

Organic & Supramolecular Chemistry

Naphthalene Peri Annelated N,N- and N,O-Heterocycles:
The Effect of Heteroatom-Guided *Peri*-Fusion on Their
Structure and Reactivity Profiles-A Theoretical EndoscopyDemeter Tzeli,^[b] Pawel Kozielowicz,^[c] Mire Zloh,^[d] Dyeison Antonow,^[e] Petros G. Tsoungas,^{*,[a]}
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An endoscopy of the little known *peri*-fused N,N and N,O-heterocycles is described herein using the density functional theory (DFT/B3LYP), the 2nd order Møller–Plesset perturbation theory (MP2) and the 6–311++G(d,p) basis set. Their salient structure features, their reflection onto aromaticity, depicted by means of certain aromaticity indicators (HOMA, I_A , ABO, PDI, FLU, NICS) and their reactivity profiles are the theme of this investigation. N and O atom(s) and their relative arrangement in the ring perturb the σ and π frames of the structures and ultimately introduce *peri* strain. The incorporation of N and O atoms in the annelated ring causes a limited π -delocalization over the whole structure, a relatively low aromatic character and a weakly polarized double bond of the heteroring. Bond

length variation, in the range of 0.01–0.05 Å, dihedral angles deviating from planarity by 1.2–4.1 Å and compressed fusion bonds, particularly *peri* ones, indicate a σ frame-triggered ring distortion of 0.6–2.6° as an “outward” stretching of the lower part of a still planar structure except one. The heteroring, as a masked enamine, hydrazone, imine, vinyl ether, oxime or imino ether, clamped onto naphthalene scaffold, appears to be the best description of this type of structures. The nature of the heteroring dictates their reactivity profile. Those housing the masked hydrazine and oxime entities exhibit a “ring α -effect”-guided reactivity, consistent with preliminary experimental findings.

1. Introduction

Condensed polycyclic (hetero)aromatic compounds (P(H)ACs) find applications as semiconductors in organic field effect transistors (OFETs), light-harvesting dyes in organic solar cells and photodetectors, near infrared fluorescent probes in bio-imaging and bio-sensing or chromophores in non linear optics.^[1] A strong interest has been directed towards the bowl-shaped molecules (known as molecular bowls), displaying extraordinary self-assembly features as well as pertinent chemical and physical properties^[2,3]

Peri-annelated PACs (and their heterocyclic congeners) consist of a naphthalene core unit, the *peri*-positions of which

are part of a (hetero) ring. Phenalene **2**, acenaphthene **3** and pyrene **4** (Figure 1) are well-known examples with many

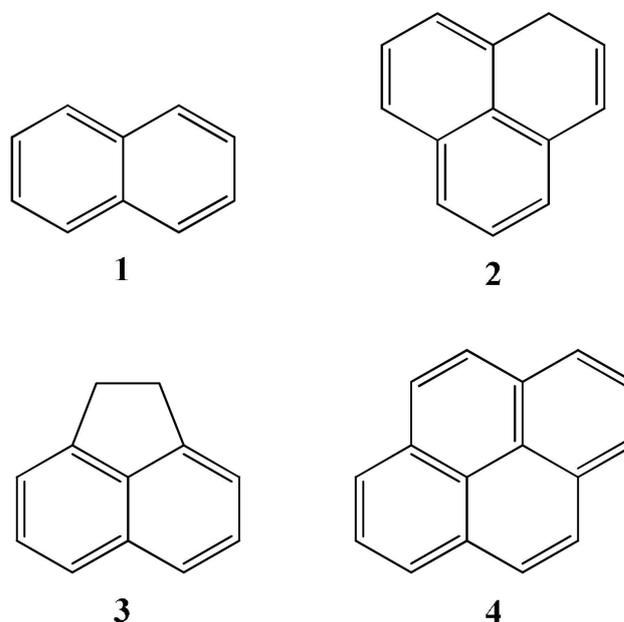


Figure 1. Naphthalene **1**, Phenalene **2**, acenaphthene **3** and pyrene **4** compounds.

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applications in materials and drugs.^[1–4] Attention to these structures has been recorded in recent years^[5,6] and eventually their synthesis and applications have been reviewed.^[7–9]

The incorporation of heteroatoms in PACs modifies the π -electron distribution, thus, leading to intriguing properties and potential applications.^[4] 1,2- or 1,3-diazanaphthalenes, also known as perimidines or peridazines, respectively, as well as their acenaphth(yl)ene hetero analogues are major members of the group of *peri*-annulated heterocycles.^[10]

N-(and N,N-), O-(and N,O-) based heterocycles are known to exhibit diverse bio(pharmaco) logical activities.^[11] Indeed, many of these structures are found in drugs, mainly due to a suitable drug-like profile.^[11,12] Within the estimated chemical space,^[13] libraries of potentially useful drug leads have been and still are built up by diverse approaches.^[14,15] *Peri*-fused N,O-heterocycles, on the other hand, are much less known.^[10] The 1,2-oxazine core structure, for example, has been a long-known research theme and its benzo analogue has also been targeted but to a limited extent.^[9,16,17] Aromaticity, its features and impact on the chemistry of heterocyclic compounds, drugs included, have been investigated and covered in reviews and book chapters.^[18] A number of approaches, of varying applicability, have been developed to evaluate the aromaticity of N-(and N,N-), O-(and N,O-) heterorings, using various indices [19] and their credibility has been assessed.^[20] Interestingly, the concept of aromaticity has been further extended to organometallic or inorganic structures, where σ -, π -, δ - (from d orbitals) or even φ - (from f orbitals) electron delocalization is at work, giving rise to the term “multifold aromaticity”.^[21] The aromaticity of azines,^[22] as well as other primarily 5- and 6-membered heterocycles,^[18,23] scrutinized by means of theoretical calculations, has been and still is an attractive research theme. To the best of our knowledge, none such investigation has been reported so far on the *peri*-annulated structures of type I (Figure 2). Intriguing

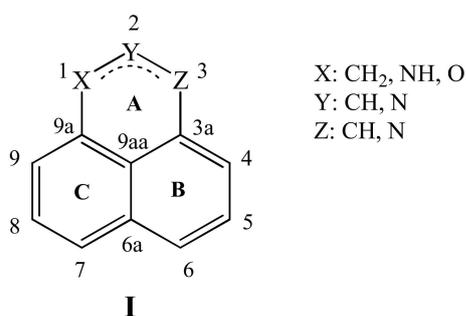


Figure 2. *Peri*-annulated structures of type I

features of this type (Figure 3, 5–11), unveiled herein, as well as their potential in synthesis, especially those of **10**, serve as a strong impetus for a theoretical insight into their aromatic character, the cornerstone of their reactivity.

It is known that ring opening of N,N- or N,O-heterocycles, asymmetric reduction in particular, provides access to optically active structures, core components in a variety of medicines.^[24]

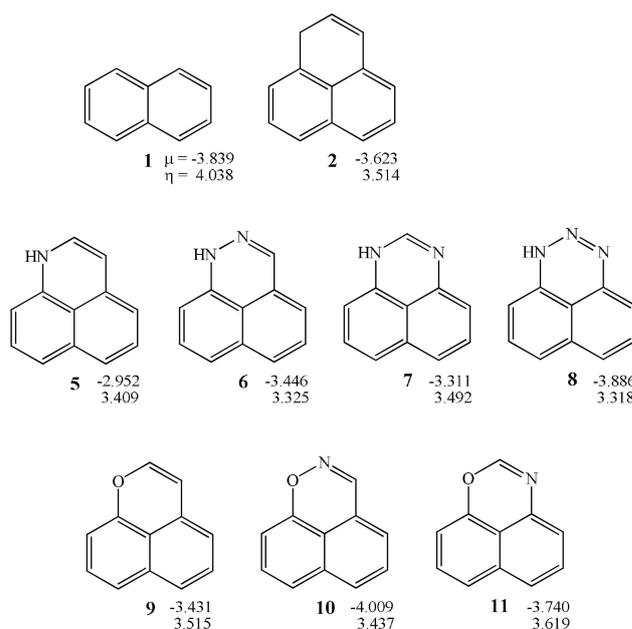


Figure 3. Naphthalene **1** and *Peri*-annulated **2** and **5**–**11** compounds. Electronic Chemical Potential μ and Chemical Hardness η are also given.

Indeed, facile ring cleavage of 1,2-oxazine **10**^[17] or arene-fused 1,2-oxazoles^[25] lead to chemically and biologically useful outcomes, for instance ring hydroxylation or generation of diaryl amines, as promising metal ion chelating ligands. It is, thus, the documented significance of these structures and their potential as key core units in (bio)organic and medicinal chemistry, biology and materials, along with some subtle experimental data,^[17,26] presently at hand, that sparked a theoretical endoscopy into the salient features of their structure and their reflection onto their reactivity profiles.

2. Results and Discussion

Peri (**1** and **8**)-positions (or substituents at those positions) in naphthalenes are in closer proximity than are *ortho*-positions.^[27] Indeed, a *peri*-distance, in a naphthalene of ideal geometry, is taken to be *ca.* 2.47–2.50 Å, compared with the 3.1 Å for an *ortho*-one. Bridging the *peri*-positions of a condensed bicycle like naphthalene (or its hetero-, mainly aza-analogues) gives rise to *peri*-annulated heterocycles^[18,23] of type I (Figure 2). *Peri* annulated structures **5**–**11** can be looked at either as benzo[*d*]-fused heterorings or as naphtho[1,8-*de*]-fused heterorings (Figure 3). Structures, having the naphthalene core in common, may be distinguished by (a) the replacement (in part or in full) of the C atoms of the *peri*-fused ring in the parent structure **2** by N and O heteroatoms and (b) their relative position, i.e., contiguously bonded, such as **6**, **8** and **10**, those one C unit apart, such as **7** and **11** and those with one ring heteroatom, **5** and **9** (Figure 3).

Worth noting is that *trends rather than actual changes* on the geometry and aromaticity features of **5**–**11** are contemplated throughout the ensuing account.

Table 1. Energy difference (ΔE) in kcal/mol, zero point corrected electronic energy difference^a (ΔE_0) in kcal/mol, Enthalpy difference^a (ΔH) in kcal/mol, and Gibbs free energy difference^a (ΔG) in kcal/mol at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) (in parenthesis) levels of theory for the isomers of the N,N-, N,N,N-, and N,O heterocycles.

	Comp.	ΔE	ΔE_0	ΔH	ΔG
N,N-compounds	6'	18.18(18.76)	18.00(17.97)	18.06(17.72)	17.93(18.31)
	6''	18.22(17.75)	18.07(22.33)	18.12(22.06)	18.00(22.86)
	7	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)
N,N,N-compounds	8'	0.002(1.03)	0.0(0.0)	0.0(0.0)	0.0(0.0)
	8''	0.0(0.0)	0.11(3.93)	0.09(4.08)	0.13(3.84)
N,O-compounds	10	32.32(34.22)	31.66(32.79)	31.77(32.17)	31.53(33.48)
	11	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)

^a At 298.150 K and 1.000 Atm.

2.1. Structure Profile

Upon annelation, the rigid naphthalene framework is forced to distortion and the latter drives the transannular *peri*-distance to contract. It has long been recognized that steric strain,^[9,28] due to bulky substitution at interfering positions, can be relieved in a number of ways, including stretching of bonds (Strain-Induced Bond Localization (SIBL) effect),^[29] in-plane or out-of-plane deflection of the substituents and distortion or buckling of the naphthalene frame.^[29]

Peri strain in 1,8-disubstituted naphthalenes^[30] and its role in the reactivity of naphthalene-based structures^[31] have drawn attention quite extensively. *Peri*(1,8)-fusion (or annelation) onto the naphthalene scaffold, on the other hand, is expected to perturb its σ and/or π frames and ultimately introduce strain. Such perturbation, triggering a ring distortion, is found in structures 5–11 (Table 1S of SI). This is evident from their C–C frame, compared with that of naphthalene 1,^[30,31] as well as their heteroring bonds.

A bond length variation from 1 of *ca.* 0.01 Å in 2, 5, 9 and *ca.* 0.02–0.05 Å in 6–8, 10 and 11 is observed. The average bond length is 0.015 Å shorter from or 0.018 Å longer than the (commonly reported values of 1.399 Å or 1.402 Å for the isolated structures of benzene or naphthalene, respectively).^[32] It is known that the N atom in azines has no significant impact on σ and π electrons, nonetheless, the latter tend to localize to a greater extent in heterocycles than in benzene.^[33] Incorporation of one heteroatom in the *peri*-fused ring, as in 5 and 9, has no appreciable effect on the π delocalization ($\Delta_R = 0.001$ – 0.005 Å) through N₁-C_{9a} and O₁-C_{9ar}, respectively. Additional heteroatoms, however, as in 6–8 or 10 and 11, do cause a more notable change ($\Delta_R = 0.01$ – 0.035 Å), being more pronounced in 9–11 (with or without the N atom). The heteroatom in both 5 and 9 does trigger some conjugation with the heteroring double bond. A *ca.* 0.01 Å contraction of the imine ring bond is observed in 7 and 11, slightly more so in the latter, when compared with 6, 8 and 10. This bond compares adequately to that of diazines^[18a,34] and a typical imine bond in Schiff bases^[35] or oximes.^[36] The weak polarization of this bond is apparently a result of a lone pair effect,^[37] i.e., a through-space n - π repulsive interaction of the contiguous ring N, N or N and O orbitals, respectively, with those of the double bond, probably augmented by a lone pair repulsion among the

heteroatoms, reminiscent of the α -effect.^[38] The earlier suggested^[39] correlation of a high bond order with a short bond length is not evident in 2–11, thus, it is their σ -component apparently important and perhaps dominant in their distortion. Interestingly, it is the fusion bonds (C_{3a}-C_{9aar}, C_{6a}-C_{9aa} and C_{9a}-C_{9aa}) that suffer the overall distortion. Indeed, 2, 5 and 9 are compressed by *ca.* 0.01 Å at C_{6a}-C_{9aa} and C_{9a}-C_{9aar}, 6–8 by *ca.* 0.003–0.008 Å at all fusion bonds and 9–11 by *ca.* 0.004–0.007 Å.

Of particular note is the variation of the H₆-H₇ distance observed in 2–11 (Figure 4) and its deviation from that (H₄-H₅

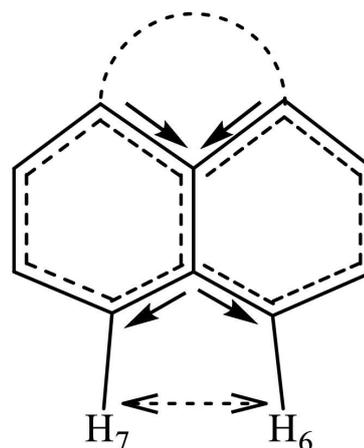


Figure 4. Schematic representation of *peri*-triggered ring deformation. Arrows indicate inward and outward stretching.

or H₁-H₈) of naphthalene 1 (Table 3S of SI). This deviation, indicative of strain, is the result of a ring deformation “outwards”, causing a stretching in the range *ca.* 0.02–0.09 Å. Diaza- and oxa- analogues 6–11 have the largest deformation (0.06–0.09 Å) against a much weaker one for mono-aza 5 or phenalene 2. Much smaller but still noticeable variations, in the range of *ca.* 0.02 Å, are evident among the other H atoms around the structures, indicative of angular strain.^[40] The H₆-H₇ distance is found essentially the same by both B3LYP and MP2 methods, in all but 9. In 9, the calculation shows a notable discrepancy among the two methods (Table 3S of SI). It is

Table 2. Frequencies (ω in cm^{-1}) of out-of-plane vibrations of the 1, 2, 5–11 compounds at the B3LYP/6-311++G** (MP2/6-311++G**) levels of theory.

Comp.	ω		type
1	173	(166)	B(176) ^a
	185	(180)	T(195) ^a
2	84	(58)	wag
	158	(146)	B
	199	(196)	T
	234	(262)	T
	376	(312)	T
5	139	(125)	T
	160	(150)	B
	213	(205)	B
	251	(231)	T
	414	(391)	wag
6	130	(125)	T
	161	(153)	B
	207	(201)	B
	246	(231)	T
	414	(413)	wag
7	137	(129)	T
	162	(156)	B
	216	(211)	B
	257	(243)	T
	426	(360)	wag
8	119	(117)	T
	161	(157)	B
	207	(204)	B
	248	(235)	T
	418	(418)	wag
9	139	(131)	T
	163	(155)	B
	213	(207)	B
	261	(247)	T
10	121	(120)	T
	161	(158)	B
	203	(203)	B
	252	(247)	T
11	137	(131)	T
	161	(157)	B
	217	(212)	B
	264	(253)	T

proposed that this may be the result of an I_p - π interaction between ring oxygen lone pair and naphthalene π density. A similar but negligible interaction clearly exists in 5. N–N and N–O lone pair repulsions outweigh the alternative I_p - π ones in 6, 7 and 9. Such interactions have been scrutinized with various arenes and have been found to be influenced by dispersion forces.^[41] The H_6 - H_7 “outward” stretching is in line with the observed compression of the fusion bonds, mainly the C_{3a} - C_{9aa} and C_{9a} - C_{9aa} ones.

More revealing of the inherent strain are the bond angles of 2–11, particularly C_3 - C_{3a} - C_{9aa} and C_{3a} - C_{9aa} - C_{9a} in the fusion region with a deviation range from 1 of 1.4–4.1° or 1.2–3.7°, respectively (Table 2S of SI). More importantly, the latter appears at a steeper orientation while the former one seems to be affected mainly by the number and arrangement but not the nature of ring heteroatoms. Thus, a sharper bay angle is observed in 5, 6, 9 and 10, a markedly larger in 7 and 8 whereas no change is found in 2 and 11. This is depicted by an

upper “inward” orientation and a corresponding “outward” bottom (C_6 - C_{6a} - C_7) orientation, witnessed by the stretching of the latter in the range of ca.0.6–2.6° and that of the H_6 - H_7 distance. Angles C_3 - C_{3a} - C_4 and C_9 - C_{9a} - X_1 (X_1 :C,N,O) show a marked deviation, in line with the overall deformation. The former is generally stretched out by ca.2–5° throughout the series. The latter, however, is found to be heteroatom-sensitive, following a similar trend in 5–8 while it is contracted by ca. 1–3° in 9–11. The distortion of the hetero ring is further demonstrated by the angle bearing the heteroatoms in 6, 7, 10 and 11 (Table 4S of SI). N atoms cause a change of ca. 5° whereas their partial replacement by an O atom results in a further change of ca.2°. The change is more enhanced in the 1,3-arrangement. Dihedral angles (Table 4S of SI), on the other hand, show that 2, 7 and 9–11 are entirely planar, 5 and 6 are virtually planar (variation in the range of ca. 0.01–0.05°) and it is only 8 that displays some notable deviation from planarity of ca.1–6°. These findings are in excellent agreement with reported experimental results.^[5,17,42]

Overall, 2–11 appear to have a distorted structure in which a somewhat “isolated” heterocycle is “anchored” onto its naphthalene scaffold and the extent of distortion rests upon (a) the number of heteroatoms, (b) their nature and (c) their arrangement in the hetero ring.

Energy differences of the N,N-, N,N,N-, and N,O-compounds are given in Table 1. Planar structures for both N,N- and N,O-compounds, are the lowest energy ones with respect to the zero point corrected energy, enthalpy and Gibbs free energy, at 298.150 K and 1.0 Atm (see Table 1). The planar structures calculated by MP2/6-311++G(d,p) are found of a ca. 4 kcal/mol lower energy than their quasi-planar variants whereas of a significantly lower energy, by ca. 0.1 kcal/mol, are the planar structures found by B3LYP2/6-311++G(d,p) (see Table 1). 7 and 11 (i.e., with the heteroatoms in non-adjacent positions) are of lower energy to 6 and 10 (with contiguous heteroatoms) (see Figure 3) by ca. 18 and 32 kcal/mol, respectively. Two minima were found, for 6 and 8, planar structures 6' and 8' and quasi-planar ones 6'' and 8''. Geminal N,N lone pair repulsion and the shorter N–N bond length, indicative of probably a σ -based ring strain or so-called “bond length strain,^[39] are considered as the cause of relative energy variations.

The out-of-plane vibrations of aromatic bicycles, such as naphthalene,^[9b,42] azanaphthalenes^[42c] and aromatic tricycles, e.g anthracene and phenanthrene [9b], have been studied before. An insight into the out-of-plane vibrations of the so far unexplored 6-membered N,N- and N,O- aromatic heterotri-cycles 5–11 is laid out herein. The lowest vibration frequency modes of 1–2 and 5–11, corresponding to their out-of-plane vibrations are given in Table 2. Three types of vibrations are observed, i.e., the butterfly (B), the twist (T), and the wag (W) modes. B and T modes are characterized by the motion of the bicyclic naphthalene skeleton. The W modes are characterized by the motions of H atoms connected to X atom (see Figure 2). The normal modes are depicted in Figure 5.

Our B3LYP and MP2 calculated vibration frequencies are in very good agreement with earlier experimentally measured out-of-plane vibrations for 1^[42] (see Table 2). The W mode for 2

Table 3. Aromaticity indices^a for azines, diazines and their *peri*-annelated naphthalene analogues.

Compound number	Compound Name	HOMA	I _A	FLU	PDI	ABO	NICS _{iso} (0) ^g	NICS _{zz} (1) ^g	
1	Benzene	0.988 ^b	100 ^{d,e}		0.101 ^f				
	Pyridine	0.995 ^b	85.7 ^{d,e}	0.001 ^f	0.097				
	Pyridazine	0.981 ^b	78.9 ^{d,e}		0.105				
	Pyrimidine	0.999 ^b	84.3 ^{d,e}	0.005 ^f	0.101				
			0.808			0.093 ^f	1.370	-8.6(-8.6)	-10.7(-10.7)
	Naphthalene	(0.795)	142 ^{d,e}	0.0116 ^f	0.073 ^f	(1.365)	-8.4 ^h	-10.5 ^h	
			0.783 ^b			0.076			
	Quinoline	0.792 ^g	134 ^{d,e}	0.015 ^f	0.072 ^f				
				0.017 ^f	0.071 ^f				
	Cinnoline		130 ^{d,e}						
	Isoquinoline		81						
Phthalazine		136 ^{d,e}							
Quinazoline		143 ^{d,e}							
2	Phenalene	0.214			0.076	1.354	6.8(7.2)	2.5(2.7)	
		(0.220)	139.3 (132.6)	0.0227	0.067	(1.254)	-6.5(-6.7)	-8.9(-9.1)	
5		0.738			0.067	1.332	6.3(7.3)	2.9(3.6)	
		(0.732)	71.5 (45.7)	0.0147	0.065	(1.232)	-5.3(-5.7)	-7.8(-8.2)	
6		0.631	141.3		0.067	1.326	7.7(8.7)	2.9(3.6)	
		(0.629)	(129.1)	0.0141	0.067	(1.225)	-5.7(-5.9)	-8.1(-8.4)	
7		0.791			0.068	1.327	8.0(8.9)	3.4(4.1)	
		(0.783)	158.4 (150.4)	0.0183	0.068	(1.223)	-6.8(-7.4)	-8.8(-9.3)	
8		0.700	134.8		0.067	1.329	10.8(11.7)	4.1(4.8)	
		(0.730)	(117.9)	0.0201	0.068	(1.233)	-7.1(-7.4)	-8.9(-9.3)	
9		0.752	83.2		0.071	1.326	6.5(7.2)	2.7(3.2)	
		(0.764)	(65.3)	0.0405	0.067	(1.229)	-6.2(-6.5)	-8.4(-8.8)	
10		0.585	108.7		0.070	1.296	7.1(7.7)	2.5(2.9)	
		(0.594)	(93.8)	0.0120	0.067	(1.194)	-6.5(-6.8)	-8.8(-9.1)	
11		0.398	144.7		0.071	1.322	8.0(8.6)	3.1(3.5)	
		(0.398)	(136.9)	0.0438	0.068	(1.222)	-7.3(-7.8)	-9.2(-9.6)	

^a DFT/B3LYP6-311 + + G**(MP2 6-311 + + G**). ^b Ref. 74; Ref. 47; Ref. 75; ^c Ref 54d. ^d Ref 54e ^e Ref. 54; Ref. 80; Ref. 41. ^f Ref 78c; Ref. 81a; ^g NICS values of the A, B and C rings, see Figure 2. ^h Ref. 66.

is the lowest one ($\sim 80 \text{ cm}^{-1}$) while that for **5** is the highest ($\sim 400 \text{ cm}^{-1}$) among out-of-plane vibrations for all structures. The B mode is lower than the T one for **1**, **2** and **5**, showing a tendency for a B type deformation (see Table 2). The T mode is the lowest in energy ($\sim 130 \text{ cm}^{-1}$) for **6–11** (B mode was measured at $ca. 160 \text{ cm}^{-1}$ and W mode was measured at $ca. 410 \text{ cm}^{-1}$ for **6–8**) (see Table 2).

2.2 Aromatic character

In discussing aromaticity of **5–11**, we should keep in mind that this concept, intriguing as it may still be, after such a massive literature on it, is, in effect, a derivative-concept of a structure profile. Furthermore, both structure and aromaticity serve the ultimate challenge of predicting the reactivity of a structure. Certain indicators, i.e., harmonic oscillator model of aromaticity (HOMA), Bird bond order uniformity (IA), deviation from Average Bond Order (ABO), para-delocalization Index (PDI), aromatic fluctuation Index (FLU) and nucleus-independent

chemical shifts (NICS) have been calculated for the **1**, **2** and **5–11** compounds..

It is known^[33,43] that σ bonds prefer equalization whereas π bonds prefer localization in aromatic rings. Their relative contribution to stability and thence to aromaticity has been a long-debated issue^[18,44] and has been concluded that both contribute to aromaticity.^[18] Clamping by annelation incurs bond localization (alternation) as does ring strain,^[45] thus, some loss of aromaticity. It has been pointed out that aromaticity can resist not only bond alternation but substantial out-of plane distortion,^[45] i.e., the ring possesses conformational flexibility (i.e., deviation from planarity).^[46–48]

The geometry perturbation of a ring reflects the σ and/or π contribution to its distortion and that can serve as an aromaticity descriptor.^[44] A similar trend is found in **5–11**, accompanied by a weak π bond alternation and a partial isolation of the heteroring. Given that π bond localization is only weakly perturbed by *peri*-fusion, then the estimated marked drop of aromaticity can only be attributed to the

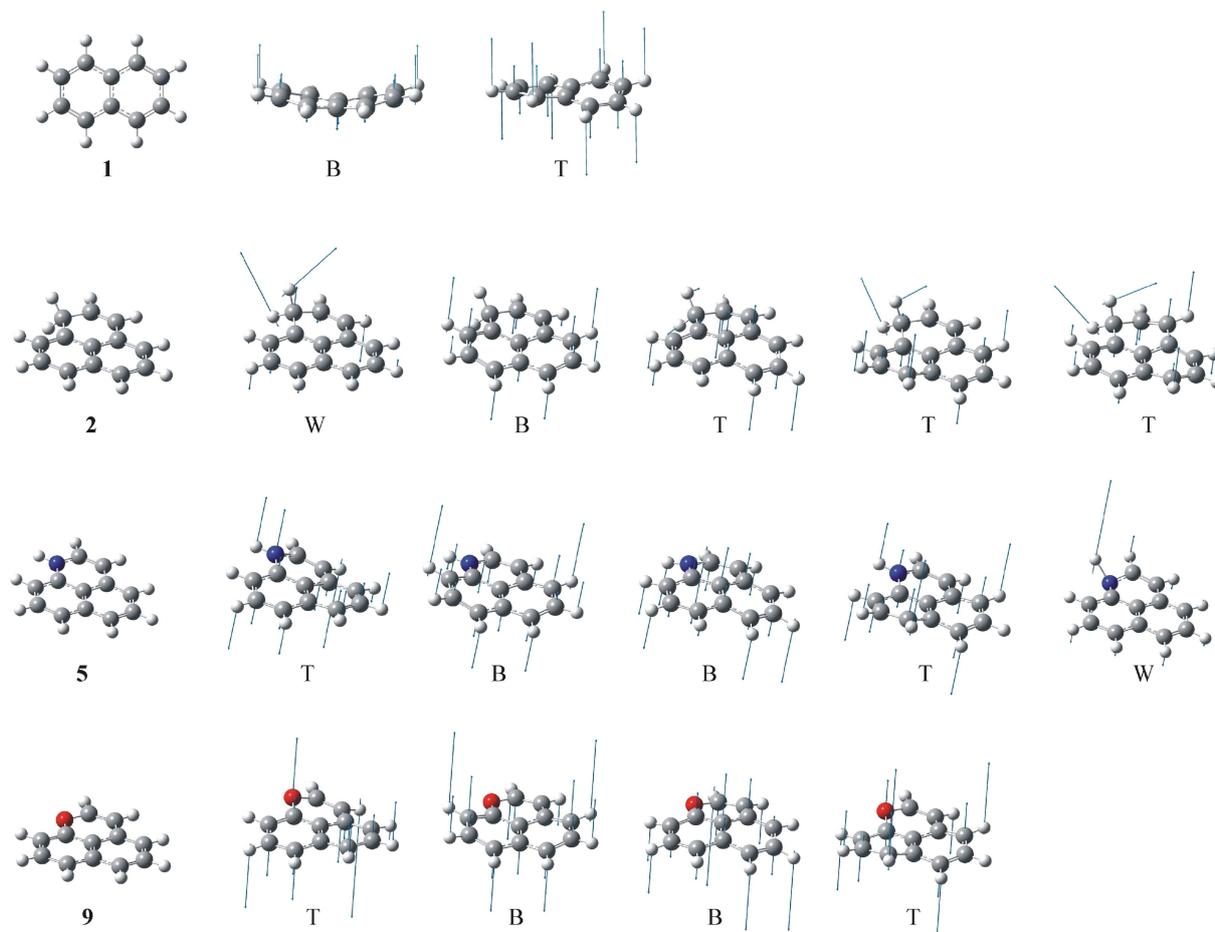


Figure 5. Normal modes of the out-of-plane vibrations for 1, 2, 5, and 9.

distortion of the σ component (Table 3). In other words, the energy cost upon fusion will be that of the compression of the σ frame.

Aza-replacement in a 6-membered ring is known to cause only a small drop of its aromaticity.^[7c,18b,22] A similar replacement in a 5-membered ring is accompanied by an increase of aromaticity, varying with the number and position of N atoms in the structure.^[23a] Measurement of the aromaticity of constituent rings in polycarbocycles^[44,45,49–52] or heterocycles^[44,52,53] has also been reported. Some discrepancies have been found in the aromaticity of the azine series 5–8 (Figure 3), the major ones of which were among contiguously and non-contiguously bonded (i.e. 1,2- and 1,3-, 1,4-) isomers.^[22] The 1,2-aza arrangement has been reported as either less aromatic by resonance energy^[54] or bond order^[44] indices or more aromatic by the *n*-center delocalization index (*n*-DI).^[55] A divergent aromaticity order has also been found in diazines and triazines, using indices such as HOMA, FLU, PDI and I_A ^[20c,53] while HOMED^[56] showed no variation between benzene and the azines. Aza-polycyclic heteroarenes, such as mono- and diaza-naphthalenes, on the other hand, have been found to be less aromatic than naphthalene (Table 3).^[42c] Similarly, all indices used herein,

unequivocally point to naphthalene as that of highest aromaticity.

What we discuss next are calculated aromaticity indices of varying physical manifestation, aiming at a reliable and safe outcome, in regard to the still existent elusive correlation between observability and quantifiability of molecular properties and eventually their reflection on reactivity profile.

HOMA follows a general pattern earlier observed in azines.^[20c,22,56] Indeed, mono-aza(oxa)-ring fused naphthalenes (5 and 9) or diaza-fused analogues, having the heteroatoms not directly bonded (7) exhibit the highest aromatic character, followed by those with contiguous polyaza-substitution (6 and 8). Phenalene 2 and the oxazines 10 and 11 appear to be the least aromatic. A still heteroatom-dependent different order, yet not a clear-cut pattern, is observed with I_A . The latter places a stronger impact on the 1,3-heteroatom arrangement and a detrimental to aromaticity effect of the O incorporation, thus, weighing 7 and 11 at the top of the aromaticity scale, followed by the diaza- and triaza- analogues 6 and 8 with 2 following closely, then 10 and mono-substituted ones 9 and 5. ABO (Table 3), on the other hand, appears to be rather insensitive to the nature, number and arrangement of the heteroatoms. Besides 2 and 10, standing out as the most and the least

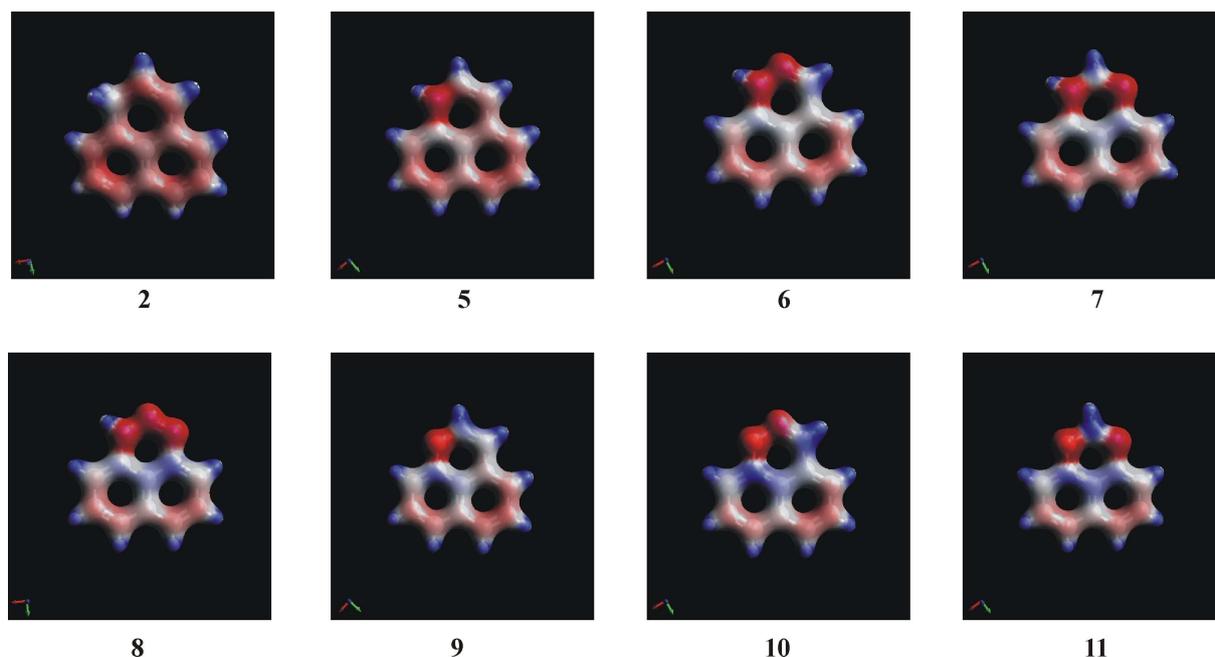


Figure 6. MED computed at the B3LYP/6-311++G(d,p) level

aromatic of the series, respectively, the aromaticity of the rest essentially falls in two groups of similar values, the highest for 5 and 8 and the lowest for 6, 7, 9 and 11.

NICS values, both in plane $\text{NICS}_{\text{iso}}(0)$ and out of plane $\text{NICS}_{\text{zz}}(1)$ have been calculated (Table 3). NICS indices are indicative of a low aromatic character of the series, keeping in mind the limitations and reservations discussed at times.^[20,57,58] MP2 values present a clearer pattern that points to and lends support to the notion of the fused “isolated heteroring” from the rest of the structure (see relevant comments elsewhere in the article). Alternative methods (e.g. NICS_{XY} scan^{181,57}) could, perhaps, offer a better depiction of π distribution over the entire structure.

In essence, however, all descriptors except HOMA seem to have given obscure outcomes throughout the series. It is important to note that all 5–11 are of lower aromaticity to 1 and geometry data indicate a “virtually isolated” heteroring.

The localization pattern of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) orbitals of 1–11 is depicted in Figure 4S of SI. The HOMO is delocalized over the largest part of the structure indiscriminately throughout the series, except around the fusion $\text{C}_{6a}\text{-C}_{9a}$ bond. The LUMO, on the other hand, tends to be delocalized to a varying extent. It is, thus, spread over 5, 10 and 11 but more locally distributed in 2, 6, 7, 8 and 9 in which it is spread over the hetero ring and virtually one of the naphthalene constituent rings.

Both HOMO-LUMO and (HOMO-1)-(LUMO+1) energy separations, $\Delta E_{\text{H-L}}$ or $\Delta E_{(\text{H-1})-(\text{L+1})}$, are quite notable throughout the series (see Figure 5S and Table 6S of the SI), indicating limited charge transfer in the ring and HOMO LUMO sensitivity to *peri*-fusion and nature of the heteroring. Indeed, incorporation of N

atoms contiguously, as in 1,2- and 1,2,3- arrangements, 6 and 8, respectively, causes no changes, in line with previously reported findings on azines.^[45,59] A marginally stronger perturbation accompanies the incorporation of O, as in 9 or partial replacement of N by O atoms, as in 10 and 11. The 1,3-arrangement (as in 7 or 11) appears to have the highest susceptibility to changes, also reflected by the observed distortion (see earlier relevant comments).

Using both B3LYP and MP2 methodologies, charges obtained by Mulliken analysis and the generally more reliable natural bond orbital (NBO), are given in Tables 7S-8S of SI, respectively, whereas local electrophilicity ω and nucleophilicity N indices are shown in Table 9S. MED and MESP contours are schematically shown in Figure 6 and Figure 7 and in Figure 6S of the SI. Electron density appears to concentrate around N and O atoms of the heteroring and over C3-C9.

2.3 Reactivity Profile

Features that dominate a structure invariably accompany or match those that dictate its reactivity profile. Indeed, looking at the structures 5–11, the *peri* bridge of the heteroring as in 6, 8 and 10 (i.e. contiguously disposed heteroatoms) are in fact a hydroxylamine (i.e., 10) or a hydrazine (i.e. 6) entity with an enhanced lone pair availability (the known α effect^[38]). This effect, coined as “ring α effect”, with no apparent impact on the ring π distribution, does appear to have a serious contribution to the σ distortion. This is, indeed, reflected on their geometry (bond lengths and angles, *peri* H–H distance). 5 and 9 integrate an enamine and a vinyl ether segment, respectively, in their heterorings while the individual heteroatoms, N in both tautomeric forms in 7 or O in 11, interact

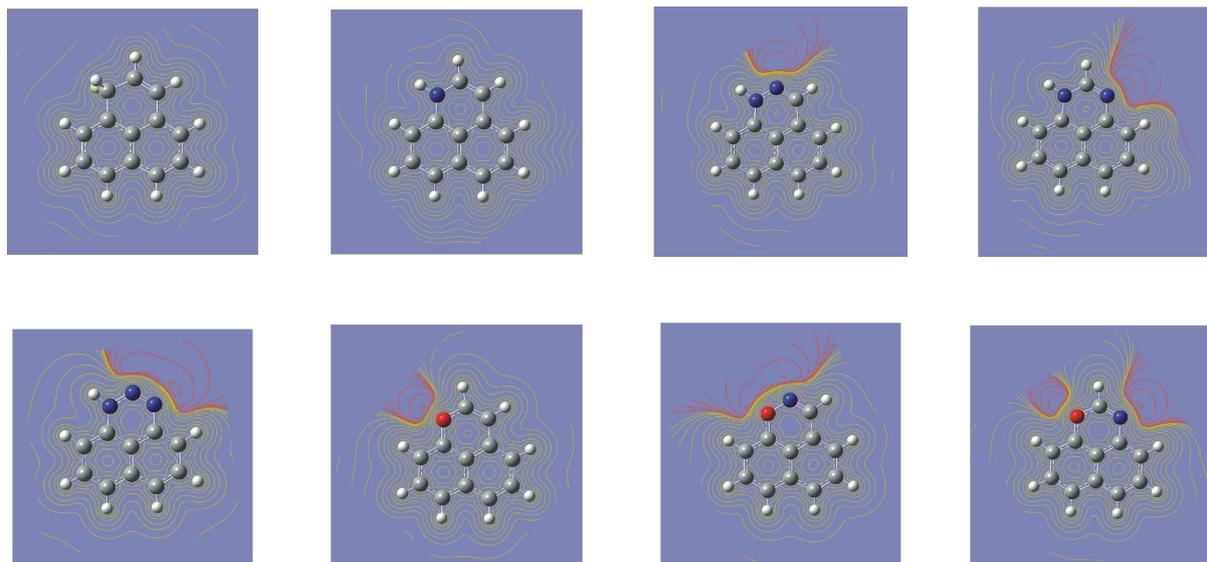


Figure 7. Contours of MESP computed at the B3LYP/6-311++G(d,p) level.

directly with the naphthalene part. These features are pertinent to the expected reactivity of the structures, e.g. facile N–O rupture of **10**^[17] or susceptibility of **6** and **10** towards electrophilic substitution.^[26]

The significance of electron density changes^[60–63] as “sensors” to reactivity are currently an issue under scrutiny. The geometry-based perturbation and extent of electron distribution, has been related to the reactivity pattern.^[64] Local electrophilicity ω and nucleophilicity N indices (Table 9S of SI) give a relatively comprehensive picture of reactive regions,^[65] thus, site selectivities towards electrophiles or nucleophiles. Indeed, the values over C-3–C-9 (Table 9S of SI), reflecting the major reactivity profile towards electrophiles, may be attributed to a combination of triggering effects. Activation in **5–7** can be directed through the masked enamine- in **5**, hydrazine- in **6** and aza enamine- in **7** whereas an NH-directed conjugation through naphthalene accounts for an activation at C-6 and C-9 with a preponderance of the latter. In **6** and **10**, the hydrazine- and hydroxylamine- α -effects, respectively, trigger an NH- or an O-driven conjugation through the naphthalene ring at C-6 (or C-7) and C-9. Similarly, the masked vinyl ether in **9** directs activation by an O-driven conjugation through the naphthalene ring, primarily at C-6 and to a lesser extent at C-3. In **11**, N- and O-driven conjugations direct preferably at C-6 and C-2 (or C-4). In **8**, an NH-driven conjugation with the naphthalene ring by both tautomeric forms of the triazine ring appears to direct preferably at C-6 (or C-7) and C-4. To a much lesser extent C-2 and C-5–7 can be considered as sites susceptible to nucleophilic attack. Looking at the chemical potential μ and hardness η values (Figure 3) as reactivity “sensors”, one may place **11** as the least and **6** and **8** as most susceptible to distortion (more reactive?) in a descending order of **11** > **2,7,9** > **5,10** > **6,8**. This susceptibility appears to succumb to the contiguity of the heteroatoms and not their nature, throughout the series.

Calculated and experimental chemical shifts, on the other hand (Tables 10 > S and 11S of SI), indicate H-9 preferably and H-4 nuclei as the most shielded ones, throughout the series, except **8** in which H-7 appears to be the most shielded one. The shielding order in **5–7** and **11** is H-9 > H-4 and this is reversed in **9** and **10**. HOMOs also have a considerable contribution at those sites. LUMOs appear to be distributed over a benzo-fused heteroring part in **6–9**, indicating one clear Clar sextet in the structures whereas a more diffuse distribution is observed in **5**, **10** and **11**.

3. Conclusions

- *Peri*-fusion has an impact on the geometry and aromaticity of the structures, i.e., it triggers a distortion by an “outward” stretching of their lower part and a corresponding “inward” compression of their upper one.
- The bond length and angle variation ranges suggest that (a) the structure suffers distortion to release strain, (b) the carbocyclic part (“in any combination”) is always more aromatic than its heterocyclic counterpart and (c) the heterocycle is somewhat “isolated” from the rest of the molecule.
- Incorporation of N and/or O atoms in the ring causes an aromaticity drop. The latter is larger when the heteroatoms are contiguously bonded, due to N–N(O) lone pair repulsion i.e., alternating N–C–N(O) is more stabilizing than N–C–C–N(O), N–N–N or N–O sequences. Of the descriptors used only HOMA appears to indicate a meaningful trend in the series.
- The mainly electrophilic profile of the series, as demonstrated by the local electro(nucleo)philicity indices as well as μ and η values, lend support to the susceptibility to distortion and expected reactivity pattern.

- The term "ring α -effect" has been coined for structures, such as **6** and **10**, to account for the observed and calculated electrophilic character over C-3-6-9 and preferably around the latter.
- The reactivity features of the heteroring apparently guide the reactivity profiles of our *peri*-annelated structures.

Supporting Information Summary

Methodology, Geometries, Energetics, NBO and Mulliken Charges, Aromaticity and Reactivity descriptors, Main Molecular Orbitals, Contours and Surfaces of MED, and NMR data have been provided in Supporting Information

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: calculations · DFT · Naphthalene · N,N-heterocycles · N,O-heterocycles · *peri*-annelated heterocycles

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