonding and charge pairing interactions. This phenomenon is often present in biological systems, where guanidinium groups, in the form of the side chain of the amino acid arginine, are vital components of enzymatic catalytic domains that participate in the binding of anionic substrates [1,2].

The ability of the guanidinium group to bind anions arises from several factors. First, the group remains protonated over a wide pH range, including physiological pH, as it has a very high pK_a value of around 12–13. Also, the geometrical orientation of this functional group is such that it aligns well with the previously mentioned anionic groups, leading to a strong interaction. As a result of these advantages, chemists in the field of molecular recognition have designed and synthesized an array of receptors containing guanidiniums for the purpose of binding anions. In this review, examples of the inclusion of guanidinium groups within

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a variety of molecular architectures are discussed, as well as the data and understanding which these studies have yielded.

2. A bicyclic scaffold containing a guanidinium group

The most prevalent scaffold into which the guanidinium group has been included involves a bicyclic system, as seen in **1**. The geometry of this structure is beneficial for the formation of discrete complexes, as the guanidinium group is constrained such that only one face contains protons available for hydrogen bonding, and thus is accessible for complexation. The synthesis of this bicyclic system was reported by McKay and Kresling in 1957 [3], and then augmented by Schmidtchen for the purpose of developing receptors [4]. Here, chiral derivatives are accessible through the use of enantiomerically pure amino acid starting materials.

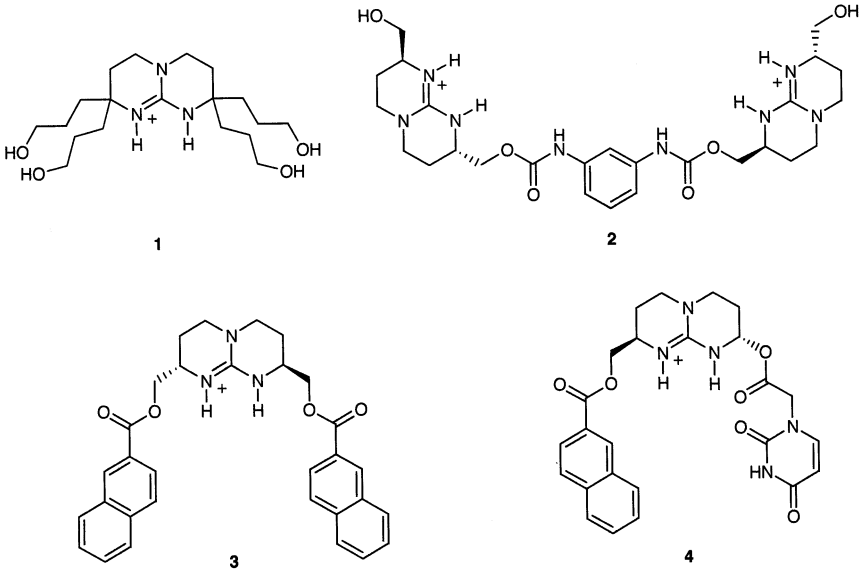
Following the publication of the synthesis, it was reported by Schmidtchen and co-workers that compounds containing this substructure, such as **1**, bound anions including *p*-nitrobenzoate in acetonitrile with a K_d estimated to be less than 10^{-4} M [5]. This was determined by ^{1}H-NMR binding studies in which resonances, especially the N–H signal, were found to shift upon introduction of a guest. Binding of a 1:1 stoichiometry was supported by the attainment of a crystal structure of the complex between **1** and acetate.

Building on this, compound **2**, which consists of two bicyclic guanidiniums attached via a urethane linker, was developed. Here, ^{1}H-NMR binding studies with dicarboxylates and biologically relevant phosphates pointed to the utility of this compound as a ditopic binder of anionic guests [6]. Also, the host was found to extract dicarboxylate guests from the aqueous phase into chloroform, and a recognition event was detected in aqueous media.

Concurrently, receptor **3**, containing naphthoyl substituents, was reported by de Mendoza and co-workers [7]. A 1:1 complex with *p*-nitrobenzoate was determined for this structure using ^{1}H-NMR titrations, as well as the extraction of the guest from aqueous to organic media. Interestingly, in this case, slight diastereomeric excesses were observed in the extraction of racemic salts, such as mandelate, naproxenate and tryptophan. This selectivity was ascribed to a three-point binding interaction between the host and guest.

Later, another derivative of this scaffold was synthesized which contained one naphthoyl as well as one uracil derived substituent appended to the bicyclic core (**4**) [8]. Here, the nucleotide derivative was attached in order to effect a base pairing interaction for the binding of guests containing an adenine moiety. In this report, the host was found to complex 3′-AMP, while showing little interaction with 3′,5′-cAMP.

Further development of the bicyclic guanidinium was performed through the attachment of a lipophilic substituent derived from Kemp's triacid which is attached to the core through a 3,6-diaminocarbazole linker (**5**) [9]. As anticipated, this compound was found to complex dideoxyadenine dinucleotide. In this case,

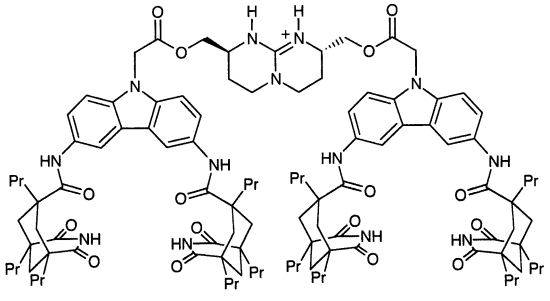


the carbazole and triacid derivative functionalities were included to interact with the bases on the corresponding guests, while the guanidinium group was expected to bind the phosphate linker. The successful attainment of these interactions in the complex was supported through NOE data.

Further development of this observation led to the corresponding host which contained only one carbazole-derivatized triacid arm [10]. This compound was designed to recognize cyclic adenosine monophosphate through interactions similar to the previous example. The resulting host was found to extract one equivalent of 2′,3′- or 3′,5′-cAMP into the organic layer with modest selectivity in favor of 2′,3′-cAMP. In a separate publication, the transport of adenine mono and dinucleoside monophosphates across model liquid membranes using these hosts was established [11]. Finally, another derivative with one binding arm and a hydroxyl group off of the bicyclic core was studied and found to be a water soluble receptor for cyclic AMP [12].

Another functionalization which yielded a receptor based on the bicyclic guanidinium core involved the introduction of one naphthalene ring as well as a crown ether into the system [13]. This structure (**6**) was designed to bind amino acids guests through interactions between the ammonium group and the host crown, the guest carboxylate with the host guanidinium group and π-stacking interactions between the aromatic groups. Selectivity in the binding of amino acids with aromatic sidechains (phenylalanine and tryptophan) over those with aliphatic chains provided evidence of associations involving the aromatic moieties. Also, chiral selectivity was observed as the chiral host showed selectivity for L-tryptophan from a racemic mixture, another piece of evidence which supports formation of all three interactions occuring in the host–guest complex. Another crown ether containing receptor was reported which also showed chiral discrimination [14]. In this case a 40% ee of L-phenylalanine over the D isomer was determined.

Receptor **7**, which contains two bicyclic guanidiniums linked by a naphthalene spacer, is another example based on this system [15]. This compound was found to bind a variety of nucleotides in methanol and water. Another study was performed in which a range of compounds was produced by varying the linker between the two subunits [16]. Here, the results revealed a large variation in the association constant of the host with anionic guests when altering the flexibility of the linker, although no direct correlation was observed.



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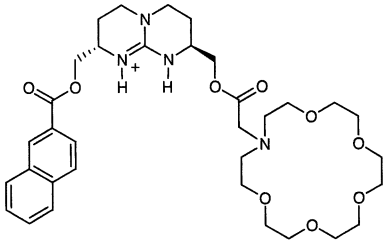

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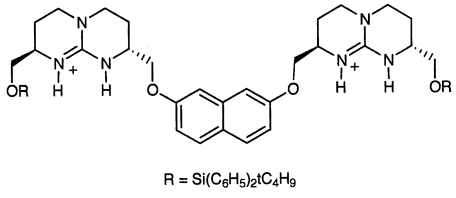

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The next advancement on this host scaffold was the introduction of a *closo*-borane substituent to a structure with two linked guanidinium groups (**8**) [17]. This alteration was made in an attempt to develop a bicyclic guanidinium host which had an overall neutral charge, but retained hydrophobic character. Although this host was found to dimerize, binding of anionic guests was still observed. Further investigations on this system

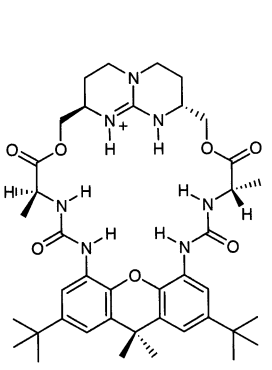
[18,19] using isothermal titration calorimetry (ITC) suggested that the association in these systems are primarily entropically driven.

In another example involving this scaffold with appended guanidinium groups, modified deoxycholic acid arms were appended to the core (**9**) to bind uronic acid guests [20]. The receptor was, indeed, found to bind these guests, showing a slight selectivity for glucuronate over galacturonate. However, the steroid arms were found to have only a small contribution in the formation of the complex. Studies regarding the optimal spacer between the bicyclic core and the pendant arms revealed that the shortest linker was most effective.

In a separate series of publications, oligomerization of the bicyclic guanidinium using thioether linkages was investigated [21,22]. The resulting structure, **10**, was determined to bind to tetraaspartate, and in doing so, increase the helicity of the short chain protein in aqueous and methanolic media, as evidenced by CD spectral changes. In these studies, NMR analysis was successfully utilized to affirm this, and to quantify the increase in helicity brought about by association of the receptor in methanol.

Further development of the bicyclic scaffold led to its inclusion within a macrocyclic system [23]. In this work, receptor **11** was designed and synthesized in which multiple functional groups capable of forming hydrogen bonds to anionic guest molecules are constrained within the macrocycle such that they point towards the interior. The host was analyzed with respect to the binding affinity towards a series of phosphate guests. While strong host–guest interactions were determined, some evidence suggested that counteranions, as opposed to the phosphate guests, reside within the macrocyclic cavity.

Finally, an example of the attachment of bicyclic guanidiniums to calix[4]arene was recently reported [24]. Here, receptor **12** and the corresponding monoguanidinium were found to enantioselectively extract amino acids into organic solvent. Results obtained indicated selectivity for both the binding and extraction of the L isomers, and up to 90% for phenylalanine.



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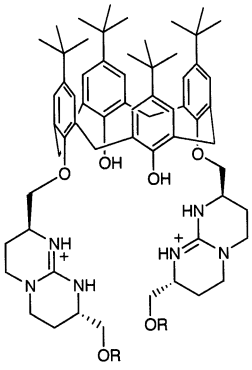

R = $Si(C_6H_5)_2{}^tBu$

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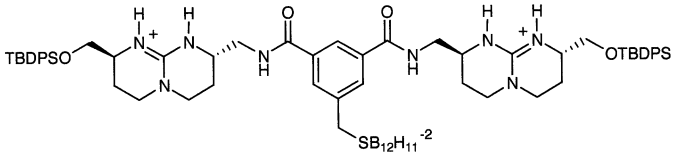
2.1. Catalysis using bicyclic guanidiniums

The study of the binding ability of the guanidinium group within the bicyclic architecture has also led to their implementation in reaction catalysis. In this work,



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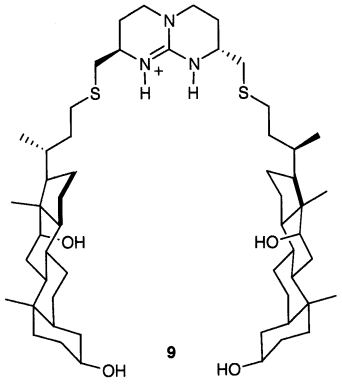

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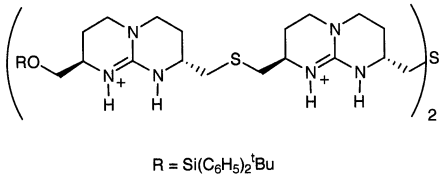

R = $Si(C_6H_5)_2{}^tBu$

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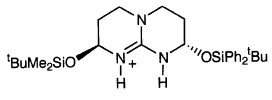
the ability to bind and thereby activate the guest towards nucleophilic substitution has been exploited. For example, de Mendoza and co-workers [25] first reported that a series of compounds, such as **13**, catalyze the addition of pyrrolidine to α,β-unsaturated lactones. The catalysis was quantified as an eightfold reduction in the half-life of the starting material using 0.1 equivalents of the bicyclic guanidinium catalyst in chloroform. This reduction in half-life dropped to about twofold when acetonitrile was used as solvent. More recent studies on this system showed that appending aromatic or amine groups to the bicycle increased its catalytic activity [26]. However, no chiral discrimination was observed in the catalysis.

Another study aimed at utilizing the bicyclic guanidinium as a catalyst involved an attempt to catalyze conjugate additions of nitroalkanes to electrophiles [27]. Here, the diphenyl-substituted bicycle (**14**) was found to bind nitronate anions in solution, and showed enantiomeric discrimination in the binding of racemic mixtures of carboxylate containing guests such as naproxenate. This compound was effective in the catalysis of the reaction between nitroalkanes and α,β-unsaturated ketones, expressing slight enantiomeric excesses (9–12%) in the products. In later studies with an unsubstituted bicyclic system, the guanidinium–nitronate anion interaction was quantified and the association constant found to be higher than that between thioether and nitronate, but lower than between the guanidinium group and carboxylate [28]. Also, an increase in C over O-alkylation of the anions was observed in the presence of the receptor.

Catalysis was also accomplished by appending the bicyclic guanidinium to a calix[6]arene, forming **15** [29]. This system successfully catalyzed the methanolysis of *p*-nitrophenylcarbonate in 1% methanol–chloroform. The catalyst was designed as a receptor for dioctanoyl-L-α-phosphatidylcholine, as this was considered a transition state analog for the hydrolysis of esters and carbonates. Here, the calix[6]arene moiety is included to interact with the trimethylammonium functionality on the guest, while the guanidinium group is to react with the guest phosphate. This catalyst acts as an artificial acetylcholinesterase, based on the ability of the host to bind a transition state analog of the enzymatic substrate.



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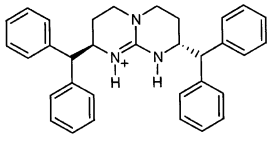

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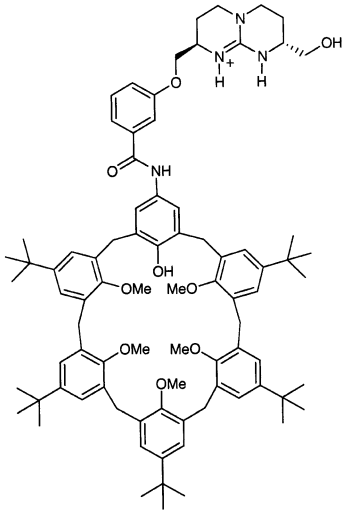

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2.2. Thermodynamics of the bicyclic guanidinium–guest interaction

As was previously mentioned, data regarding the thermodynamics of host–guest formation using the bicyclic guanidinium was reported which indicated that this association was primarily entropically driven. Further studies have elaborated on this work, leading to a more thorough understanding of the energetics involved in this complexation.

Hamilton and co-worker [30] examined the thermodynamic components of the binding of a series of guanidinium containing receptors, bicyclic, cyclic and acyclic, with acetate as guest. In this study, a dependence upon the guest counterion was discerned, as well as weak desolvation upon complexation in more competitive solvents. The compounds with the potential to form linear bidentate hydrogen bonds formed the strongest associations and generally the entropic and enthalpic terms were found to be favorable for binding. In more competitive media, such as methanol, though, the enthalpic contribution dropped, indicating that reorganization of solvent molecules drives the complexation in the higher dielectric solvents.

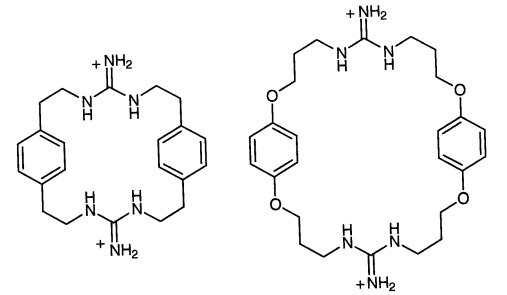
Another study on the energetics of these associations involved the analysis of a series of bicyclic guanidiniums with varying substituents towards the binding of benzoate in acetonitrile [31]. Here, the changing of substituents at locations outside of the binding pocket was found to alter the entropy and enthalpy of binding. Since these changes did not directly impede guest binding, the results were attributed to changes in the solvation of the system. Also, the associations were all found to generate positive entropic terms, suggesting that they are overall entropically driven. Finally, a dependence on the counterion in binding affinity was observed.

3. Receptors with guanidinium groups linked by rigid cyclic spacers

Another series of compounds with preorganized guanidinium groups involves a variety of cyclic spacers linking two of these functional groups. In these cases, rigid spacers with defined geometries are generally

implemented to preorganize the guanidinium moieties and thus provide the orientation for guest binding purposes. This was first exemplified in 1978 when Lehn and co-workers reported the incorporation of guanidinium groups into macrocycles **16**, **17**, and **18** [32]. The stability constants of these hosts with phosphate were determined through analysis of pH titration curves.

Later, Hamilton and co-workers [33] reported bis-guanidinium containing host **19** which they synthesized for the purpose of binding phosphodiester guests. The isophthaloyl spacer was used to situate the guanidinium groups in a suitable geometry to bind the trigonal-bipyramidal guests. Also, an acylguanidinium group, with a lower pK_a value than guanidinium, was used to facilitate proton transfer for potential catalysis. Proton NMR studies of this compound indicated that an intramolecular hydrogen bond is formed between the guanidinium group and the carbonyl oxygen, introducing rigidity into the structure.



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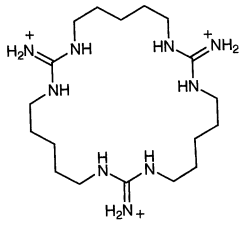

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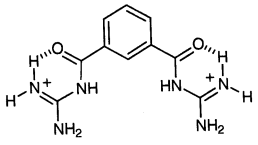


19

One guest was found to bind inside the cavity formed by the two guanidinium groups, while in the presence of excess guest, further binding occurs at the periphary. These second and third interactions were found to be much weaker than the first association. Further investigation of **19** revealed the ability of this structure to accelerate the inter and intramolecular phosphodiester cleavage of bound guests [34]. Indeed, a 700-fold increase over the absence of catalyst was observed in the presence of the receptor. With the corresponding monoguanidinium, however, this dropped drastically, as a 2.5-fold increase was determined over the uncatalyzed scenario.

The formation of a rigid cleft was also implemented in the design of **20**, in which octahydroacridine is used as the spacer between two aminoimidazoline groups [35]. The design of this host was such that these two functional groups would be oriented in a converging fashion, reminiscent of the geometry of the active site of staphylococcal nuclease. Thus, it was anticipated that this compound should enhance phosphodiester hydrolysis through stabilization of the dianionic phosphorane intermediate. In the binding studies with dibenzyl phosphate, both 1:1 and 2:1 guest to host stoichiometries were observed. However, only 1:1 binding was observed in more competitive media such as 2:1 DMSO–D_2O. In this solvent, **20** was found to bind the guest with an association constant of $3.6 \times 10^2\ M^{-1}$, while guanidinium chloride showed no binding. Analysis of a bis-aminoimidazoline control receptor having a pentane linker demonstrated that the octahydroacridine scaffold imparted 1.8 kcal mol^{-1} of stabilization in the binding of uridine 5′-monophosphate in water [36].

This work was later expanded upon with the study of the isolated stereosisomers of **20** and a related structure containing a hexahydrodicyclopenta[*b*,*e*]pyridine linker [37]. Here, the binding of the guest was found to be affected by the spacial orientation of the binding groups and the guest counterion. With tetraphenylboron counterion, the *meso* form of the host showed the highest affinity, while with chloride, the *d*,*l* forms were optimal for binding. This was ascribed to a specific interaction between chloride within the host–guest complex, which was observed in the X-ray crystal structure. Finally, in a later publication, this compound was found to catalyze the cleavage of mRNA with a 20-fold increase over the uncatalyzed reaction [38]. The extent of reaction was quantified using polyacrylamide gel electrophoresis of the reaction mixtures.

The guanidinium group has also been incorporated into melamine derivatives for binding 6-azaflavin [39]. Receptor **21**, developed for this purpose, was found to bind the guest in a 1:1 stoichiometry as evidenced by ^{1}H-NMR and absorbance shift data. Binding was found to increase with the number of hydrogen bonds and cooperativity was observed between the melamine and guanidinium moieties, leading to a large binding affinity in the formation of a quintuple hydrogen bond. Later, this sytem was also found to bind flavin semiquinone radicals with an even higher affinity than the oxidized species as evidenced by cyclic voltammetry [40]. This work was elaborated upon in the development of a series of analogous structures [41]. Here, the kinetic effect of hydrogen bonding in the oxidation activity of 6-azaflavin was further explored.

Compound **22**, which contains two guanidinium groups and a hydroxyl group, was developed by Göbel and co-worker [42] to study the binding and reaction with phosphates. While the host was found to bind phosphate guests, the inclusion of the guanidinium groups also led to increased reactivity of the hydroxyl

group towards phosphorylation. Here, the reaction was found to be 380,000 times faster than the corresponding non-guanylated reactant, phenylethanol. Thus, the guanidinium groups increase the reactivity through the binding and activation of the phosphate guest. Finally, this rate increase was determined to be much lower in the corresponding structure which contained acyclic guanidinium groups.

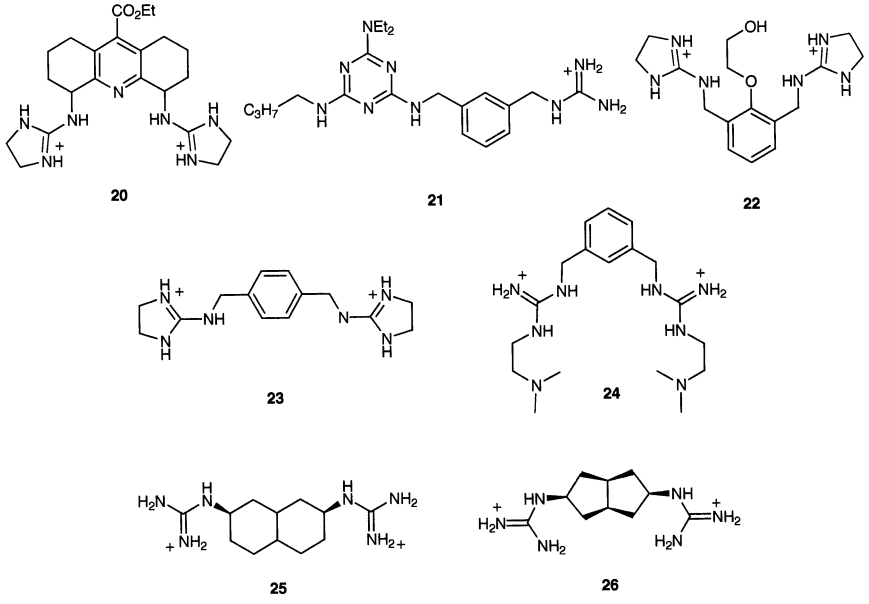
Another structure including two linked guanidinium groups was reported (**23**) using a *para*-substituted benzene linker [43]. In initial reports, this receptor was found to bind glutarate well in competitive media, with a association constant of 4.8×10^2 M^{-1} in 25% D_2O–DMSO solution. Later, ITC measurements were undertaken in order to further understand the binding in this system [44]. In this case, the guanidinium host was compared to the corresponding bis-urea and -thiourea hosts, with the bis-guanidinium forming a stronger interaction. Inspection of the binding energetics showed that upon increase of the polarity of the solvent, the binding became more endothermic overall with a favorable entropic term. The resulting conclusion is that in non-competitive media, binding is driven by strong hydrogen bonding, while in competitive solvents, solvent liberation is the driving force. This binding was also studied using non-aqueous affinity capillary electrophoresis, which showed a decrease in affinity with decreased dicarboxylate chain length [45].

One study of guanidinium containing receptors focused on structures which contained appended amine bases in order to increase phosphodiester catalysis [46]. A series of compounds was synthesized with identical bases: trialkylkamines, pyridines or imidazoles, attached to each of the guanidinium groups. These groups were used to bind phosphodiester guests, while the amino groups were incorporated to deprotonate a hydroxyl group on the substrate leading to catalysis. Here, the analog containing trialkylamine bases (**24**) was found to be the optimal catalyst. The efficacy of this catalysis was analyzed spectroscopically using 2-hydroxypropyl-*para*-nitrophenolphosphate as substrate.

Compound **25**, which contains two guanidinium moieties linked through a *trans*-decalin spacer is another example of the inclusion of this functional group within a scaffold [47]. This structure was found to bind phosphoric acid diester anions, however, only weak catalysis was observed.

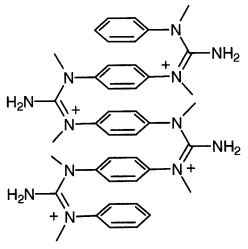
Receptor **26** was developed such that the two guanidinium groups would be oriented in parallel fashion to bind the side chains of helical peptides [48]. In order to perform this study, a family of 16-mer peptides was created in which the distance between aspartic acid residues in the chain was varied. Here, the receptor showed the highest affinity for the peptide with aspartic acid moieties three residues apart. Data also showed increased helicity upon addition of the host and that the binding occurred preferentially with the helical peptides. Further investigation with analogous hosts showed decreased affinity [49].

Two tetraguanidines, including **27**, were developed for the purpose of binding DNA [50]. The multilayered structure of these compounds makes them suitable for



binding into the minor grooves of double stranded DNA. Furthermore, sequence specificity for the 3′-GAA-5′ region was determined for the two structures.

In addition, the incorporation of guanidinium group into RNA has recently been reported [51]. In these RNA analogs, the phosphodiester linkages in the backbone have been replaced by guanidinium groups to form polycationic strands. The goal of this work is to obtain receptors with increased affinity towards DNA and RNA by increasing electrostatic interactions upon complexation.



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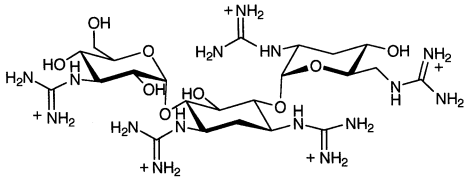

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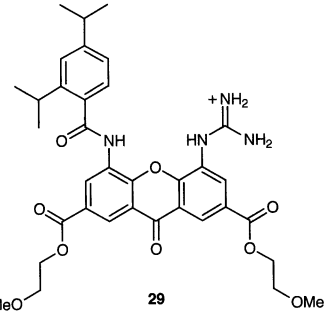

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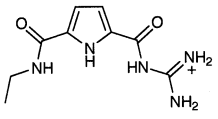

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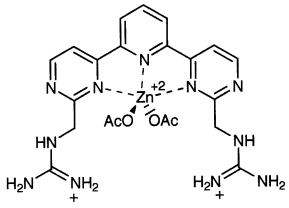

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Another example of the appending of guanidinium groups to biological compounds is the development of guanidinoglycosides by Tor and co-workers [52]. Here, guanidinium groups were formed on saccharide scaffolds such as tobramycin, in this case generating **28**. This was performed in an effort to increase affinity for RNA over the parent aminoglycosides through the introduction of guanidinium functionalities. The resultant compounds were found to have 5–10 times greater inhibitory activity.

Attachment of a guanidinium groups to xanthone led to the development of receptor **29** [53]. In this structure, extra interaction sites are built in: the xanthone NH hydrogen bond donor and the diisopropylbenzoate for stacking. Here, data in the analysis of certain carboxylates indicated a proton transfer from the host rather than a binding event. As a result, a series of acids with varying acidities were tested for binding affinity. In general, a large shift in binding affinity was observed with minimal changes in guest acidity. For instance, the association increased 1000-fold from decanoic acid (pK_a 4.9) to monochloroacetic acid (pK_a 2.86).

In another effort to increase the number of binding sites adjacent to a guanidinium groups, linkage to pyrrole was performed (**30**) [54]. This design was intended to utilize the pyrrole NH to facilitate the binding of *N*-acetyl amino acids. Binding affinities of these guests were found to be much greater than the parent acetyl guanidinium groups. Also, selectivity was determined for the phenylalanine derivative over other amino acids due to side chain interactions with the host. Later, a series of analogous compounds, including a chiral example, were studied [55]. In this case, slight enantioselectivites were detected. Finally, a related structure was found to self assemble in solution in an entropically driven oligomerization [56].

Host compound **31** was developed which utilizes a 2,2′:6,2″ terpyridine-type ligand complexing zinc [57]. This receptor was designed to bind aspartate and glutamate through three-point interactions in the host–guest complex. In order to measure the binding affinity, a dye-displacement assay was implemented, in which the binding of the guest is detected through the competitive displacement of a UV-active dye which has been pre-associated to the host. Using pyrocatechol violet as dye, a large spectral shift (ca. 200 nm) was observed upon binding of the guest due to displacement

of the dye from the metal center. The interaction of the guest amine group with zinc was found to dominate the binding. However, the association of the carboxylates of aspartate with the guanidinium groups were found to increase binding, leading to selectivity over other amino acids, including glutamate.

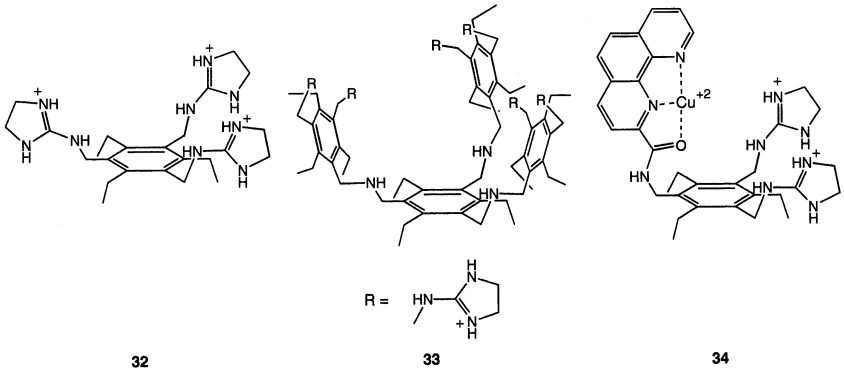
4. Guanidinium groups incorporated into the triethylbenzene scaffold

The triethylbenzene substructure is another molecular design in which guanidinium functionalities have been exploited in the development of host molecules. The utility of this platform has been recently reviewed [58]. In this scaffold, a benzene ring is functionalized such that the binding groups alternate with ethyl groups off the ring. Due to steric repulsions between the adjacent groups, a conformation in which the binding groups are oriented on one face of the ring with the ethyl groups on the opposite is preferentially formed. This effectively creates a cavity surrounded by the binding groups which is favorable for the association of small molecule guests.

In 1997, Anslyn and co-workers [59] reported **32**, based on the threefold substitution of the triethylbenzene scaffold with aminodihydroimidazolium groups. The target guest for this receptor was citrate as the geometrical orientation of the three guanidinium groups complemented the tris-carboxylate containing guest species. The host was found to have an association constant of $7 \times 10^3\ M^{-1}$ with citrate in pure water. The analogous host with ammonium groups was also tested, but the binding constant was less than half that of **32**, illustrating the importance of the guanidinium groups. Also, a model compound lacking the ethyl groups was studied with similar results, revealing the benefit of the steric gearing in the host. The structure of the complex was also verified through obtaining X-ray crystallographic data. Finally, this receptor was later found to successfully detect the citrate content of various sports drinks using fluorescence and absorbance analyses of a dye displacement assay [60].

Another receptor based on the triethylbenzene scaffold is compound **33** [61]. This structure was designed to bind the polyanionic secondary messenger inositol triphosphate (IP_3) as it contains six guanidinium groups in such a geometry as they are oriented towards the inside of the cavity. Again, a dye displacement assay was utilized to probe the affinity of the host for the guest, and indicated a strong association. The corresponding ammonium analog was also tested and was found to have similar binding affinities to **33**, but was less specific as to which guests it bound. The sensitivity of the analysis was increased through displacement of a fluorescent dye upon analyte binding.

The next receptor of this type reported (**34**) included two aminoimidazolium groups and a phenanthroline–copper complex [62]. In this case, the metal complex was introduced both as an extra binding site for the citrate guest and to allow for the signaling of binding.



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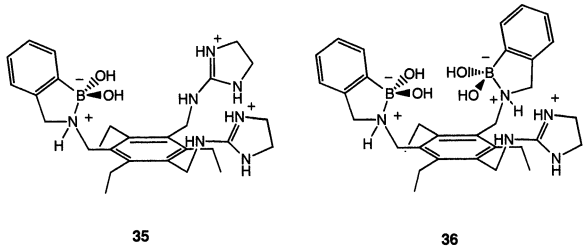

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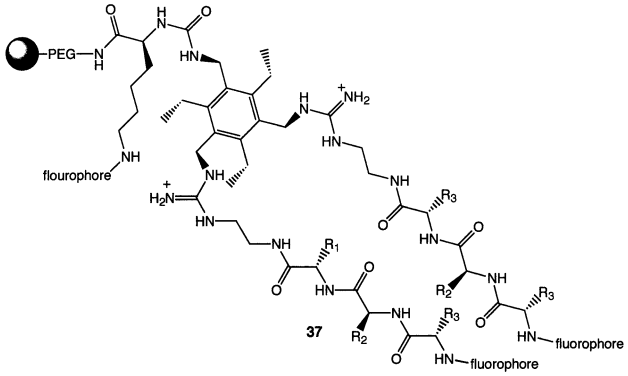
Introduction of the metal to the phenanthroline led to the quenching of the ligand fluorescent signal. The binding of citrate could then be observed due to the reemergence of this signal upon binding of the guest to the metal center. This analysis was used to determine the binding of citrate to the host and was successfully utilized to quantify citrate in sports drinks.

Receptor **35** exemplifies further exploration of this scaffold [63]. In addition to the two aminoimidazolium groups, a boronic acid functionality is appended to the scaffold to bind diol containing guests. The chosen guest in this case was tartrate, as the two carboxylates were complimented by the guanidinium groups and the diol by the host boronic acid. The linker to the boronic acid also features an amine and a benzene ring to geometrically orient the group towards the cavity. For the dye displacement assay, alizarin complexone was chosen as it contained the same functionalities as the guest, but was expected to show weaker affinity due to the spacial orientation of these groups. Indeed, visible color changes were observed upon guest introduction. The results indicate that tartrate was selectively bound over succinate, but not over malate. Nevertheless, the receptor was successfully used to determine the tartrate–malate concentration in grape-derived beverages such as wines.

Further elaboration on this work led to the development of host compound **36**, which contains two boronic acids as well as one aminoimidazolium group [64]. This host was targeted at the binding of gallate-like molecules. The detection of these guests is attractive as their presence is used in the determination of the age of scotch whiskies. Dye displacement using pyrocatechol violet signalled the binding of these compounds to the host. Applying these results, the receptor was successfully implemented in the determination of the ages of scotch whiskies.

Another approach to obtaining a receptor of this type involved the formation of a library of compounds based on a rationally designed core [65]. The goal of these studies was to develop a sensor for ATP. The designed core of this structure consisted of a resin-bound triethylbenzene scaffold with two guanidinium groups. A combinatorial library was then obtained by growing peptide arms off the guanidinium groups. Finally, fluorophores were added to the peptide arms and to a lysine linker for detection purposes. The resulting library was screened fluorometrically for ATP binding through inspection using UV light to obtain potential hosts. These were then sequenced and resynthesized. In the final analysis, receptor **37** with Ser–Tyr–Ser residues on the peptide arms showed selectivity for ATP over AMP and GTP.

A similar study previously reported involved the analysis of guanidinium tweezer compound **38** [66]. This compound was screened with a 1000 member resin-bound tripeptide library biased with hydrophobic residues. The receptor was functionalized with a dansyl fluorophore for sensing purposes and beads that exhibited fluorescence following addition of the receptor were selected. Analysis of hits showed trends as 95% of the bound peptides contained valine at the C-terminus and 40% included the *t*-butyl ester of glutamate in the central position. The reverse experiment was also attempted in which a 125 member library based on **38** was synthesized and screened with a dansylated tripeptide guest from the initial study. However, no binding was observed in this case.



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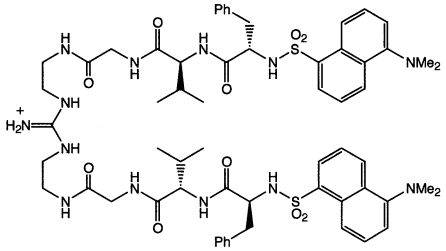

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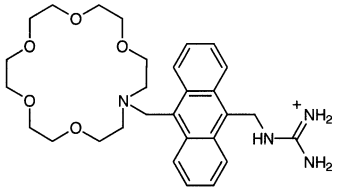
5. Receptors with covalently attached signalling groups

Another series of guanidinium containing receptors reported have featured the covalent attachment of this binding unit to known signalling devices. In 1996, de Silva et al. [67] reported a receptor of this type, **39**, with azacrown, anthracene and guanidinium groups linked in series. This host was designed to complex γ-aminobutyric acid (GABA) through interactions between the host guanidinium group and guest carboxylate as well as the host azacrown and the guest ammonium. The anthracene moiety was included so that binding of the guest by the azacrown amine disrupted photoinduced electron transfer (PET) quenching of the anthracene fluorescence. As was expected, binding of the guest was detected by an increase in fluorescence. A control compound lacking the guanidinium group showed no fluorescence change in the presence of GABA, while

glutamic acid, the physiological precursor to GABA also had no detectable effect.

Another example of this concept was published by Beer et al. [68], compound **40**, which consists of a guanidinium group linked to a ferrocene unit. This host bound inorganic phosphate guest through hydrogen bonding to the guanidinium group. Upon complexation, the redox signal of the ferrocene was affected as oxidation of the group was facilitated by the introduction of the negative charge of the guest. Hence, the binding of the guest could be detected through redox analysis. Next, compound **41** was established as a luminescent sensor for phosphate and phosphodiester guests [69]. Here, two neutral acylaminoimidazolinegroups were linked to bipyridine, which then became one unit of a tris-bipyridine ruthenium(II) complex. Binding was detected by alteration of both the absorbance and fluorescent signals of the host, with a large fluorescence change potentially caused by rigidification of the complex.

Later, receptor **42** was reported containing a guanidinium group linked to pyrene [70]. Upon the formation of a 2:1 complex of the host to inorganic phosphate, a large change in the ratio of the excimer and monomer emission of the hosts was observed. With monoanionic guests, however, this change was not observed. Compound **43**, which contains two iminoylthioureas, and the corresponding compound with 1,2,4-thiadiazoles have been reported [71]. Binding of carbonate, bicarbonate and hydrogen phosphate was achieved with these hosts. Fluorescence enhancements and spectral shifts occurred upon association.



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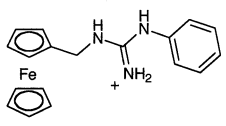

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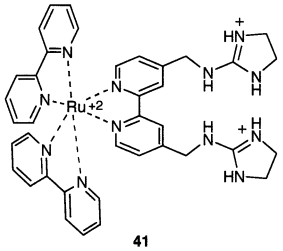

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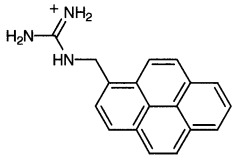

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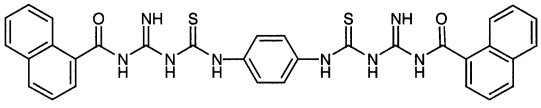

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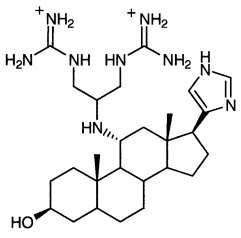
6. Guanidinium groups attached to steroid scaffolds

Steroids represent another class of platforms to which guanidinium groups have been attached in order to achieve anion binding. The utility of steroid derivatives for molecular engineering has been reviewed [72]. Structures in which bicyclic guanidiniums were attached to steroids were previously discussed in the bicyclic guanidinium section.

In this realm, receptor **44**, with two adjacent guanidinium groups protruding from a steroid scaffold, was reported [73]. Here, 12 guanidinium containing molecules with widely varying structures were analyzed for cleavage of the RNA model compound 2-hydroxypropyl *para*-nitrophenyl phosphate (HPNPP). Of these, steroid-based **44** was found to be optimal, showing a 10-fold increase in the rate of cleavage of HPNPP over simple bis(guanidinium) compounds and threefold faster uridylyl(3′,5′)uridine cleavage over background hydrolysis.

Another example is steroid **45**, developed by Davis and Lawless [74]. This structure contains a guanidinium group and two carbamate functional groups. This was used in the enantioselective recognition and extraction of *N*-acetyl amino acids from aqueous solution into chloroform. Selectivity of 9:1 in the extraction of L over D isomers was achieved for valine and phenylalanine, while other amino acids also showed good selectivity. This work was further developed with the production and analysis of a series of compounds based on this example. Here, up to 10:1 enantioselectivity was observed. More recently, further studies of this type have been performed [75].



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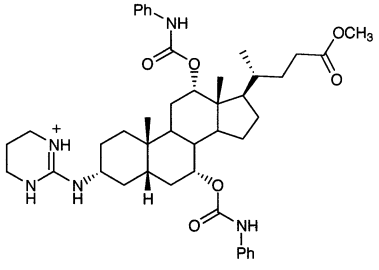

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7. Amphiphilic guanidinium monolayers

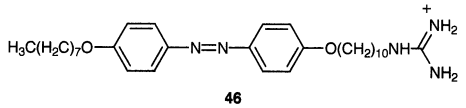
Another series of investigations involving guanidinium groups is the inclusion of this group within amphiphilic molecules designed to form monolayers at the air | water interface. Recognition of anionic guests by these monolayers has been determined to occur at this interface. For example, Kunitake and co-workers have reported the amphiphilic guanidinium containing

receptor **46** [76]. This structure forms a monolayer in pure water. Binding of the phosphate guests ATP and AMP was detected via changes in the π–A curve, which relates to the molecular packing in the monolayer. Here, ATP led to a condensed curve, while AMP caused expansion of the curve, revealing that the identity of the guest could be discerned by the type of signal change in the monolayer.

Langmuir–Blodgett films of **46** were produced and analyzed using XPS and FT-IR. A 1:3 ratio of ATP to amphiphile was observed, while 1:1 associations were determined for AMP. Binding constants for the complexation were quantified as 1.7×10^7 and 3.2×10^6 M^{-1} for ATP and AMP, respectively, although these constants cannot be directly compared to those in solution phase systems. Also, it was deduced that the binding occurred through a phosphate–guanidinium interaction at the air | water interface, while the counter-anion was not found to be involved in the association. In further studies of this structure, an enhanced affinity for UMP relative to AMP was reported [77].

In a later publication, new amphiphiles containing octadecyl (**47**) and dioctadecyl guanidinium amphiphiles were designed, synthesized and studied [78]. From this, it was reported that the octadecylguanidinium monolayer showed greater expansion of molecular area than the dioctadecylguanidinium system. In this case, the binding of a series of dicarboxylate guests was followed. Again, the change in π–A isotherm was different depending on the guest being complexed. In general, the molecular area of the monolayer increased with the number of methylenes in the spacer from oxalate to adipate. Also, oxalate and phthalate caused condensed monolayers, while *cis*-1,2-cyclohexanedicarboxylate and 1,1-cyclohexanediacetate led to expansion, once again illustrating the sensitivity of this method to the structure of the guest.

Another study involving amphiphilic guanidinium groups focused on the recognition of aqueous dipeptides at the air | water interface [79]. For this purpose, mixed monolayers containing compound **48**, with a guanidinium group, and a dioctadecyl glycylglycinamide amphiphile were studied. Binding of GlyLeu dipeptide to this mixed monolayer was quantified ($K_a = 6.4 \times 10^3$ M^{-1}) using a Langmuir isotherm, and the two monolayers cooperatively bound this substrate. This binding affinity was greatly enhanced over other single-component and mixed monolayers. Also, the binding of the LeuGly dipeptide dropped by one-third, indicating the specificity of the mixed monolayer for the structure of the guest.



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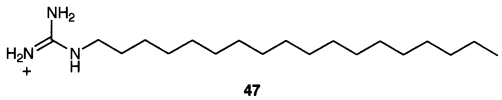

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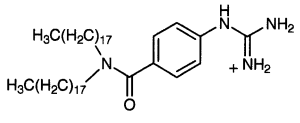

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8. Outlook

In the field of anionic guest recognition using guanidinium functionalized receptors, a wide variety of hosts have been designed and studied. In this research, concepts such as preorganization, introduction of extra binding sites for guests, catalytic activity, and thermodynamics of binding have been explored in depth, leading to a vast increase in the understanding of the behavior of these systems. In spite of these advancements, the goals which drive this realm of research, such as the mimicking of the binding selectivity and catalysis of biological systems, have yet to be fully realized. Specifically, further advances in the binding affinity of host–guest complexes in aqueous media, increased selectivity of receptors for a given substrate, including enantiodiscrimination, further exploration of the catalytic abilities of guanidinium containing compounds and an even deeper understanding of the chemical principles which drive these interactions would all be beneficial. Thus, this field remains open for new and creative research geared towards achieving these goals.

References

[1] D.W. Christianson, W.N. Lipscomb, Acc. Chem. Res. 22 (1989) 62.
[2] F.A. Cotton, E.E. Hazen, Jr., M.J. Legg, Proc. Natl. Acad. Sci. 76 (1979) 2551.
[3] A.F. McKay, M.E. Kreling, Can. J. Chem. 35 (1957) 1438.
[4] F.P. Schmidtchen, Chem. Ber. 113 (1980) 2175.
[5] G. Müller, J. Riede, F.P. Schmidtchen, Angew. Chem. Int. Ed. Engl. 27 (1988) 1516.
[6] F.P. Schmidtchen, Tetrahedron Lett. 30 (1989) 4493.
[7] A. Echavarren, A. Galán, J.-M. Lehn, J. de Mendoza, J. Am. Chem. Soc. 111 (1989) 4994.
[8] A. Galán, E. Pueyo, A. Salmerón, J. de Mendoza, Tetrahedron Lett. 15 (1991) 1827.
[9] A. Galán, J. de Mendoza, C.M. Bruix, G. Deslongchamps, J. Rebek, Jr., J. Am. Chem. Soc. 113 (1991) 9421.
[10] G. Deslongchamps, A. Galán, J. de Mendoza, J. Rebek, Jr., Angew. Chem. Int. Ed. Engl. 31 (1992) 61.
[11] C. Andreu, A. Galán, K. Kobiro, J. de Mendoza, T.K. Park, J. Rebek, Jr., A. Salmerón, N. Usman, J. Am. Chem. Soc. 116 (1994) 5501.
[12] Y. Kato, M.M. Conn, J. Rebek, Jr., J. Am. Chem. Soc. 116 (1994) 3279.

[13] A. Galán, D. Andreu, A.M. Echavarren, P. Padros, J. de Mendoza, J. Am. Chem. Soc. 114 (1992) 1511.
[14] A. Metzger, K. Gloe, H. Stephan, F.P. Schmidtchen, J. Org. Chem. 61 (1996) 2051.
[15] P. Schliessl, F.P. Schmidtchen, J. Org. Chem. 59 (1994) 509.
[16] W. Peschke, F.P. Schmidtchen, Tetrahedron Lett. 36 (1995) 5155.
[17] M. Berger, F.P. Schmidtchen, J. Am. Chem. Soc. 118 (1996) 8947.
[18] M. Berger, F.P. Schmidtchen, Angew. Chem. Int. Ed. 37 2694.
[19] M. Berger, F.P. Schmidtchen, J. Am. Chem. Soc. 121 (1999) 9986.
[20] M. Segura, V. Alcázar, P. Padros, J. de Mendoza, Tetrahedron 53 (1997) 13119.
[21] M.W. Peczuh, A.D. Hamilton, J. Sánchez-Quesada, J. de Mendoza, T. Haack, E. Giralt, J. Am. Chem. Soc. 119 (1997) 9327.
[22] T. Haack, M.W. Peczuh, X. Salvatella, J. Sánchez-Quesada, J. de Mendoza, A.D. Hamilton, E. Giralt, J. Am. Chem. Soc. 121 (1999) 11813.
[23] V. Alcázar, M. Segura, P. Prados, J. de Mendoza, Tetrahedron Lett. 39 (1998) 1033.
[24] L. Fang, G.-Y. Lu, W.-J. He, Z.-S. Wang, L.-G. Zhu, Chin. J. Chem. 19 (2001) 317.
[25] V. Alcázar, J.R. Morán, J. de Mendoza, Tetrahedron Lett. 36 (1995) 3941.
[26] M.M. Portugués, V. Alcázar, P. Prados, J. de Mendoza, Tetrahedron 58 (2002) 2951.
[27] A.P. Davis, K.J. Dempsey, Tetrahedron: Asymmetry 6 (1995) 2829.
[28] B.R. Linton, M.S. Goodman, A.D. Hamilton, Chem. Eur. J. 6 (2000) 2449.
[29] F. Cuevas, S.D. Stefano, J.O. Magrans, P. Prados, L. Mandolini, J. de Mendoza, Chem. Eur. J. 6 (2000) 3228.
[30] B. Linton, A.D. Hamilton, Tetrahedron 55 (1999) 6027.
[31] M. Haj-Zaroubi, N.W. Mitzel, F.P. Schmidtchen, Angew. Chem. Int. Ed. Engl. 41 (2002) 104.
[32] B. Dietrich, T.M. Flyes, J.-M. Lehn, L.G. Pease, D.L. Fyles, J. Chem. Soc. Chem. Commun. (1978) 934.
[33] R.P. Dixon, S.J. Geib, A.D. Hamilton, J. Am. Chem. Soc. 114 (1992) 365.
[34] V. Jubian, R.P. Dixon, A.D. Hamilton, J. Am. Chem. Soc. 114 (1992) 1120.
[35] K. Ariga, E.V. Anslyn, J. Org. Chem. 57 (1992) 417.
[36] D.M. Perreault, X. Chen, E.V. Anslyn, Tetrahedron 51 (1995) 353.
[37] D.M. Kneeland, K. Ariga, V.M. Lynch, C.-Y. Huang, E.V. Anslyn, J. Am. Chem. Soc. 115 (1993) 10042.
[38] D.M. Perreault, L.A. Cabell, E.V. Anslyn, Bioorg. Med. Chem. 5 (1997) 1209.
[39] N. Tamura, T. Kajiki, T. Nabeshima, Y. Yano, J. Chem. Soc. Chem. Commun. (1994) 2583.
[40] T. Kajiki, H. Moriya, S. Kondo, T. Nabeshima, Y. Yano, Chem. Commun. (1998) 2727.
[41] T. Kajiki, H. Moriya, K. Hoshino, T. Kuroi, S. Kondo, T. Nabeshima, Y. Yano, J. Org. Chem. 64 (1999) 9679.
[42] M.-S. Muche, M.W. Göbel, Angew. Chem. Int. Ed. Engl. 35 (1996) 2126.
[43] E. Fan, S.A. Van Arman, S. Kincaid, A.D. Hamilton, J. Am. Chem. Soc. 115 (1993) 369.
[44] B.R. Linton, M.S. Goodman, E. Fan, S.A. van Arman, A.D. Hamilton, J. Org. Chem. 66 (2001) 7313.
[45] M.B. Peddicord, S.G. Weber, Electrophoresis 23 (2002) 431.
[46] V. Jubian, A. Veronese, R.P. Dixon, A.D. Hamilton, Angew. Chem. Int. Ed. Engl. 34 (1995) 1237.
[47] R. Gross, J.W. Bats, M.W. Göbel, Liebigs Ann. Chem. (1994) 205.
[48] J.S. Albert, M.S. Goodman, A.D. Hamilton, J. Am. Chem. Soc. 117 (1995) 1143.
[49] J.S. Albert, M.W. Peczuh, A.D. Hamilton, Bioorg. Med. Chem. 5 (1997) 1455.
[50] R. Fukutomi, A. Tanatani, H. Kakuta, N. Tomioka, A. Itai, Y. Hashimoto, K. Shudo, H. Kagechika, Tetrahedron Lett. 39 (1998) 6475.
[51] (a) D.A. Barawkar, B. Linkletter, T.C. Bruice, Bioorg. Med. Chem. Lett. 8 (1998) 1517;
(b) N. Kojima, I.E. Szabo, T.C. Bruice, Tetrahedron 58 (2002) 867.
[52] N.W. Luedtke, T.J. Baker, M. Goodman, Y. Tor, J. Am. Chem. Soc. 122 (2000) 12035.
[53] M. Martín, M. Almaraz, J. Hernández, A. Tejeda, M.C. Caballero, J.R. Morán, Heterocycles 50 (1999) 47.
[54] C. Schmuck, Chem. Commun. (1999) 843.
[55] C. Schmuck, Chem. Eur. J. 6 (2000) 709.
[56] C. Schmuck, Tetrahedron 57 (2001) 3063.
[57] H. Aït-Haddou, S.L. Wiskur, V.M. Lynch, E.V. Anslyn, J. Am. Chem. Soc. 123 (2001) 11296.
[58] G. Hennrich, E.V. Anslyn, Chem.-Eur. J. 8 (2002) 2119.
[59] A. Metzger, V.M. Lynch, E.V. Anslyn, Angew. Chem. Int. Ed. Engl. 36 (1997) 862.
[60] A. Metzger, E.V. Anslyn, Angew. Chem. Int. Ed. Engl. 37 (1998) 649.
[61] K. Niikura, A. Metzger, E.V. Anslyn, J. Am. Chem. Soc. 120 (1998) 8533.
[62] L.A. Cabell, M.D. Best, J.J. Lavigne, S.E. Schneider, D.M. Perreault, M.-K. Monahan, E.V. Anslyn, J. Chem. Soc. Perkin Trans. 2 (2001) 315.
[63] J.J. Lavigne, E.V. Anslyn, Angew. Chem. Int. Ed. Engl. 38 (1999) 3666.
[64] S.L. Wiskur, E.V. Anslyn, J. Am. Chem. Soc. 123 (2001) 10109.
[65] S.E. Schneider, S.N. O'Neil, E.V. Anslyn, J. Am. Chem. Soc. 122 (2000) 542.
[66] M. Davies, M. Bonnat, F. Guillier, J.D. Kilburn, M. Bradley, J. Org. Chem. 63 (1998) 8696.
[67] A.P. de Silva, H.Q.N. Gunaratne, C. McVeigh, G.E.M. Maguire, P.R.S. Maxwell, E. O'Hanlon, Chem. Commun. (1996) 2191.
[68] P.D. Beer, M.G.B. Drew, D.K. Smith, J. Organomet. Chem. 543 (1997) 259.
[69] S. Watanabe, O. Onogawa, Y. Komatsu, K. Yoshida, J. Am. Chem. Soc. 120 (1998) 229.
[70] S. Nishizawa, Y. Kato, N. Teramae, J. Am. Chem. Soc. 121 (1999) 9463.
[71] G. Hennrich, H. Sonnenschein, U. Resch-Genger, Tetrahedron Lett. 42 (2001) 2805.
[72] A.P. Davis, Chem. Soc. Rev. (1993) 243.
[73] T. Oost, A. Filippazzi, M. Kalesse, Liebigs. Ann. (1997) 1005.
[74] A.P. Davis, L.J. Lawless, Chem. Commun. (1999) 9.
[75] B. Baragaña, A.G. Blackburn, P. Breccia, A.P. Davis, J. de Mendoza, J.M. Padrón-Carrillo, P. Prados, J. Riedner, J.G. de Vries, Chem. Eur. J. 8 (2002) 2931.
[76] D.Y. Sasaki, K. Kurihara, T. Kunitake, J. Am. Chem. Soc. 113 (1991) 9685.
[77] D.Y. Sasaki, K. Kurihara, T. Kunitake, J. Am. Chem. Soc. 114 (1992) 10994.
[78] A. Kamino, H. Koyano, K. Ariga, T. Kunitake, Bull. Chem. Soc. Jpn. 69 (1996) 3619.
[79] K. Ariga, A. Kamino, X. Cha, T. Kunitake, Langmuir 15 (1999) 3875.