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The betaine pool: molecular guests in medicinal chemistry and molecular hosts in supramolecular chemistry

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Abstract

The most relevant aspects of azolium(pyridinium)azolate betaines with a variety of spacers **1** is reviewed. An interdisciplinary approach to their chemistry is currently directed towards medicinal chemistry, supramolecular chemistry and advanced organic materials.

Keywords: Betaines; Imidazolium(pyridinium)azolate inner salts; Azolylimidazolium(pyridinium) salts; Biological properties; Molecular recognition; Advanced materials

A survey of possible novel heterocyclic structures shows that betaines form a pool of highly dipolar chemical entities with low molecular weight [1,2]. Both fundamental and practical interests in heterocyclic betaines are due to their dipolar character, the driving force that modulates their chemistry.

For some years we have focused our attention on heterocyclic betaines of azolium(pyridinium)azolate with a variety of spacers **1** together with their protonated counterparts **2** [3,4]. The chemistry of this ensemble of highly dipolar compounds is described in the six interconnecting boxes shown in Fig. 1.

1. Synthesis and structure

The general synthetic pathway for the inner salts **1** consists in the deprotonation of their precursors: the azolylimidazolium (pyridinium) salts **2** (Fig. 2). The apparent directness of this transformation does not imply that it is either simple or trivial. The method of choice to remove the inorganic counteranion and the acidic NH proton from the azole ring is based on the use of strongly basic anion-exchange resins (OH^- form) [4–6]. Therefore, the key precursors are the quaternary salts **2** and their synthesis has been accomplished using the alternatives shown in Fig. 2.

Among these synthetic approaches to the target quaternary heteroaromatic salts **2**, the most attractive route is the formation of the π-excessive ring from appropriate functionalised quaternary intermediates **3**, and this needs to be studied in detail for each case [4–7]. This pathway has been followed efficiently for the synthesis of an ensemble of 2-substituted benzimidazoles with different spacers (Fig. 3).

The structure and physical facets of betaines **1** are gathered in Fig. 4; the highly dipolar character has a powerful influence on their physical and chemical behaviour. Indeed, this ensemble of compounds **1** offers the unusual possibility of the coexistence of two terminal rings, joined through different spacers, with opposite characteristics within heteroaromatic systems: a π-deficient nucleus (cation, acceptor [8]) and a π-excessive nucleus (anion, donor [8]).

We have studied the physico–chemical properties, mainly in liquid solution, with the aim of gaining further insight into these dipolar building blocks through their role in noncovalent interactions both in liquid solution and in the solid state. The results validate their intrinsically high dipolar nature, which implies strong intermolecular forces without prejudice to their propensity to hydration. For reliable interpretation of data measured in solution, however, not only the intermolecular solute–solute interactions but also the solute–solvent interaction forces must be taken into

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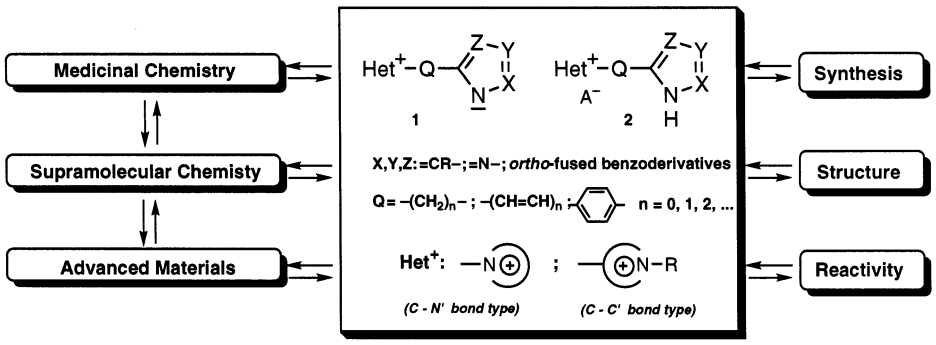


Fig. 1. Chemistry of heterocyclic betaines [4].

account [3,9]. To reduce the perturbing dominance of these effects as much as possible, the anhydrous sample **1** must be used at high dilution, and the water of the solvent should be reduced.

Experimental molecular geometries (X-ray analysis) and dipole moments of **1** form the basis of theoretical studies. The method of choice to predict the trends of betaines **1** observed experimentally is the AM1 SCF-MO [4,5].

2. Reactivity aspects

Heterocyclic betaines and compounds with betaine character of general type **1** provide an attractive basic set for the study of their chemical reactivity in both ground and excited states (Fig. 5). The background offered by Kauffmann's areno-analogy principle [8] permits heteroaromatic fragments to be related with classical functional ones. Accordingly, the cationic and anionic heteroaromatic components of betaines **1** are nonclassical functional groups and their susceptibility towards specific organic reactions should be modulated for synthetic applications [10,11].

Thus, both the π-excessive nucleus and the π-deficient one modulates its reactions and transformations in response to the other, as well as the nature of the spacer and the link with the quaternary ring. Moreover, the basicity of the azole anion is that of a classical azolate perturbed by the spacer [3,12].

The imidazolium quaternary moiety has proved to be fairly stable within betaines **1** and derivatives **2**. The plausible formation of by-products through generation of stable *N*,*N*′-disubstituted imidazol-2-ylidenes (stable nucleophilic carbenes [13–15]) has not been detected to date [4,6].

The most relevant facets of betaine chemical behaviour studied so far are:

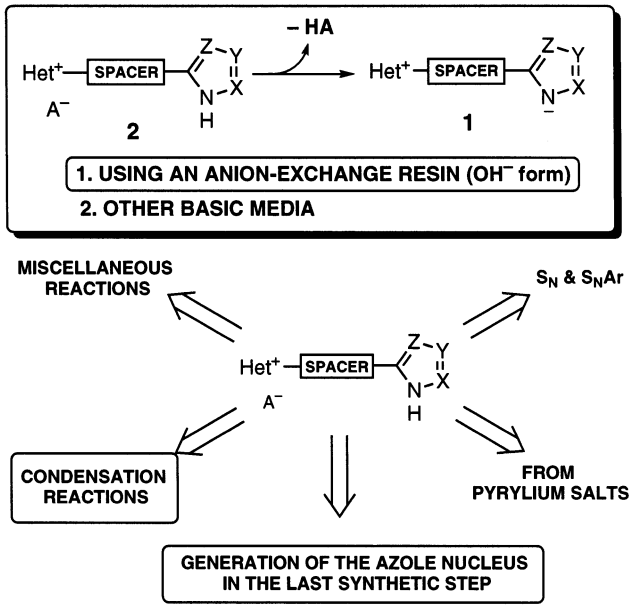


Fig. 2. Synthetic approaches to the synthesis of heterocyclic betaines **1** and their precursors the azolylimidazolium(pyridinium) salts **2**.

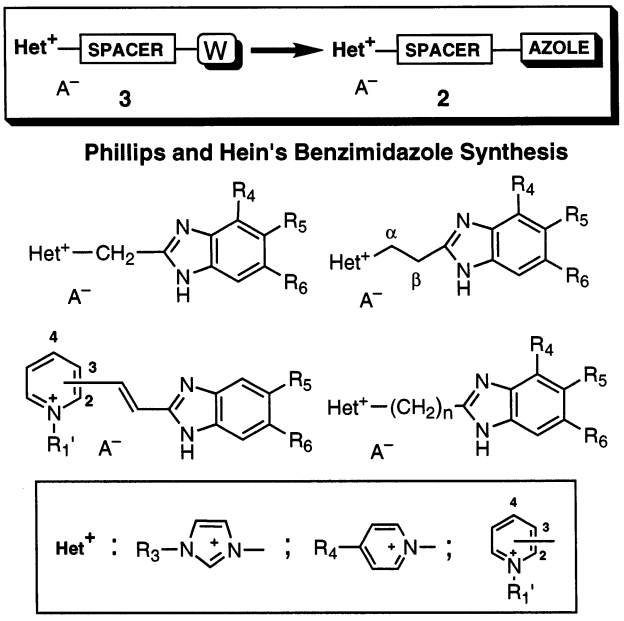


Fig. 3. Phillips and Hein's benzimidazole synthesis: generation of the azole nucleus in the last synthetic step [4–7].

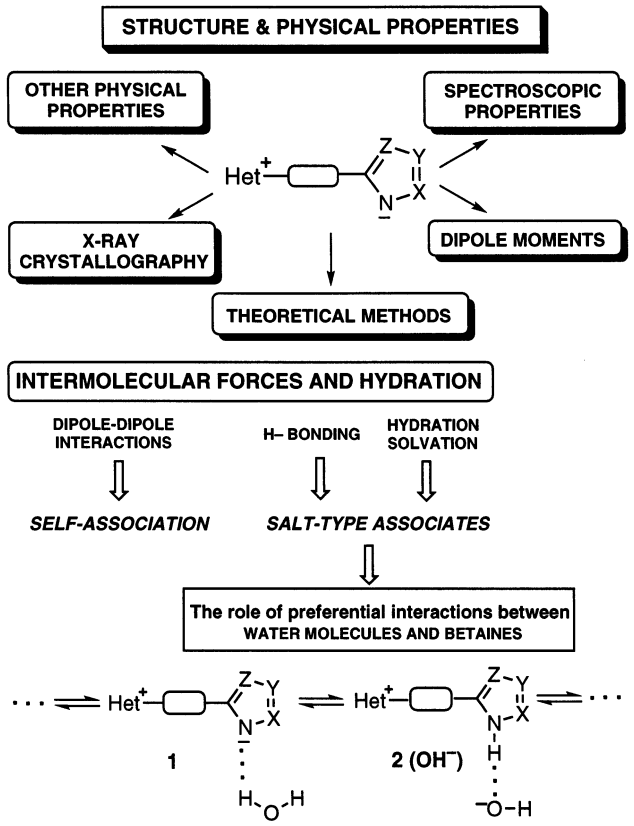


Fig. 4. Structural and physical facets of heterocyclic betaines with several interannular spacers.

1. β-elimination processes;
2. the susceptibility of the spacer to oxidation; and
3. 1,4-dipolar cycloaddition reactions.

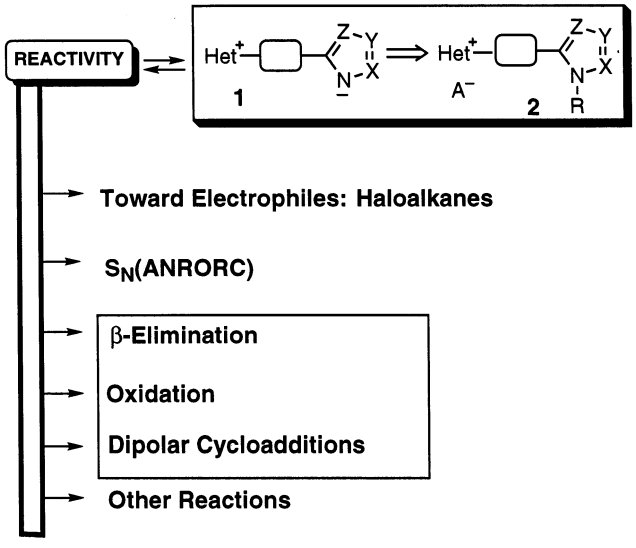


Fig. 5. Topics in the reactivity of heterocyclic betaines.

2.1. β-Elimination

A type of β-elimination reactions have been observed within a set of quaternary salts **4** containing an ethylene spacer. Thus, several 1-(2-benzimidazol-2-ylethyl)-pyridinium salts **4** were found to undergo a type of β-elimination and were transformed, at room temperature, into their corresponding 2-vinyl-1*H*-benzimidazoles **5** using an anion-exchange resin (OH^- form). Without doubt, this is a practical preparation of the almost unknown vinylbenzimidazoles monomers [16,17].

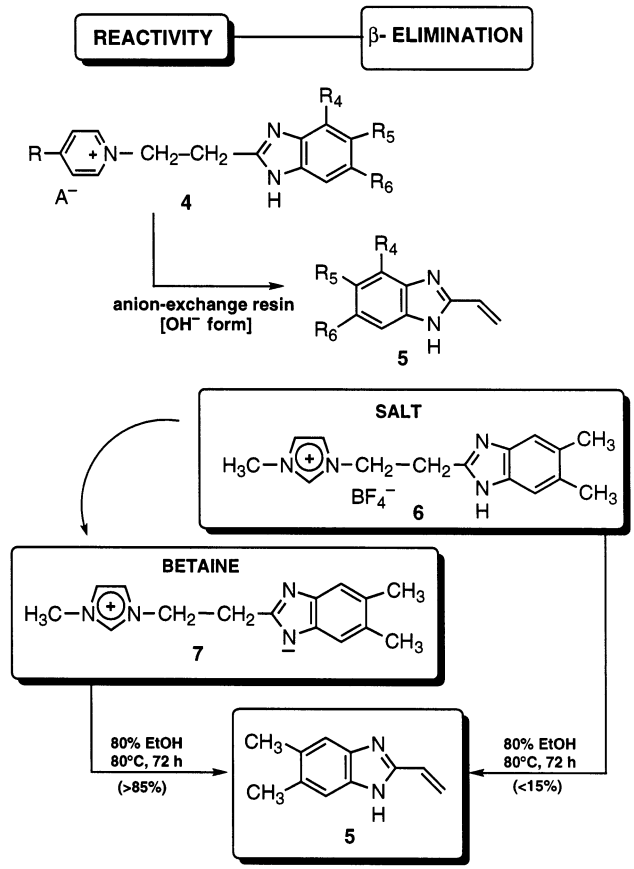
In contrast, the 1-(2-benzimidazol-2-ylethyl)imidazolium salts (e.g. **6**), result in clean conversion to the targeted betaines with an ethylene spacer (e.g. **7**, see Scheme 1). From the hypothesis that the betaine structure is necessary for β-elimination, we undertook the following study [17,18]. The model compound pairs selected were the dimethylbenzimidazoles **6** (salt) and **7** (betaine), and then under the same experimental conditions the dipolar substrate **7** experiments β-elimination as expected, whereas the cationic counterpart **6** gave the vinylbenzimidazole **5** in rather low yield. In this connection, several *N*-(2-benzimidazol-2-ylethyl)pyridinium cations and the imidazolium analogues, with the same activating group, had shown that for leaving groups of similar basicity, pyridine is a better nucleofuge than 1-methylimidazole [18,19].

We also studied the tendency of benzimidazolylethylpyridinium (**4**), benzimidazolylethylimidazolium (**6**) and the corresponding betaines **7** (Scheme 2) to undergo a nucleophilic substitution versus a type of β-elimination [18] in dipolar, non protic solvents (e.g. acetonitrile, pyridine). In these conditions the product formation was dependent on the nature of the starting substrate: the 1,5-diazocine system was obtained from salts **4** and **6** whereas the corresponding 2-vinylbenzimidazole **5** was formed from betaines **7**.

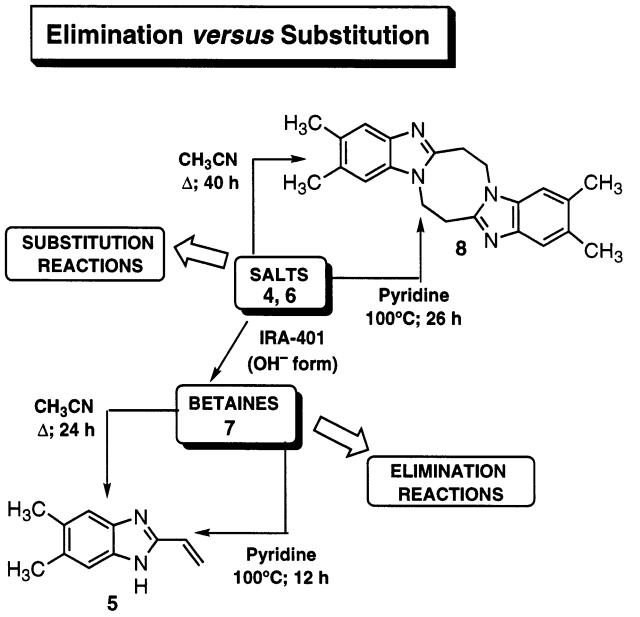
2.2. Spacer oxidation

The effect of electronic stabilisation of radicals has been subject of fruitful research and for its description several different names are used [20,21]. Dewar deduced from perturbation theory that radicals should be strongly stabilised when both an electron-attracting and an electron-donating substituent are present at the radical centre. From experimental evidence of such stabilisation, Katrizky proposed the term *merostabilisation* for carbon-centred radicals, and Balaban independently developed a similar concept for nitrogen-centred radicals which he called "push–pull". Some time later, these effects for free radicals were referred to as captodative and further developed by Viehe.

A concurrent application of the areno-analogy principle and the captodative effect has been exemplified for



Scheme 1. Efficient synthesis of 2-vinylbenzimidazoles from betaines with an ethylene spacer.



Scheme 2. β-Elimination vs. nucleophilic substitution reactions in ethylpyridinium(imidazolium) salts.

several examples of 1-alkyl-4(3)-(1*H*-azolyl)pyridinium salts **9** (4-pyridinium) and **10** (3-pyridinium). Accordingly, the character of the nonclassical acceptor and donor heteroaromatic moieties modifies the proclivity of the methylene spacer to spontaneous oxidation to the oxomethyl analogues (e.g. **11**–**13**) [10]. The chemical stability to oxidation of a set of compounds **9** and **10** built up from acceptor and donor subunits linked by a methylene spacer is still under development [11,20].

As shown in Fig. 6, for the 4-pyridinium derivatives **9** air was sufficient for oxidation to their corresponding oxomethyl analogues **11** and **12**. A different situation holds for the 3-pyridinium derivatives **10** since the π-deficient character is decreased. By changing the nature of the azole ring from 2-benzimidazolyl group (e.g. the oxomethyl counterparts **13**) to 1,2,4-triazol-3(5)-yl group, it was possible to achieve stable 1-alkyl-3-[1,2,4-triazol-5(3)-ylmethyl]pyridinium salts **14**. Surprisingly, this chemical stability persists in the corresponding

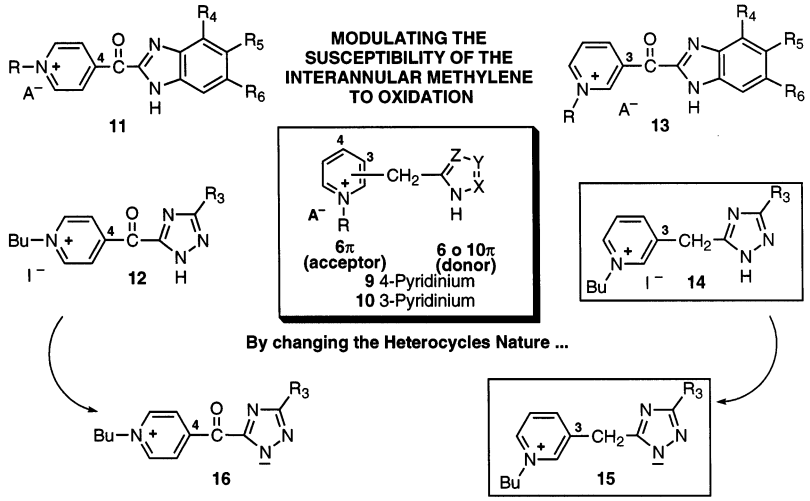


Fig. 6. Variable propensity to spontaneous oxidation of the methylene spacer.

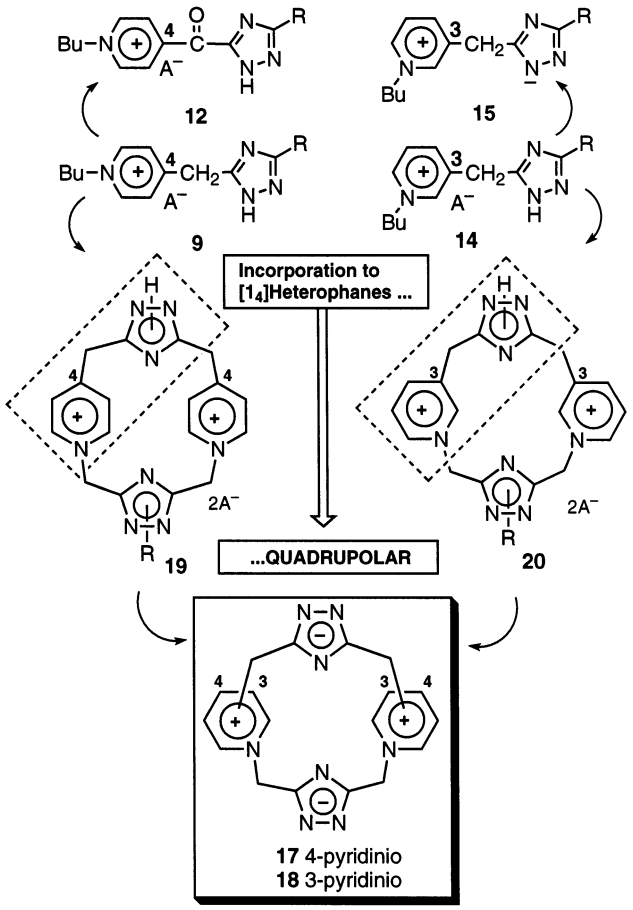


Fig. 7. [1_4]Heterophanes containing stable methylene spacers.

betaines **15**, indicating that proclivity to oxidation depends on the nature of the building block [10,11,20].

Moreover, we have focused our attention on the synthetic utility of the aforementioned spontaneous oxidation, since it appears to be an attractive way of access to the hitherto unknown oxomethylpyridinium triazolate inner salts (e.g. **16**, see Fig. 6) with a functionalised spacer [20]. In this connection, heterocyclic betaines with a methylene spacer (e.g. **15**) have recently been incorporated as building blocks for the construction of novel quadrupolar [1_4]heterophanes (see below, Fig. 7). In either the dipolar or the quadrupolar chemical entities, an oxomethyl spacer may allow an entrance to the hydroxymethyl counterpart that implies systems containing stereogenic center(s), and the hydrophilic/lipophilic balance can thus be modulated. Reduction of the oxomethyl spacer to the hydroxymethyl analogue may afford chiral systems of relevance in the realm of molecular recognition [11,20].

More elaborate heteropolyaromatic substrates such as the quadrupolar [1_4](*meta–para*)$_2$heterophane **17** and [1_4]*meta*heterophane **18**, together with their immediate precursors **19** and **20** have been explored (Fig. 7) [11].

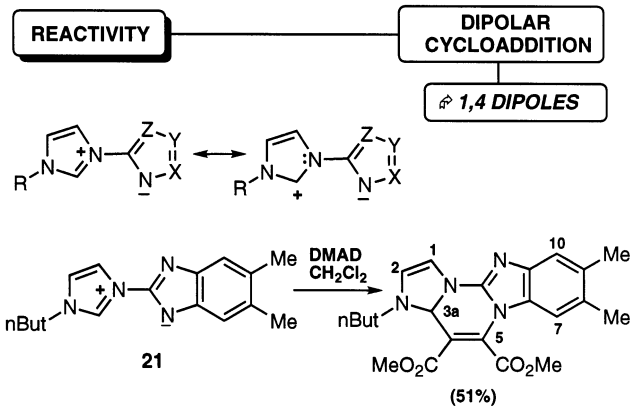
In contrast to the building block of type **9**, the quadrupolar [1_4](*meta–para*)$_2$heterophane **17** and its precursor **19** turned out to be highly stable in air, whereas the stability of [1_4]*meta*heterophanes **18** and **20** was predictable since no atmospheric oxidation was observed for their betainic counterparts **15** [10,20]. Whatever the structural features that prevent oxidation may be, the [1_4]heterophane framework modulates the susceptibility to oxidation and permits access to the hitherto unknown stable quadrupolar molecules **17** and **18**.

In conclusion, for several examples of azolylmethylpyridinium salts **9** and **10** the spontaneous oxidation of the methylene linker depends on the nature of their heterocyclic components. For the π-deficient nucleus the relative order was 4- > 3-pyridinium substitution, whereas for the π-excessive ring the interrelation was 2-benzimidazole > 3(5)-triazolate ≫ 3(5)-triazole [20]. It has been possible, however, to gain access to novel quadrupolar [1_4](*meta–para*)$_2$azolophanes **17** with a 3,5-bis[1-methyl-4-pyridiniomethyl]-1,2,4-triazolate subunit, which reveals that the structural features conferred by the heterophane architecture lead to molecules that are stable to oxidation. The chemical stability of [1_4]*meta*azolophanes **18** is consistent with the betainic subunits (see Figs. 6 and 7).

2.3. 1,4-Dipolar cycloadditions

In the domain of dipolar cycloaddition reactions, the centre of attention has focused on a 1,3-dipolar archetype which has emerged as a prominent synthetic method, whereas 1,4-dipolar cycloadditions have been rather neglected. The main reason is that known 1,4-dipoles are rather reactive intermediates and, while of considerable theoretical interest, they present a somewhat limited range of structural variation [22–24].

Mesomeric betaines **21** (of C–N′ bond type) are suitable for studying the behaviour of dipoles, the dipolar moiety containing more than four π electrons. Thus, their use in 1,4-dipolar type cycloadditions is a potentially attractive route for the synthesis of variety of heterocyclic structures and new polycyclic ring systems [3,22] (Scheme 3).



Scheme 3. 1,4-Dipolar cycloadditions in mesomeric betaines.

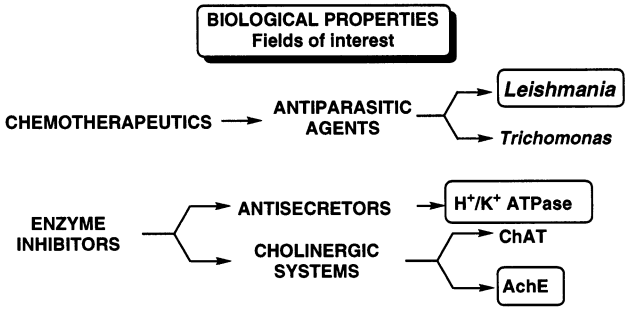


Fig. 8. Some possibilities of the biological behaviour of heterocyclic betaines [4,27].

The behaviour of the imidazolium benzimidazolate betaine **21** toward dipolarophiles has been studied, and a new tetracyclic structure—a 1:1 adduct—has been isolated using equimolecular amounts of **21** and dimethylacetylenedicarboxilate (DMAD) [22].

In summary, betaines **1** comprise a diverse collection of small molecules whose dipolar character constitutes the distinct aspect that has a dominant influence on their reactions. Moreover, these unusual molecular entities provide an ideal set for chemical reactivity studies both in ground and excited states—cycloaddition reactions, thermal and photochemical transformations, photodimerisations and flash pyrolysis, among others.

3. Interdisciplinary facets

The past quarter of a century has witnessed decisive advances in the quest for unnatural products. Their interest cuts across all the branches of chemistry, especially those on the boundaries with biology and physics [25]. New synthetic methodologies, some inspired by biological processes, have thrilled chemists, and allowed the exponential discovery of unique unnatural compounds exhibiting novel properties that were unthinkable a few years ago.

The prospects of this vast array of highly dipolar chemical entities **1** include their use as building blocks in a variety of chemical architectures, and their capacity for specific biological and physical behaviour are of interest at present. An interdisciplinary approach to the chemistry of heterocyclic betaines **1** and derivatives **2** must result from cooperative efforts directed towards medicinal chemistry, supramolecular chemistry and advanced organic materials (see Fig. 1) [4].

3.1. Biological properties

Among the different aspects of heterocyclic betaines **1** we are interested in developing, we have delved into the potential biological properties. So far, betaines **1** and derivatives **2** have been studied in the fields of chemotherapeutics (antiparasitic activity) and enzyme inhibitors towards H^+/K^+-ATPase [4,26], choline acetyltransferase (ChAT) and acetylcholinesterase (AchE) [4,27] (Fig. 8).

The antiparasitic screening has shown that 1,5,6-trimethyl-benzimidazolyltriphenylpyridinium salt **22** presents the best profile against *Leishmania donovani* [4] (Fig. 9).

Concerning enzyme inhibitors, a variety of mesomeric betaines **23** (and the corresponding *N*-benzimidazolylpyridinium salts) have been reported in connection with the mechanism of action and the underlying chemistry of potent H^+/K^+-ATPase pyridiniumsulfoxidebenzimidazoles (PSBs) [4,26]. Sulfoxides PSBs [26], through an acid-catalysed pathway, were transformed into compounds containing quaternary pyridinium moieties. Protonation of PSBs pro-

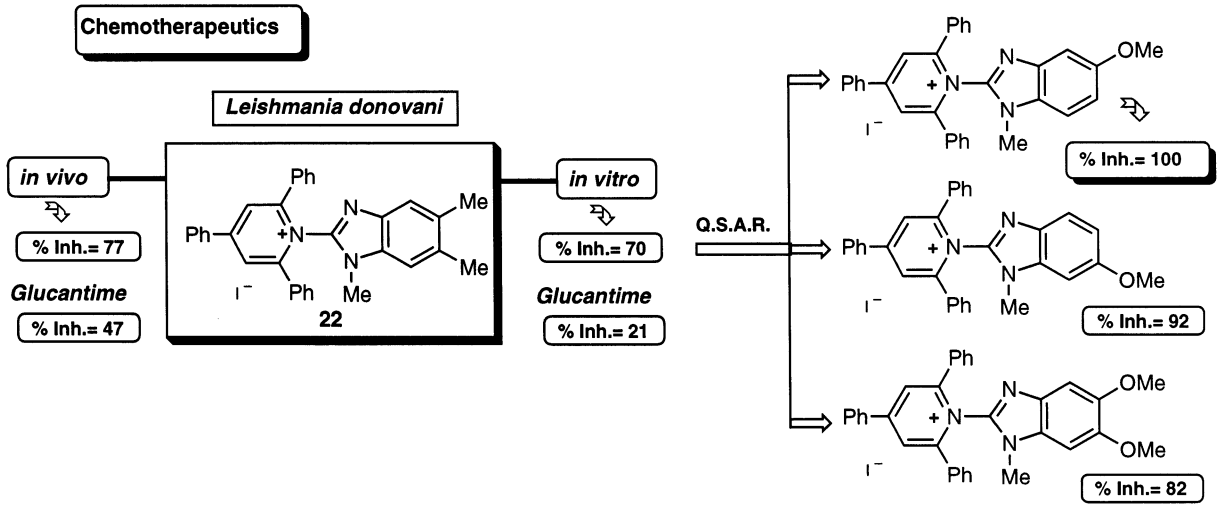
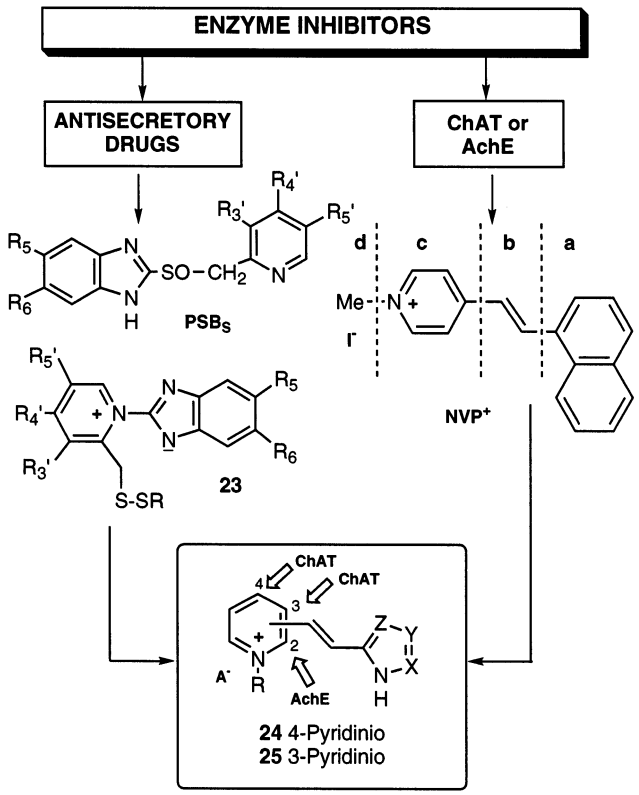


Fig. 9. Pyridinium salts **22**: a new class of chemotherapeutic agents [4].



Scheme 4. Azolylvinylpyridinium salts as enzyme inhibitors.

duces a consecutive cascade of transformations that are mainly dependent of the conditions applied.

Several series, within quaternary pyridinium compounds, have been shown to be specific enzyme inhibitors, for example certain (*E*)-stilbazolium salts (*N*-naphthylvinylpyridinium salts) NVP^+ (Scheme 4) strongly inhibit ChAT. Synthetic inhibitors of this enzyme are of interest in the pharmacological study of aspects that are dependent on cholinergic systems, e.g. selectivity between ChAT and AChE, neuropathological states, and specific cognitive functions [27].

In 1988, de Bernardis et al. [28] summarised the research on structure–activity relationships (SAR) in NVP^+ analogues, which indicate that there are four capital structural moieties at regions a, b, c and d (Scheme 4). This study [28] aimed to ascertain the influence of the substituents on the pyridine nitrogen atom (site d) on NVP^+ derivatives upon inhibition of ChAT in vitro, and some new NVP^+ analogues were found to be highly potent.

We have designed a new type of extended π-system aza-analogue of (*E*)-4-[2-(1-naphthylvinyl]-1-substituted pyridinium salts (NVP^+) and its inhibitory activity towards ChAT has been evaluated in vitro. Among the several examples of quaternary salts synthesised **24** (4-pyridinio) and **25** (3-pyridinio), an indolylvinylpyridinium salt of type **24** is the only one to show a very low ChAT inhibition [27]. The molecular modelling study is highly illustrative of the behaviour of such compounds towards ChAT and of their interaction with the recognition site. Thus, several selected cations together with the reference NVP^+ compound were studied at the PM3 and AM1 levels. At the global minima, all the compounds are planar, which, from the electron charge distribution, shows a degree of polarisation similar to the NVP^+ model compound. However, the fitting of all optimised structures indicated that only the indole 4-pyridinio derivative showed the same aromatic fragment orientation as NVP^+, which allows us to define a volume that is not accessible to ligands in the enzyme, and consequently lead us to a refined model of the ChAT recognition site.

In a preliminary communication, we pointed out [29] that by using the semiempirical method PM3, coplanar structures were seen to be the most energetically stable for the NVP^+ ChAT inhibitors (Scheme 4). Later, we confirmed that the minima calculated by PM3 correspond exactly to the minima predicted at the AM1 level [27]. In this connection, some time later, Cavallito and colleagues [30] also reported a molecular modelling study of some ChAT inhibitors related to NVP^+ and indicated that the choice of the computational method AM1 for application to the NVP^+ type ChAT inhibitors (Scheme 4) was made on the basis of the results obtained with MNDO, AM1 and PM3 on biphenyls. We believe, however, that biphenyls are not comparable with the NVP^+ compounds. In the first place, the sterical hindrance of biphenyls is not so pronounced within the NVP^+ series, where the aromatic rings are separated by an (*E*)-vinylene spacer, which gives the planar structures greater stability. Secondly, the presence of a cationic charged nucleus in the NVP^+ molecules makes the comparison even less feasible [3–5].

In conclusion, our studies suggest that the previously established coplanarity and polarisation criteria are not enough to account for the ChAT inhibitory activity of the ensemble constituted by (*E*)-aryl(heteroaryl)-vinylpyridinium salts NVP^+, **24** and **25** [27,29]. The molecular modelling study sheds light on their structure and suggests that steric requirements may play a very important role in their enzyme interactions. Furthermore, it provides a definition of the volume that is inaccessible to ligands at the recognition site and, consequently to a reasonably refined binding mode of NVP^+ and their aza analogues to ChAT.

As for AchE inhibitors, several members within the 2-pyridinium derivatives **1** and **2** have displayed inhibitory activity in vitro at the micromolar level. The design and synthesis of structural analogues more or less distant from the molecules found to inhibit AchE (e.g. **26**) are under study (see Fig. 10).

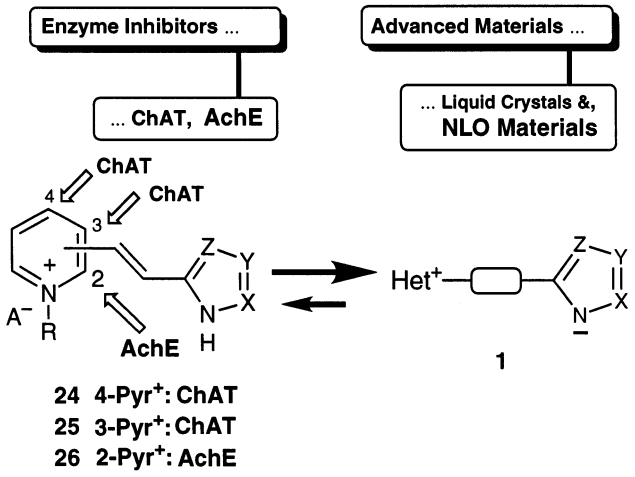


Fig. 10. Medicinal chemistry and advanced materials interphase [5,31].

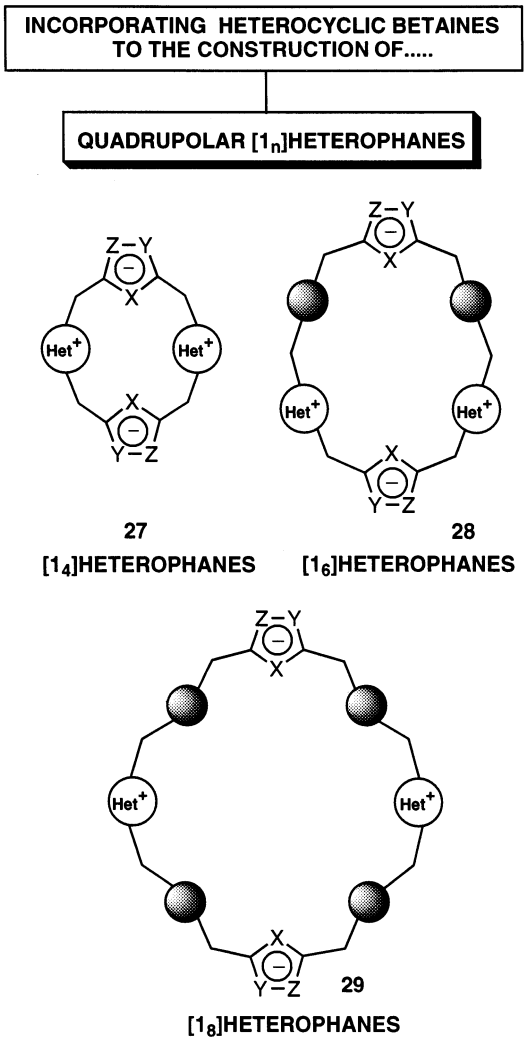
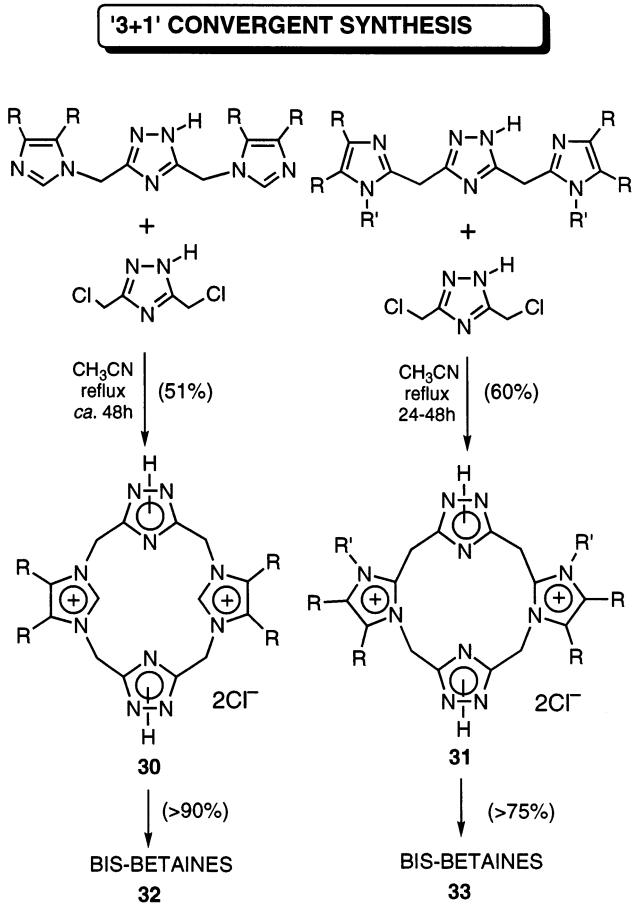


Fig. 11. Novel quadrupolar [1_n]heterophanes.



Scheme 5. Synthetic approach leading to quadrupolar [1_4]heterophanes.

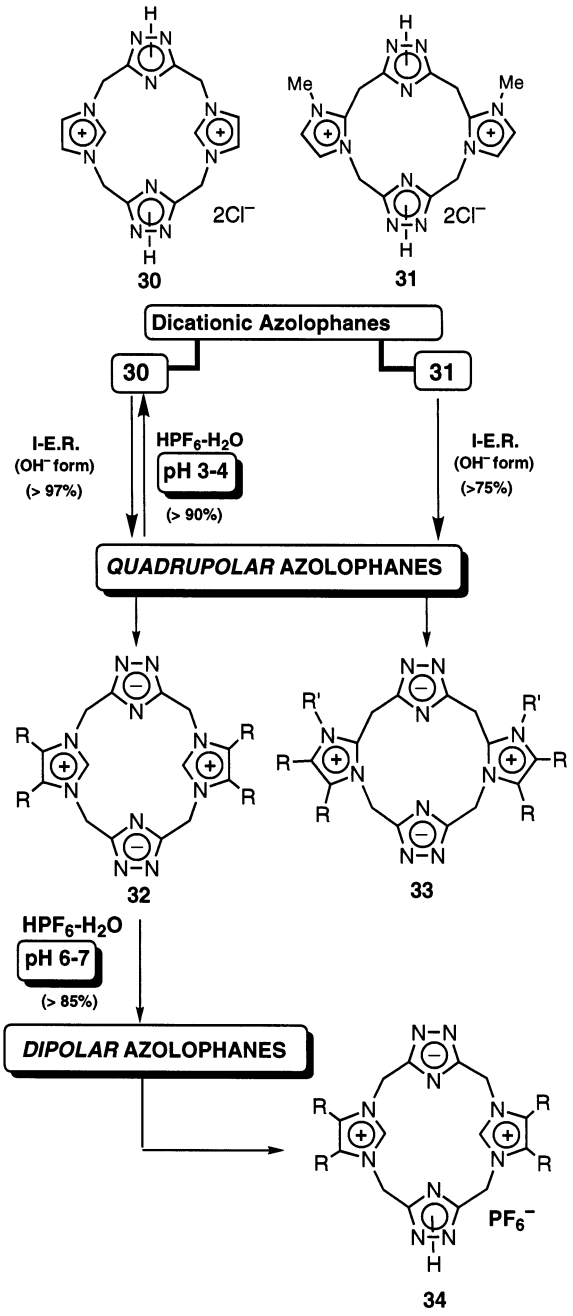
3.2. Advanced materials

It may be relevant to consider that betaines **1** and derivatives **2** are ideal substrates for developing novel organic advanced materials [3–5]. Recently, pyridinium azolate betaines with several spacers of general type **1** have been found to be applicable within second-order nonlinear optical (NLO) materials. Indeed, different types of heterocyclic betaines **1** have been found to display extremely large first hyperpolarisability in theoretical studies [31] and experimental measurements [32].

The development of dipolar and cationic substrates **1** and **2** is a relevant interdisciplinary goal at the meeting of chemistry with biology and physics (Fig. 10) [3–6].

3.3. Molecular recognition

To seek further insight into the chemistry of heterocyclic betaines (Fig. 1), we have examined into their application as building blocks of a variety of molecular architectures within the realm of molecular recognition.



Scheme 6. Synthesis of dipolar and dicationic azolophanes.

The difficulty resides in the selection of the host models. In this sense, the inexhaustible diversity of molecular architectures in macrocyclic systems—natural and synthetic—may allow the design of novel substrates whose chemical features have a dominant influence upon specific biological properties [25,33].

Cyclophanes, phanes and heterophanes, together with different types of calixarenes, constitute a source of inspiration for the design of novel molecular hosts. They represent a broad array of molecules and shapes [33] but none is related to the quadrupolar [1_n]heterophanes **27**–**29** (Fig. 11). The ring components present in heterophanes are normally uncharged heteroaromatic moieties, and in the few cases in which they bear a charge, they are usually quaternary pyridinium nuclei [33,34]. Moreover, many impressive cyclophanes with the ability to bind ions have been described [33], although few of them have been reported to bind anions [35], despite the increasing interest in anion complexation [36].

Since a quadrupolar [1_4]azolophane **27** was prepared some time ago [37], a part of our quest for novel

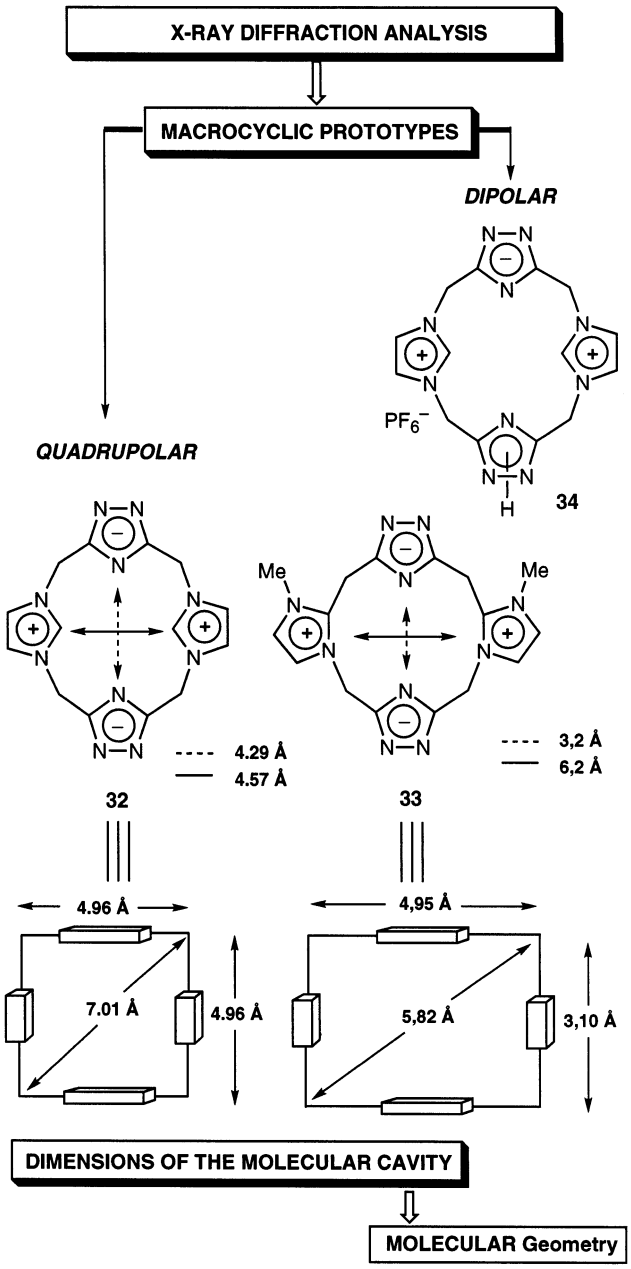


Fig. 12. Macrocyclic models for X-ray crystallographic study.

organic substrates built up from betaine subunit(s) has dealt with quadrupolar macrocyclic architectures (Fig. 11).

A direct synthetic approach—convergent '3 + 1' synthesis—permitted a simple entrance to the first examples of bis-betaines **32** and **33** (Scheme 5), illustrating a prototype of phanes with a quadrupolar nature [37–39].

The salts **30** and **31** can be converted efficiently into the quadrupolar azolophanes **32** and **33** by treatment with a hydroxide anion exchange resin (Amberlite IRA-401). Consequent acidification, rigorously monitored by a pH meter, of solutions containing the macrocyclic bis-betaine **32** using HPF_6(aq) (Scheme 6) facilitates the isolation of the macrocyclic dipolar betaine **34** or, in more acidic conditions, the recovery of the dicationic azolophane **30**. The preparation of dipolar azolophanes or dicationic azolophanes from quadrupolar azolophanes is dependent upon the pH of the medium, and this approach has led to the synthesis of quadrupolar [1_4] [39], [1_6] and [1_8] [40] heterophanes.

The information gained from the solid state structures of the quadrupolar [1_4]*meta*heterophane **32** and the [1_4](*meta*–*ortho*)$_2$heterophane **33**, and the dipolar [1_4]*meta*heterophane **34** (Fig. 12) is of great benefit in evaluating their capacity to function as synthetic host molecules.

Particularly interesting is the crystal packing [41] of the quadrupolar [1_4](*meta*–*ortho*)azolophane **33** · $4H_2O$, which is mainly governed by hydrogen bonding networks, strong intermolecular interactions with water together with weak interactions, either intramolecular or with water (Fig. 13).

As an extension of the incorporation of heterocyclic betaines as building blocks in [1_n]heterophanes, we have successfully designed and synthesised an ensemble of dicationic heterophanes incorporating imidazolium rings as the π-deficient heteroaromatic moiety linked by 1,3-disubstituted benzene rings, in order to enhance their potential for anion complexation. For example, the dication **35** · $2Cl^-$ · $2H_2O$ (Fig. 14) has a solid state

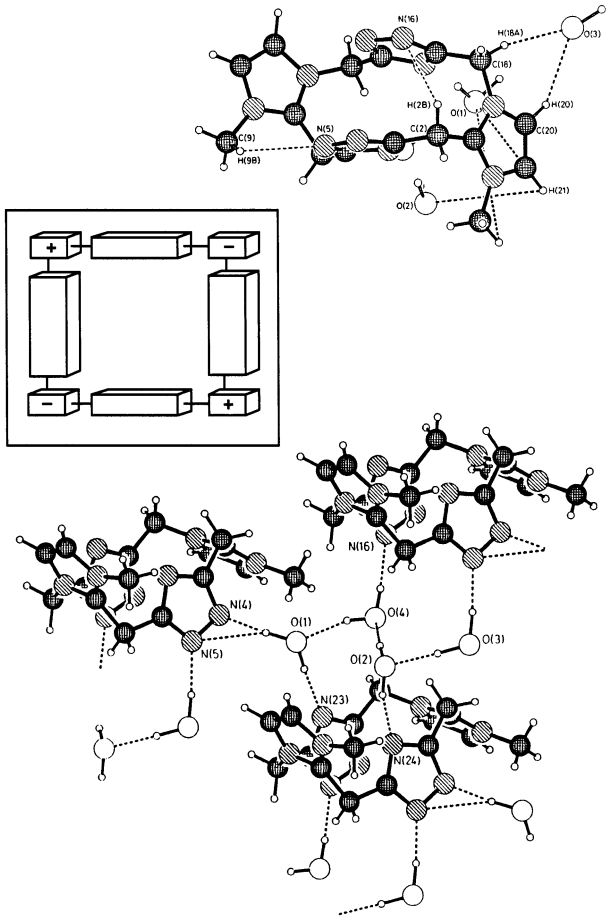


Fig. 13. bis-Betaine **33** · $4H_2O$: intramolecular C–H···N and C–H···O hydrogen bonding revealed by X-ray crystallography.

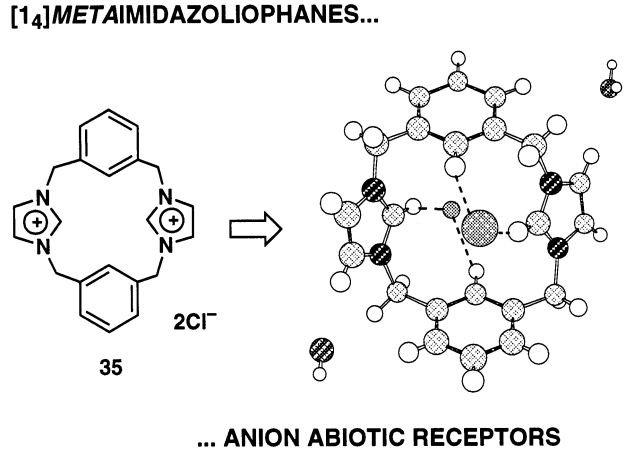


Fig. 14. Solid state structure of the dicationic heterophane **35** · $2Cl^-$ · $2H_2O$.

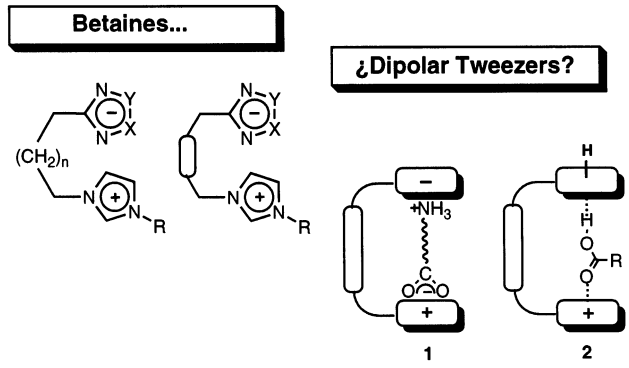


Fig. 15. Heterocyclic betaines as molecular tweezers.

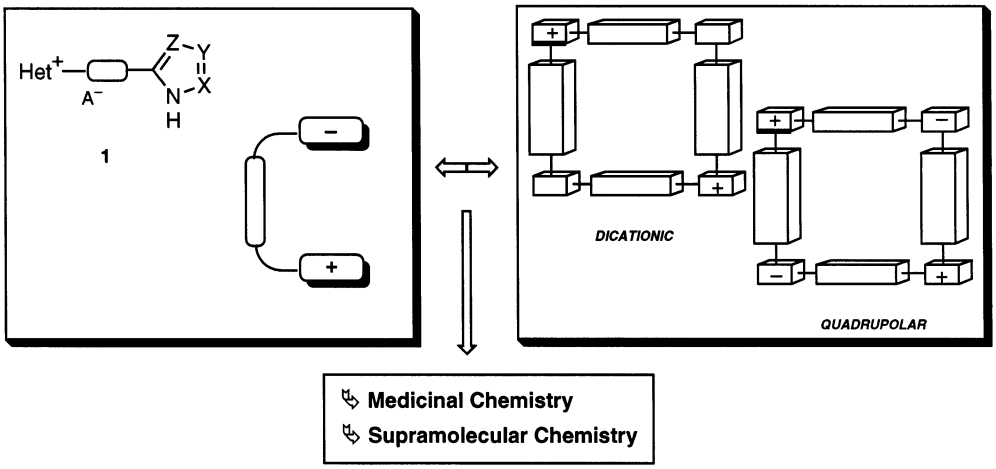


Fig. 16. Heterocyclic betaines: molecular guests in medicinal chemistry and molecular hosts in supramolecular chemistry.

structure in which the chloride counter-ions are noncovalently bound to the macrocyclic framework [42]. The ability of the macrocycle to bind anions can also be exploited during their synthesis [43].

The macrocyclic hosts described above are highly preorganised in their conformation, however, such preorganisation is not necessarily vital for strong and selective binding. In a parallel study, we have prepared some open-chain heterocyclic betaines [6]—whose charged subunits are separated by long alkyl chains—which could potentially function as molecular tweezers (Fig. 15) by an induced-fit mechanism.

Heterophanes containing heterocyclic betaines as building blocks have emerged as a novel family within [1_n]heterophanes and their dipolar or quadrupolar nature confer unusual properties to the host molecular architecture, and may permit the formation of host–guest complexes. Efforts are under way to expand this work in to novel systems, such as the dipolar building blocks which could act as dipolar tweezers along with dicationic and quadrupolar heterophanes with different cavity sizes and shapes (Fig. 16), seeking further insight with regard to their structural and physical facets, together with their capacity for specific molecular recognition behaviour.

4. Final remarks

Progress in the search for new organic substrates can emerge from the ideas outlined in this review, pursuing the observation of specific properties for these compounds, which we would like to approach both from the medicinal and supramolecular chemistry perspectives.

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