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Theoretical Study of *Z,E*-Isomerism of the *meso*-Azabridge in Pyrazine-Fused 5,5′-Diphenylazadipyrromethenes

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This study presents a conformational analysis of pyrazine-fused aza-dipyrromethenes (aza-DIPYs) using quantum chemical calculations. The influence of various substituents (–H, –Et, –Ph, –O-Ph, –O-tBu, –O-2,6-iPr₂Ph) on the preferred configurations of the aza-DIPY backbone was systematically investigated. Intramolecular hydrogen bonding between the NH group in one pyrrolo[3,4-b]pyrazine fragment and nitrogen atom in the pyrrolenine or pyrazine ring in another determines Z,Z and Z,E configurations of the aza bridge. Conformational analysis was performed with CREST, followed by DFT optimization. The results reveal that substituents inducing steric hindrance near the pyrazine nitrogen atoms (e.g., –O-Ph, –O-tBu, –O-2,6-iPr₂Ph) strongly favor and stabilize the Z,Z conformation. In contrast, unsubstituted and phenyl-substituted derivatives exhibit a significant population of the Z,E conformer. These findings provide insights into the structural preferences of pyrazine-annulated aza-dipyrromethenes and offer guidance for the rational design of corresponding aza-BODIPY dyes with tailored conformational stability.

Keywords: BODIPY, Quantum chemical calculations, conformational analysis, heterocycles.

Теоретическое исследование *Z,E*-изомерии *мезо*-аза мостика в 5,5′-дифенилазадипиррометенах

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В данной работе представлен конформационный анализ пиразин-аннелированных аза-дипиррометенов (аза-DIPY) с использованием квантово-химических расчетов. Систематически исследовано влияние различных заместителей (–H, –Et, –Ph, –O-Ph, –O-tBu, –O-2,6-iPr₂Ph) на предпочтительные конфигурации аза-DIPY остова. Конформационный поиск выполнен с помощью программы CREST с последующей DFT-оптимизацией. Результаты показывают, что заместители, создающие стерические затруднения вблизи атомов азота пиразинового кольца (например, –O-Ph, –O-tBu, –O-2,6-iPr₂Ph), однозначно стабилизируют Z,Z-конформацию. Напротив, незамещенные и фенилзамещенные производные демонстрируют значительную долю Z,E-конформера. Полученные данные раскрывают структурные предпочтения пиразин-аннелированных аза-дипиррометенов и могут быть использованы для направленного дизайна соответствующих аза-BODIPY красителей с заданной конформационной стабильностью.

Ключевые слова: BODIPY, квантово-химические расчёты, конформационный анализ, гетероциклы.

Among the BODIPY-type dyes there is an increasing interest to their aza-analogues, aza-BODIPY,[1,2] in which the central methine bridge (–CH=) is replaced by an aza-bridge (–N=). The interest in aza-BODIPY stems from versatile functionalization of these dyes, which allows for precise tuning of their light absorption and emission properties.[3-5] The nitrogen atom in the bridging *meso*-position also enhances the intersystem crossing, leading to a higher triplet state quantum yield, making them highly efficient for certain applications while retaining strong fluorescence.[6]

In contrast, ring-fused aza-BODIPY structures have been relatively unexplored. Since first report on benzo-fused aza-BODIPY obtained by E.A. Luk'yanets from phthalonitrile and arylmagnesium bromides,[7] only a few studies have been published. One of them[8] demonstrates the influence of the aryl substituents in the 5,5'positions on the spectral properties of aza-BODIPY complexes, as well as their effect on the yields of the resulting aza-DIPY and aza-BODIPY. It was also shown both 1,2- and 2,3-dicyanonaphthalene can form naphthalene fused aza-DIPY, the boron(III) complex can be obtained only from 1,2-naphthalene derivative.[9] Expansion of the π-electron system through annulation of large aromatic fragments also cannot be ruled out.[10,11] The introduction of a binaphthyl moiety imparts interesting optical properties to aza-BODIPY complexes due to their chirality.[12]

Fused benzene rings can be replaced with heterocyclic fragments and additionally modified by introduction of substituents. However, only one heterocyclic analog of aza-BODIPY containing fused pyrazine rings was so far reported. Kobayashi and coworkers synthesized this complex from 5,6-diethylpyrazino-2,3-dicarbonitrile and studied its sensing properties for ammonium ions in solution.[13] Recently, most theoretical studies of BODIPY dyes have emphasized the dependence of their optical properties on substituents.[14] For example, Brown has thoroughly examined the issue of the TD-DFT method systematically overestimating excitation energies for the BODIPY and aza-BODIPY family of fluorophores.[15]

However, to approach the synthesis of aza-dipyrromethenes with various substituents in the pyrazine ring, it is necessary to understand whether the formation of the aza-dipyrromethene molecule is so straightforward. Indeed, for dipyrromethenes, their *meso*-aza and benzo-fused analogues only one configuration of the *meso*-bridge stabilized by intramolecular pyrrole-pyrrolenine NH…N hydrogen bonding is possible, namely *Z,Z*-configuration. For the pyrazine fused aza-dipyrromethens an alternative *Z,E*-configuration can be also stabilized by intramolecular hydrogen bonding between pyrrolic NH group and one of the pyrazine nitrogens. Such effect was recently demonstrated for pyrazine fused diazatripyrrines obtained by hydrolytic deboronation of boron(III) complex of hexachlorotripyrazinosubporphyrazine.[16] In this case one of the aza-bridges have *Z,Z*- and another *Z,E*-configuration, which are stabilized by intramolecular hydrogen bonds of the pyrrolic NH group with pyrrolenine and pyrazine nitrogens respectively. The appearance of the various conformers (more precisely, configurations) is shown in Figure 1. It is worth noting that unlike *Z,Z*- and *Z,E*-confi-gurations, *E,E*-configuration is highly unlikely due to the absence of H-bonding and steric hindrance between the fused fragments.

In this communication, we report the results of the conformational study performed for the series of pyrazine fused aza-DIPYs bearing various substituents at the periphery (Figure 1) and compare the influence of alkyl, aryl, alkoxy and aryloxy groups of stabilization of *Z,Z*- or *Z,E*-configurations (Table 1).

Table 1. Percentage distribution of conformers depending on the substituents in the pyrazine ring of aza-DIPY, hydrogen bonds lengths and difference in free energy (Δ*G*) at 298.15 K between configurations calculated by B3LYP/pcseg-2.

-R	*Z,Z*-configuration		*Z,E*-configuration		Δ*G*, kcal/mol
	%	H-Bond length, Å	%	H-Bond length, Å	
-H	37	2.05	63	1.84	-0.3
-Et	~100	2.00	~0	1.73	1.5
-Ph	9	1.99	91	1.84	-1.1
-O-*t*Bu	100	2.04	n.f.	-	-
-O-Ph	~100	2.05	~0	-	10.9
-O-2,6-*i*Pr$_2$Ph	100	2.01	n.f.	-	-

n.f. – not found

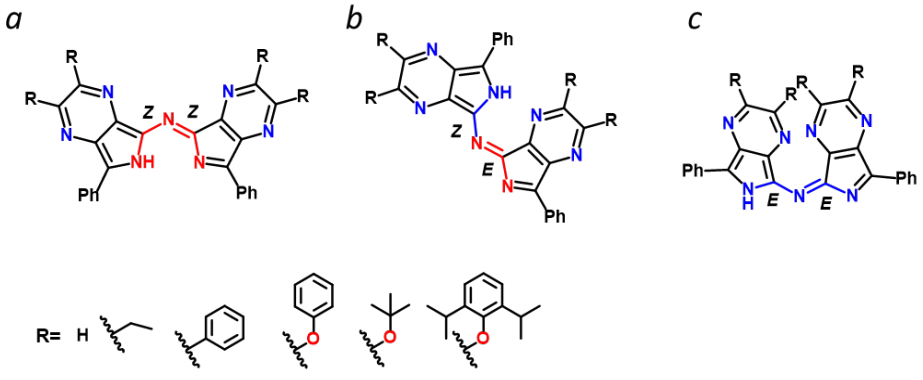

Figure 1. Representation of conformal diversity of studied compounds a – *Z,Z*-, b – *Z,E*-, c – *E,E*-conformers.

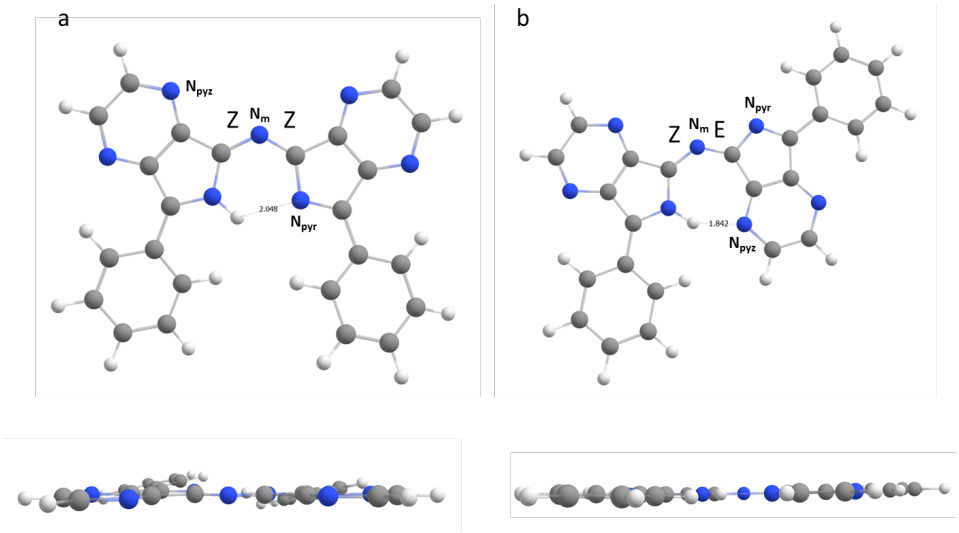

Figure 2. Molecular structures of pyrazine fused aza-DIPY: a – *Z,Z*- and b – *Z,E* configurations.

A preliminary search for conformers was performed using the CREST program (gfn2/XTB).[17,18] Further DFT optimization of the structures was carried out using the ORCA 5.0.3 program[19,20] using B3LYP functional[21-24] with pcseg-2 basis set[25] and Chemcraft program[26] was used for visualization of the molecular models.

In the case of unsubstituted aza-DIPY *Z,Z*- and *Z,E*-configurations have very small difference in energy (only 0.32 kcal/mol). Some predominance of *Z,E*-configuration is very likely connected with stronger hydrogen bonding. Indeed the H-bond NH…N(pyrazine) in *Z,E*-conformers is by *ca.* 0.2 Å shorter than NH…N(pyrrolenine) in *Z,Z*-conformer (1.842 and 2.048 Å, respectively). The strength of the hydrogen bonds was also evaluated within the framework of AIM (Atoms In Molecules) theory[27] using two criteria proposed by Espinosa[28] and Emamian and coworkers.[29] The results obtained for *Z,Z*- and *Z,E*-configurations (6.2 *vs.* 10.2 kcal/mol and 5.1 *vs.* 8.2 kcal/mol, respectively) confirm a stronger hydrogen bond in the case of the *Z,E*-configuration. In addition, *Z,E*-configuration allows more planar structure (Figure 2). The tilting angles between phenyl rings and pyrrole fragments are <2° in *Z,E*, and ~12° in *Z,Z* conformer. It should be noted that length of both N_m-C bonds formed by bridging *meso*-nitrogen are close to one another (1.327 Å and 1.301 Å in *Z,Z*- and 1.320 Å and 1.304 Å in *Z,E*-conformer) and evidences about strong conjugation between both pyrazinopyrrole fragments.

Introduction of alkyl, alkoxy and especially aryloxy groups in the pyrazine rings leads to stabilization of *Z,Z*-configuration. Alternative *Z,E*-configuration is completely disfavored evidently due to strong steric hindrance between substituents in pyrazine ring in one fragment and α-phenyl group in the neighboring pyrrolic unit.

Interestingly that *Z,E*-configuration of the *meso*-bridge is stabilized in the presence of phenyl substituents in the pyrazine fragments. The dihedral angle between phenyl groups and pyrazine ring (37.2 degrees) allows considerable conjugation increasing the donor properties of pyrazine nitrogens and their ability to form hydrogen bonds. The tilt angle of the phenyl substituent in the 5-position of the pyrrole/pyrrolenine fragment depends on the configuration. In the case of Ph_4-azaDIPY, the 5,5'-phenyl groups are tilting by *ca.* 13-14° in *Z,Z*-configuration, and by 18.2 and 3.2 degrees in *Z,E*-configuration. A major factor determining larger stability of the *Z,E*-configuration for Ph_4-azaDIPY is that the distance between adjacent phenyl rings in pyrrolic and pyrazine fragments (3.26 Å) is much larger than between neighboring 5,5'-phenyl rings in the *Z,Z*-conformer (2.72 Å).

In conclusion, it is worth noting that the nature of the substituents at the pyrazine ring has a significant effect on the structure and conformational preferences of pyrazine-fused aza-DIPY. The introduction of substituents that create significant steric hindrance near the pyrazine nitrogen atoms stabilizes *Z,Z*-conformer. At the same time, the absence of substituents or the introduction of planar substituents (*e.g.*, phenyl substituents) favors the preferential formation of the *Z,E* configuration stabilized due to $N_{pyr}H…N_{pyz}$ hydrogen bond.

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