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Bispidine-based bis-azoles as a new family of supramolecular receptors: the theoretical approach

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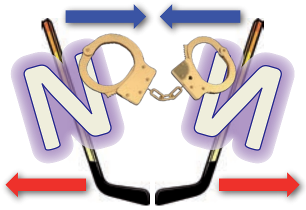
Two new bis-azoles derived from 1,5-dimethylbispidin-9-one were synthesized and structurally characterized. In both cases the bispidine backbone adopts the double chair conformation, which is also confirmed by calculations. In both structures, the azole rings are spatially pre-reorganized for the supramolecular interactions with the proper substrates like electron-rich aromatic compounds; the origin and nature of tiny intramolecular interactions are discussed in view of conformation stability.



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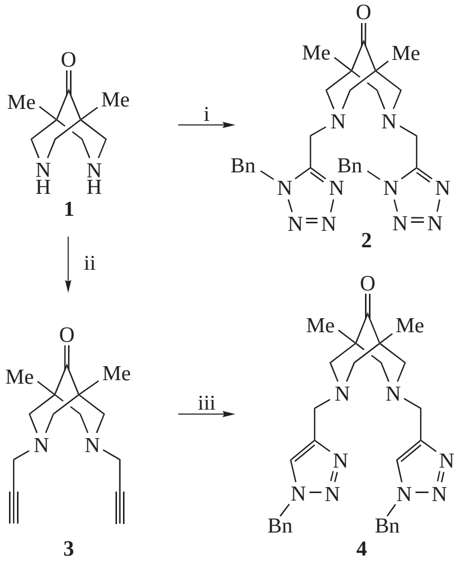
Supramolecular interactions are in the heart of the homogeneous catalysis.[1] Indeed, the proper spatial orientation of reacting molecules leading to the desired product with pre-designed stereochemistry should be governed by the multiple interactions between reactants and catalyst. In view of this, the proper spatial preorganization of the functioning part of the catalyst is of crucial importance. One of the ways to achieve this goal is using the modular molecules comprising more of less conformationally rigid central part (backbone, core) and several peripheral side groups ('pendant arms'). We have successfully explored such a central core as 3,7-diazabicyclo[3.3.1]nonane (bispidine) and similar diazamacrocyles. For example, the use of bispidines as components of H-bond-mediated supramolecular gels is reported,[2] bispidinoles as potent thrombin inhibitors are known,[3,4] also bispidines with additional amino-acid residues or 2-pyridyl groups at positions 2 and 4 could be respected as highly pre-organized complexones towards Cu and useful ligands for ^{64}Cu-based radiopharmaceuticals.[5–8] Moreover, several bispidines and their derivatives demonstrated promising biological activity.[9–13] Recently, triazine-substituted dispidines were exploited for efficient transmembrane H^+/Cl^- cotransport agents[14] and for pH-gated chloride transport agents.[15]

Bispidine itself combines two secondary amino groups predeterminally located in space with wide possibilities for their further functionalization.[16] For example, the introduction of alkyne groups and consequent [3+2]-cycloaddition make it possible to obtain a new class of triazole-based symmetrical tetradentant ligands, with which studying the cooperative interaction of two pendant arms with substrate molecule is convenient. At the same time, one could alkylate the secondary nitrogens with diverse alkylating agents, *e.g.*, tetrazolylmethyl halogenides. Surprisingly, such easy functionalization reactions in the bispidine chemistry were not reported before these studies.

Here, we describe the synthesis, structural and theoretical studies on new bis-triazole and bis-tetrazole conjugates with bispidine. The computer modeling of the possible supramolecular complexes formed by new receptors with several cases of important molecules are also reported.

The starting compound, 1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonan-9-one **1**,[17] was successfully alkylated by either propargyl bromide or 1-benzyl-5-chloromethyl-1*H*-tetrazole (Scheme 1). The latter reaction directly led to the target bis-tetrazole product **2**.



Scheme 1 *Reagents and conditions*: i, 1-benzyl-5-chloromethyl-1*H*-tetrazole, DIPEA, MeCN, reflux, 18 h, 93%; ii, $HC{\equiv}CCH_2Br$, DIPEA, MeCN, reflux, 6 h, 71%; iii, BnN_3, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, Bu^tOH, H_2O, room temperature, 36 h, 80%.

To obtain the bis-triazole product **4**, dipropargyl intermediate **3**[18] was reacted with benzyl azide under the conditions of CuAAC.

The structures of products **2** and **4** were confirmed by NMR spectroscopy and X-ray diffraction (XRD) studies.[†]

In the beginning of this project the resulting conformation of the bispidine backbone was not obvious, since many tiny factors usually govern the resulting geometry.[19–21] Such factors include, at least, the nature of the substituent at nitrogens, the presence of aryl group at positions 1 and 5 of bispidine molecule, and the presence/absence of a carbonyl group at position 9.

The analysis of Cambridge Structural Database (CSD) has revealed that conformations for 1,5-dimethyl and 1,5-diphenyl derivatives are slightly different. For 1,5-dimethyl compounds (altogether 8 structures, which are not protonated and do not contain any metal ions), only for 3,7-di-*tert*-butyl compound the boat–chair conformation is realized,[22] while for all others chair–chair one is found in the solid state. On contrast, in the case of 1,5-diphenyl substituted bicycles the chair–boat conformation is more frequent.[23] The exceptions are found for the substituents at N's, which lead to a substantial flattening of the configuration of the nitrogen atom, especially, for amides.[2]

The surprising case is the structure of bis-*N*-tosyl substituted bispidine, where the conformational polymorphism was found: two structures are characterized by the chair–chair conformation and chair–boat in the case of methyl derivative[24,25] and chair–chair for phenyl one. Interestingly, the N···N distance for phenyl derivative is shorter (2.76 Å) than for methyl one (~2.80 Å).[26]

The short review of CSD shows that, in general, the conformational preferences of bispidinones are mainly determined by so-called 'hockey-stick effect' that predicts the preferential existence of the chair–boat conformation due to spatial repulsions of the electron-rich nitrogen lone pairs.[19] At the same time, we cannot exclude that N···N interaction in bispidinones is of attractive character as it was previously observed for some other heteroatomic derivatives of bicyclo[3.3.1]nonanes.[27,28]

Despite of high steric volume of substituents at both nitrogen atoms in molecules of **2** and **4**, their XRD investigation reveals the similarity in the conformation of the bispidine backbone, *i.e.*, in both cases the molecules exist in a double chair conformation (Figure 1).

Although the conformation of bicyclic backbone in compounds **2** and **4** is the same, the mutual orientation of substituents is different. In the case of bis-triazole product **4**, the substituents form intramolecular C–H···N bond, with the H···N distance equal to 2.32 Å and CHN angle of 155°. At the same time, in the crystal of bis-tetrazole derivative **2** the shortest C–H···N contact is found for the interaction between the methylene group C(18) and nitrogen N(7) (H···N 2.44 Å, C–H–N 175°).

It is of note that in molecule **4** the substituents at N(3) and N(7) atoms have a *gauche* arrangement with respect to the nitrogens lone pairs (n_N). In the molecule of **2**, only one of the substituents would acquire the similar *gauche* arrangement, but the other, on the contrary, is antiperiplanar with pseudotorsion angles $n_{N(3)}$–C(12)–C(13) and $n_{N(7)}$–C(25)–C(26) of 51.4 and 176.2°. In this case, for the substituent located antiperiplanarly, the expected shortening of the N(7)–C(25) bond [1.455(1) Å] is observed taking into account the stereoelectronic interaction $n_{N(7)} \rightarrow \sigma^*$[C(25)–C(26)], as compared with the length of N(3)–C(12) bond [1.461(1) Å], and elongation of C(25)–C(26) bond [1.455(1) Å] is observed, compared to C(12)–C(13) value [1.494(1) Å]. It is remarkable that the N(7) atom is mostly flattened, since the sum for the bond angles with the participation of the N(7) atom is 340.4(1)°, whereas the same value for all other nitrogen atoms of the bicycle in both structures varies in the range of 332.0–335.2(1)°.

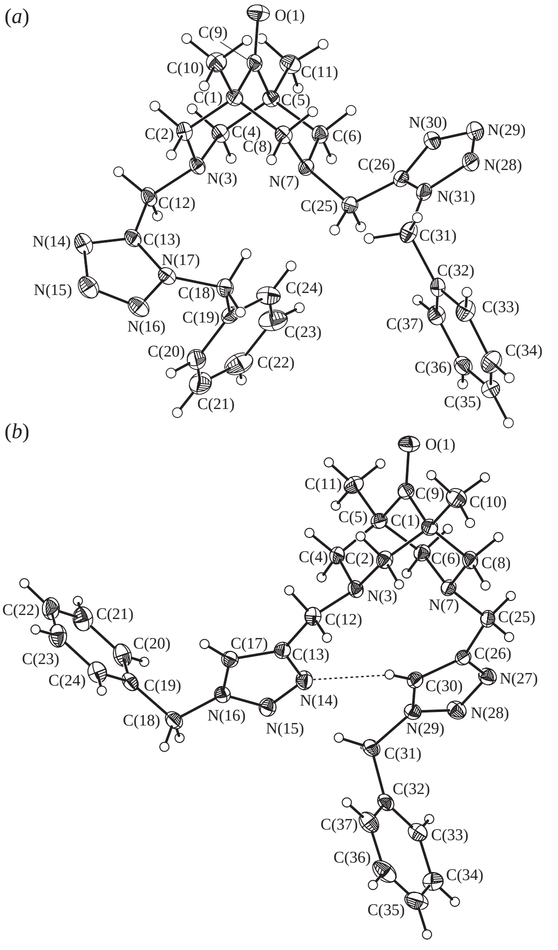


Figure 1 The general view of molecules of (*a*) **2** and (*b*) **4** in representation of atoms by thermal ellipsoids (p = 50%).

Despite the difference in mutual positions of the substituents discussed above, the transannular non-bonding interactions N(3)···N(7) in both compounds **2** and **4** are virtually the same, 2.808(1) and 2.818(1) Å, respectively.

In order to analyze the nature of intramolecular interactions in compounds **2** and **4**, we have performed DFT calculations [PBE1PBE/6-311+G(d,p)] using XRD data as the starting geometry. The calculations showed that geometry in the isolated state and solid were rather close to each other. In particular, in both structures the conformation of a double-chair is preserved. At the same time, the mutual orientation of the 'triazole arms' differs significantly from the crystal one, and they are not interconnected by the intramolecular C–H···N contacts. On the contrary, in the case of the 'tetrazole-arms' the stereoelectronic arrangement and intramolecular C–C···N contacts with the atoms of the bicycle are also observed.

The presence of stereoelectronic interactions in the latter case is unambiguously confirmed based on NBO analysis. According to the second perturbation analysis, the stereoelectronic interaction

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[†] *Crystallographic data for* **2** ($C_{27}H_{32}N_{10}O$). At 120 K colorless crystals are monoclinic, space group $P2_1/c$, a = 9.1345(4), b = 24.9881(11) and c = 11.3309(5) Å, β = 94.3470(10)°, V = 2578.9(2) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.320 g cm^{-3}; 27572 reflections measured (2θ < 60°), 7507 reflections independent (R_{int} = 0.0378); R_1 = 0.0459 [for 5813 reflections with $I > 2\sigma(I)$], wR_2 = 0.1133, GOF = 1.014.

Crystallographic data for **4** ($C_{29}H_{34}N_8O$). At 120 K colorless crystals are triclinic, space group $P\bar{1}$, a = 8.5270(5), b = 10.8755(7) and c = = 14.9278(9) Å, α = 96.6377(12)°, β = 105.4770(12)°, γ = 95.9562(13)°, V = 1312.02(14) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.293 g cm^{-3}; 15024 reflections measured (2θ < 60°), 6921 independent reflections (R_{int} = 0.0224); R_1 = 0.0412 [for 5586 reflections with $I > 2\sigma(I)$], wR_2 = 0.1216, GOF = 0.924.

CCDC 1969853 and 1969854 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

$n_{N(7)} \rightarrow \sigma^*$[C(25)–C(26)] is characterized by an energy of 9.2 kcal mol^{-1}, which is slightly higher than the energy of stereoelectronic interactions $n_{N(7)} \rightarrow \sigma^*$(C–H) (~8.2 kcal mol^{-1}).

The nature of the shortened N···N contact responsible for the stabilization of a double chair conformation in **2** and **4** was subjected to topological analysis of the electron density distribution function with the QTAIM theory.[29] Using the QTAIM formalism, one can distinguish the binding interatomic interactions from all other contacts. When the distribution of ρ(r) in molecule or crystal is known, one can answer the question whether the bonding interaction takes place or not by the search for the bond critical point (3,–1) and predict with high accuracy the energy of weak intermolecular interactions (E_{cont}) on the basis of the potential energy density function v(r) – the correlation suggested by Espinosa *et al.* (CEML).[30] The search for critical points showed that a critical point of type (3, –1) is observed. Based on the parameters of the Laplasian of electron density, as well as local energy density, we can conclude that this interaction is of closed-shell type. Estimation of its energy based on the CEML led to a value of 3.3 kcal mol^{-1}. For comparison purposes, it should be noted that a similar value for the attractive interaction of HC–H···N(7) in an isolated molecule (H···N 2.35 Å) of the tetrazole derivative is 2.5 kcal mol^{-1}.

Solution NMR data prove that both molecules are conformationally flexible that allowed us to state that bis-azoles could be efficient receptor molecules for several electron-rich aromatic substrates. Indeed, the preliminary quantum chemistry calculations revealed that both molecules **2** and **4** could form stable supramolecular complexes with benzene, thiophene, phenol, dopamine and similar electron-rich aromatic guest molecules. For example, according to DFT calculation for the most suitable pincer-like conformation, *i.e.*, with parallel azoles rings, the stable supramolecular complex with benzene between the rings has been found.

The preliminary theoretical estimations (DFT calculations) clearly show that double chair conformations of **2** and **4** are generally well suited to use these compounds as supramolecular tweezers.

For example, optimization of the slightly simplified model of **4** in which Ph groups were replaced by hydrogen atoms (Figure S7, see Online Supplementary Materials) have revealed that tweezer form rather stable supramolecular complex with benzene molecule due to interactions with nitrogen atoms of the bicyclic fragment (C–H···N contacts are 2.33 Å), π-stacking interactions with N···C separation as small as 3.13 Å. Finally, benzene molecule is also involved in the C–H···π interactions. All the above contacts according to QTAIM correspond to attractive interactions with the total energy according to CEML slightly exceeding 10 kcal mol^{-1}.

In conclusion, we have invented two novel supramolecular receptors. The analysis of the role of intramolecular interactions in the stabilization of a particular conformation of bispidine backbone was carried out. The possibility of supramolecular bonding between bis-azole bispidines and aromatic guest molecules for these receptors was estimated.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.028.

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