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On the molecular and supramolecular properties of *N*,*N*′-disubstituted iminoisoindolines: Synthesis, spectroscopy, X-ray structure and Hirshfeld surface analyses, and DFT calculations of two (*E*)-*N*,*N*′-bis(aryl)iminoisoindolines (aryl = 2-*tert*-butylphenyl or perfluorophenyl)

Rodrigo S. Bitzer [a], Lorenzo C. Visentin [a, 1], Manfredo Hörner [b], Marco A.C. Nascimento [a], Carlos A.L. Filgueiras [a, c, *]

[a] Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, 21941-909, Brazil
[b] Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, RS, 97105-970, Brazil
[c] Departamento de Química, Universidade Federal de Minas Gerais, Belo Horizonte, MG, 31270-901, Brazil

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ABSTRACT

Supramolecular studies of iminoisoindoline-derived compounds have been prompted by their biological and photophysical properties. In this article, we report the synthesis, spectroscopy, X-ray structural characterization, and DFT study of two *N*,*N*′-(aryl)-disubstituted 1-iminoisoindolines, namely (*E*)-*N*,*N*′-bis(2-*tert*-butylphenyl)iminoisoindoline (2-*t*-BuPhimiso) and (*E*)-*N*,*N*′-bis(perfluorophenyl)iminoisoindoline (F_5Phimiso). Our X-ray structural analyses have shown that the isoindoline N2 atom of 2-*t*-BuPhimiso is slightly pyramidalized whereas the respective atom of F_5Phimiso displays the expected trigonal planar geometry. The supramolecular arrangement of 2-*t*-BuPhimiso comprises one-dimensional chains along the [101] direction formed by C—H$\cdots\pi_{arene}$ interactions, in which the isoindoline ring behaves as a hydrogen-bond donor. For 2-*t*-BuPhimiso, DFT calculations at the B97-D3/6-311G** level have shown that the dimer formed by this C—H$\cdots\pi_{arene}$ contact displays a binding energy of −12.83 kcal mol^{-1}. Product F_5Phimiso assembles in the crystal state through type-I F_3 synthons in addition to C—H···F, C—$F^{\delta-}\cdots\pi_F^{\delta+}$, and $\pi_{arene/F}$—$\pi_{arene/F}$ stacking interactions. Accordingly, our DFT-D3 calculations have confirmed that these interactions synergistically play a dominating role in the crystal packing of F_5Phimiso. Finally, the relative stability of the (*Z*) and (*E*) isomers of each product has been evaluated at the DFT level of theory. Our calculations have shown that the (*E*) forms are the most stable ones.

1. Introduction

In 1909, Thiele and Schneider reported the synthesis of the first 1-iminoisoindoline, namely *N*,*N*′-bis(phenyl)iminoisoindoline (Phimiso) [1]. Besides, they described the preparation of a Pt(IV) salt containing protonated Phimiso, giving birth to the chemistry of *N*,*N*′-disubstituted 1-iminoisoindolines (Fig. 1) [1]. Thiele and Schneider's synthetic method, which includes the facile 1:2 condensation reaction of *ortho*-phthalaldehyde with a primary amine [1], has been widely employed in the preparation of symmetrically and unsymmetrically *N*,*N*′-disubstituted 1-iminoisoindolines [2–16] despite the availability of alternative procedures [17–23]. Furthermore, synthetic strategies inspired by Thiele and Schneider's work have provided straightforward access to *N*-aryl-4-arylimino-5,6-dihydro-4*H*-thieno[3,4-*c*]pyrroles [24,25] as well as tri and tetracyclic amidines [26,27].

* Corresponding author. Departamento de Química, Universidade Federal de Minas Gerais, Belo Horizonte, MG, 31270-901, Brazil.
E-mail addresses: rodrigobitzer@gmail.com (R.S. Bitzer), lorenzo.visentin@nanobusiness.com.br (L.C. Visentin), hoerner.manfredo@gmail.com (M. Hörner), chaer01@gmail.com (M.A.C. Nascimento), calfilgueiras@gmail.com (C.A.L. Filgueiras).
[1] Present address. Nanobusiness Informação e Inovação Ltda, Incubadora de Projetos, Instituto Nacional de Metrologia, Qualidade e Tecnologia, Duque de Caxias, RJ, 25250-020, Brazil.

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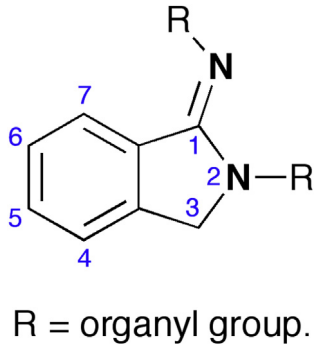

Fig. 1. (*E*)-*N*,*N*′-disubstituted 1-iminoisoindoline.

A number of iminoisoindoline-derived compounds display attractive biological, catalytic or optical properties [28]. Specifically, some (*E*)-*N*,*N*′-bis(aryl or heteroaryl)iminoisoindolines exhibit antiproliferative activity against tumor cell lines in addition to DNA binding properties [12,13], whereas (*E*)-*N*,*N*′-bis(5-methyl-3-isoxazolyl)iminoisoindoline shows antifungal activity against four pathogenic species [5]. Although these results are encouraging, research on the pharmacological properties of *N*,*N*′-disubstituted 1-iminoisoindolines is still in its infancy. On the other hand, much attention has been directed toward the biological activities of *N*(2)-monosubstituted 1-iminoisoindolines [29,30]. Several palladacycles bearing (*E*)-*N*,*N*′-(aryl)-disubstituted 1-iminoisoindolines as bidentate monoanionic [C,N] ligands were synthesized by Chitanda et al. [9,11,31]. Some of them behave as precatalysts in C–C coupling reactions [9,11]. Recently, the ability of (*E*)-*N*,*N*′-bis(2-picolyl)iminoisoindoline to act as a tridentate N,N,N-donor ligand has been exploited in the building up of photoluminescent Co(II) and Cu(II) coordination architectures [14]. Likewise, we and others have searched for functional metal complexes containing *N*,*N*′-(heteroaryl)-disubstituted 1-iminoisoindolines [4,7,32–34]. Since some photophysical properties, such as solid-state electro and photoluminescence, are strongly affected by intermolecular forces [35], the supramolecular characterization of new iminoisoindoline-derived compounds constitutes an important step in the development of isoindoline-based electronic and optoelectronic devices.

Single-crystal X-ray diffraction studies have disclosed that *N*,*N*′-disubstituted 1-iminoisoindolines occur as (*E*) isomers in the crystal state [2,5b,6,8,12,20,21]. Conversely, protonated Phimiso crystallizes as (*Z*) isomer [36]. In 2006, Akkurt et al. showed that the crystal packing of (*E*)-*N*,*N*′-bis(5-methyl-3-isoxazolyl)iminoisoindoline involves C–H$\cdots\pi_{arene}$ and π–π interactions [5b]. In 2007, Zhu et al. revealed that the supramolecular arrangement of (*E*)-*N*,*N*′-bis(2-pyridyl)iminoisoindoline (2-pyimiso) displays π–π stacking contacts involving both arene and heteroarene rings [6]. Four years later, Sović et al. described the C–H$\cdots$N$_{py}$ interactions existing in the crystal structure of 2-pyimiso [12]. Though rather limited in scope, these X-ray structural studies point out the crucial role played by the isoindoline ring in the self-assembly of 1-iminoisoindoline solid supermolecules.

As part of our ongoing interest in the structural attributes of iminoisoindoline-based molecules [33,34], we have embarked on a project aiming at uncovering molecular and supramolecular properties of symmetrically *N*,*N*′-disubstituted 1-iminoisoindolines. In this article, we report the synthesis, spectroscopic characterization, and X-ray structure and Hirshfeld surface analyses of (*E*)-*N*,*N*′-bis(2-*tert*-butylphenyl)iminoisoindoline (2-*t*-BuPhimiso) and (*E*)-*N*,*N*′-bis(perfluorophenyl)iminoisoindoline (F$_5$Phimiso). In addition, relative total energies of the (*E*)- and (*Z*)-stereoisomers of each product have been calculated using density functional theory (DFT). According to our supramolecular analyses, 2-*t*-BuPhimiso assembles in the crystal state through C–H$\cdots\pi_{arene}$ interactions, whereas F$\cdots$F, C–H$\cdots$F, C–F$\cdots\pi_F$ and $\pi_{arene/F}$–$\pi_{arene/F}$ stacking contacts occur in the crystal arrangement of F$_5$Phimiso (π_F stands for perfluorinated ring). Finally, counterpoise-corrected binding energies of these intermolecular contacts have been evaluated using D3 dispersion-corrected DFT (DFT-D3).

2. Computational and experimental details

2.1. General details

Unless otherwise stated, reagent grade solvents and starting materials were purchased from commercial sources and used as received or purified according to standard procedures. $CDCl_3$ (Cambridge Isotope Laboratories, Inc.), MeOH, EtOH and iPrOH were degassed and stored over activated 4 Å molecular sieves prior to use. Both 2-*t*-BuPhimiso and F$_5$Phimiso were synthesized following Thiele and Schneider's method [1]. Melting points (M.p.) were determined using glass capillary tubes in a Mel-Temp II (Lab. Devices, Inc.) apparatus. Elemental (C, H, and N) microanalyses were performed using a PerkinElmer 2400 CHN elemental analyzer.

2.2. Spectroscopic measurements

Infrared spectra were recorded on a Nicolet Magna-IR 760 FTIR spectrometer. They were collected using KBr pellets (4000–400 cm^{-1}) and a resolution of 4 cm^{-1}. The FTIR spectra are shown in Fig. S1. ^{1}H NMR spectra were acquired at 293 K using a Bruker DPX200 spectrometer operating at 200.13 MHz. The chemical shift (δ/ppm) values were determined relative to $SiMe_4$ (δ_{TMS} 0.00) with internal reference to the $CDCl_3$ residual signal (δ 7.26). Geminal ^{1}H–^{1}H coupling constants (^2J) are given in Hz.

2.3. Preparation of 2-t-BuPhimiso

Three drops of 88–91% formic acid were added to a solution of *ortho*-phthalaldehyde (1.258 g; 9.38 mmol) and 2-*tert*-butylaniline (4.0 mL; 25.6 mmol) in MeOH (20 mL). The resulting mixture was stirred at room temperature for 12 h. After this period, yellow crystals were isolated by filtration, washed with cold MeOH (3 × 10 mL), and recrystallized from EtOH (40 mL). Single crystals suitable for X-ray diffraction measurements were grown by slow evaporation at atmospheric pressure of a dilute solution of 2-*t*-BuPhimiso in 1:1 MeOH:iPrOH. Yield: 1.897 g (4.78 mmol; 51%). M.p.: 206–209 °C. *Anal.* Calc. for $C_{28}H_{32}N_2$ (FW 396.6): C, 84.80; H, 8.14; N, 7.06%. Found: C, 84.23; H, 8.29; N, 7.02%. FTIR (KBr pellet, ν_{max}/cm^{-1}): 3129w, 3091w, 3057w, 3018w, 3010w, $\nu(CH)_{arene}$; 2988w, 2971sh, 2954 m, 2904 m, 2854 m,br, $\nu(CH)_{methyl}$ and $\nu(CH)_{methylene}$; 1652vs, $\nu(CN)_{imine}$; 1609 m, $\nu(CC)_{isoindoline}$; 1598sh, 1570sh, 1564 m, 1435 m, $\nu(CC)_{phenyl}$; 1588 m, $\nu(CC)_{isoindoline}$ + $\nu(CC)_{phenyl}$; 1496sh, 1444 m, $\delta(CH_2)_{methyl}$; 1480s, 1466s, $\nu(CC)_{phenyl}$ + $\delta(CH_2)_{methyl}$; 1394sh, 1356 m, $\rho_w(CH_3)$; 1377s, $\rho_w(CH_3)$ + $\rho_w(CH_2)_{methylene}$; 783 m, 767 m, 758 m, 751s, 732s, π(CH). ^{1}H NMR (200.1 MHz, $CDCl_3$, δ/ppm): 1.23 (s,br, 18H, CH_3), 4.71 (d, ^2J = 15.6, 1H, CH_2), 4.95 (d, ^2J = 15.6, 1H, CH_2), 6.74–7.57 (m, 12H, aromatic protons). The methylene protons are diastereotopic and constitute an AB coupling system ($\Delta\nu_{AB}$ = 47.7 Hz and ^2J = 15.6 Hz).

2.4. Preparation of F5Phimiso

Three drops of 88–91% formic acid were added to a solution of *ortho*-phthalaldehyde (0.470 g; 3.50 mmol) and 2,3,4,5,6-pentafluoroaniline (1.942 g; 10.6 mmol) in EtOH (10 mL). The