Synthesis of Fused Perimidinium Derivatives and Investigation of Their Structure by ab Initio Calculations

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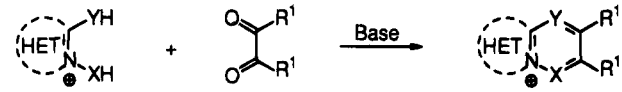
A series of perimidinium salts have been prepared by N-alkylation and N-amination methods. These salts were condensed with 1,2-dicarbonyl compounds and quinones (Westphal condensation) to produce pyridazino[2,3-*a*]perimidinium and, in one case, pyrido[2,3-*a*]perimidinium derivatives. Two of these heteroaromatic cations were studied by ab initio calculations at the SCF (self-consistent field) level using different basis sets. From Mulliken population analysis and geometrical considerations, it is predicted that the pyrrole-like nitrogen of the perimidinium moiety is lying out of the planarity, thus reducing the interaction with the fused pyridazinium ring.

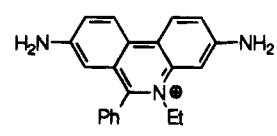
Our recent studies have demonstrated that the Westphal condensation (Chart 1) is one of the easiest methods for preparing polycyclic systems containing a bridgehead quaternary nitrogen.[1] Although the classical procedure was described for "C–C substrates",[2] a variety of 1,2-diketones also react with "N–N"[3] and "N–C substrates".[1] The reaction was proven to be the key step in the preparation of a variety of azinium[1-4] and azolium[5] cations and was applied to a simple synthetic route to Flavocorylene,[1c] an alkaloid incorporating the indolo[2,3-*a*]quinolizinium ring system. More recent studies also showed good regioselectivity when unsymmetrically substituted 1,2-diketones were used.[6]

The above studies were initiated with the goal of finding an easy route from simple heterocycles to new classes of DNA intercalators.[7] The typical synthetic

Chart 1



N-N Substrates: X = Y = NH
N-C Substrates: X = NH; Y = CHR
C-C Substrates: X = CHR; Y = CHR
HET = Heteroaromatic



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intercalating agents such as ethidium bromide **1**,[8] celiptium **2**,[9] and other heteroaromatic cations used as chromophores in bis-intercalators[7,10] have as a common characteristic a quaternary nitrogen, usually achieved by alkylation of the neutral heterocycle. In spite of the fact that the clinical properties of DNA-intercalating agents strongly depend on minor chemical modifications, no attention has been paid to chromophores with bridgehead quaternary nitrogen. This fact and recent finding by Gago et al.[11] on the role of the electrostatic term of the stacking interactions and the importance of modulating the dipole moment of the intercalating chromophores stimulated our interest in the DNA-binding properties of these classes of chromophores.

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Although it is too early to discuss our overall plan for the different unusual heterocycles which we have chosen as candidates for further transformation into polycyclic cations, perimidine is seen to be an interesting example, with unusual electronic properties in that it is one of the few azines that simultaneously shows characteristics of a π-deficient and a π-excessive system.[12] Furthermore, perimidine itself and a series of perimidine derivatives have been reported to have in vivo antitumoral activity and DNA-intercalating properties.[13] In this paper, we report on the synthesis of pyridazino[2,3-*a*]perimidinium derivatives and one example of a pyrido[2,3-*a*]perimidinium salt, and with the aid of ab initio calculations, structural information on some of them is provided.

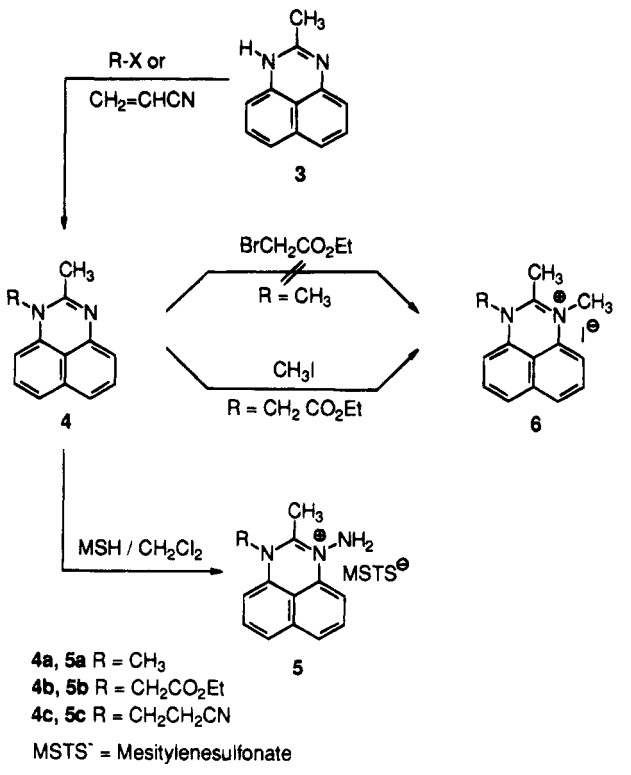
Computational Methods

The electronic structures of the cationic pyridazino[2,3-*a*]perimidinium derivatives were studied using ab initio MO techniques. Theoretical calculations were performed at the SCF (self-consistent field) level of theory. All geometrical optimizations were carried out using Schlegel's algorithm.[14] The 3-21G[15] basis set was used to optimize the geometries. The energies were recalculated by single point calculations at the HF/6-31G** and the MP2/6-31G**[16] levels of theory on the HF/3-21G geometries. The charges were obtained from the Mulliken population analysis of the HF/6-31G** wave function. All calculations were performed using the GAUSSIAN-92 programs.[17]

Results and Discussion

In general, perimidine derivatives were difficult compounds with which to work. The π-excessive nature of the naphthalene ring makes the compounds susceptible to aerial oxidation, and the yields in several reactions are low even under an inert atmosphere. The 2-methylperimidine **3** was prepared according to the method reported by Whiterturst,[18] and subsequent N-alkylation and cyanoethylation was carried out following the procedure described by Paragamian.[19] The N-alkylated derivatives **4** were easily transformed into the salts **5** (N−C substrates) by amination with (*O*-mesitylenesulfonyl)hydroxylamine (MSH) in dicloromethane at room temperature (Scheme 1). This method was previously reported by Tamura[20] for the preparation of salt **5a** (92% yield), and we also obtained the salts **5b,c** in good yields using this method (80% for **5b** and 74% for **5c**). The derivative **4c** was also aminated with hydroxylamine-*O*-sulfonic acid (HOSA) to yield the salt **5c** in lower yield

Scheme 1



(52%). To obtain the derivative **6** as a model for the C−C substrates, the 1,2-dimethylperimidine **4a** was allowed to react with ethyl bromoacetate in dimethoxyethane in the presence of 1 equiv of sodium hydride. After several hours at room temperature, the starting material was consumed and the reaction mixture was worked up to afford the hydrobromide of **4a** as the main product. This result was unexpected since the reaction of 1-methylperimidine with ethyl bromoacetate has been reported to yield the N-alkylated derivative in 55% yield. An alternative preparation of the salt **6** by methylation of the derivative **4b** with a large excess of methyl iodide in ethyl acetate at reflux for 8 h gave the desired salt in 73% yield.

Having the desired substrates on hand, we next studied their reaction with different 1,2-dicarbonyl compounds. Initial experiments were carried out by using previously developed standard conditions with sodium acetate as base and acetone as solvent. Under these conditions, the N−C substrates (salts **5a−c**) reacted with several 1,2-diketones such as 2,3-butanedione, 3,4-hexanedione, and benzyl to afford the pyridazino[2,3-*a*]-perimidinium derivatives **7** (Scheme 2). When quinones such as 1,2-acenaphthenequinone and 9,10-phenanthrenequinone were used, derivatives **8** and **9** were obtained.

The highest yields were obtained with salt **5a** and quinones or benzyl. However, when aliphatic diketones and/or salts **5b,c** were reacted, the condensation products were obtained in moderate to low yields. Furthermore, when these conditions were applied to salt **6** (C−C substrate), the salt was extensively recovered after 24 h at reflux, and no evidence of the formation of the condensation product was observed. We therefore tested other bases such as *n*-butylamine and triethylamine and solvents such as ethanol or *N,N*-dimethylformamide (DMF). As a result of these studies, we found that the triethylamine/ethanol system was the best combination not only to increase the yields obtained with **5a** and

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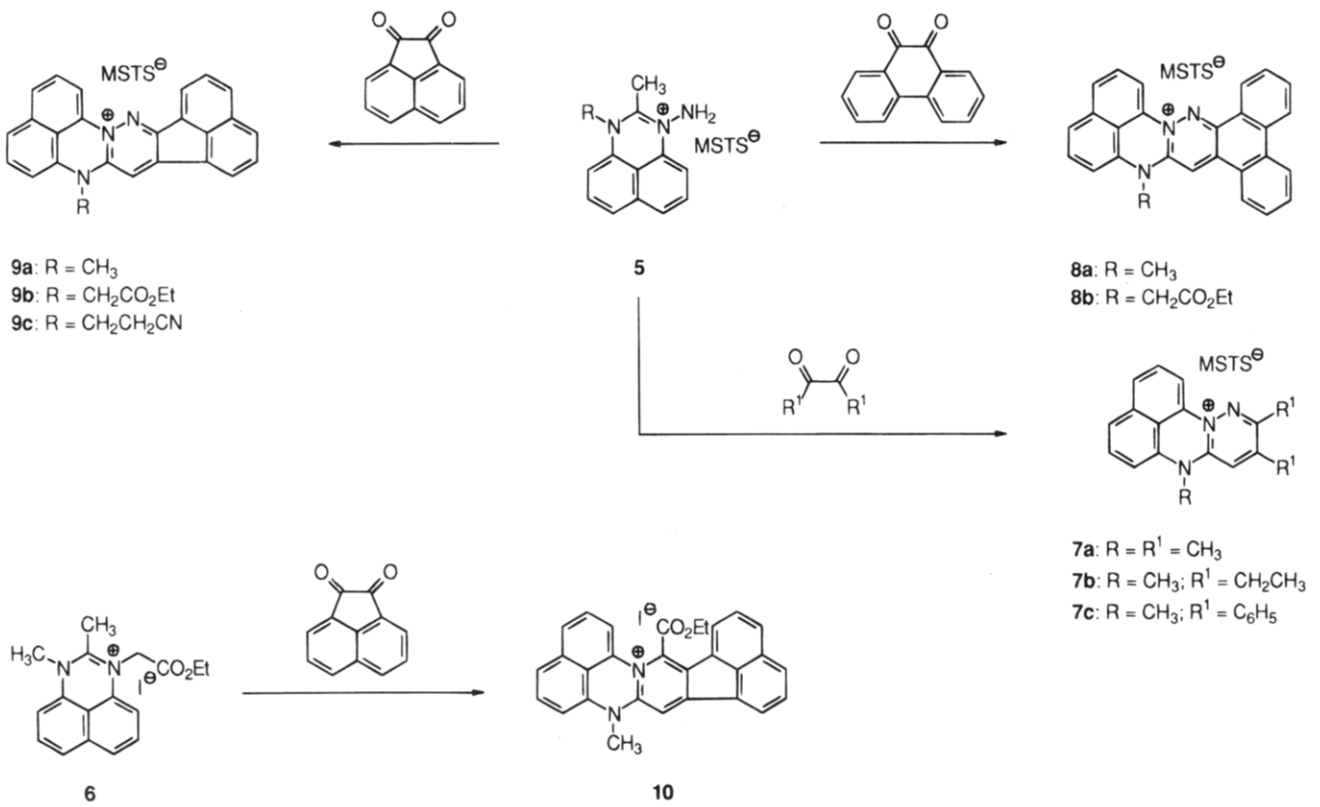
Scheme 2



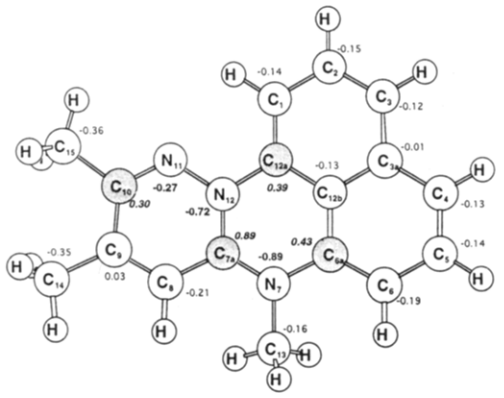


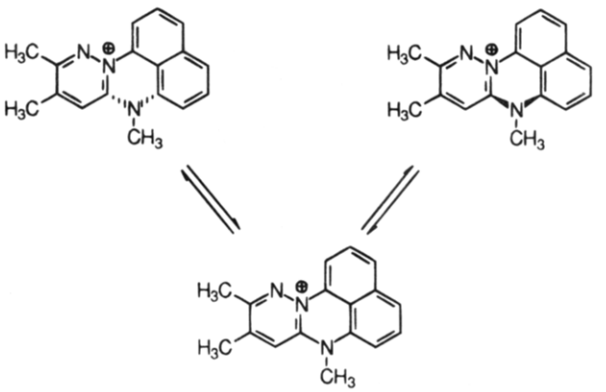
Figure 1. Optimized geometry and atomic charges for compound **7a** obtained at the HF/6-31G** level.

aliphatic diketones but also to improve in some cases those achieved with salts **5b,c**. However, our efforts to obtain the condensation products from salt **6** were fruitless, except in the case of 1,2-acenaphthenequinone which afforded a moderate yield (36%) of the condensation product **10**.

When titration of compounds **7**−**10** with calf thymus DNA in aqueous solutions was attempted in order to determine hypochromicity and DNA-binding constants, all the compounds were found to be insufficiently soluble for reliable data to be obtained, and precipitation of partially soluble complexes occurred in different common buffers.

Since up to now we have not been able to overcome this problem, we decided to investigate the electronic structure of the fused perimidinium cations obtained. Hence, compounds **7a** and **9a** were chosen for the study of their electronic densities and molecular geometric structures using ab initio theoretical techniques.

The geometry of cation **7a** is presented in Figure 1, and the calculated geometrical parameters obtained are listed in Table 1. The fully optimized structure shows C_1 symmetry which is slightly nonplanar with the N7 atom lying 11.6° out of the plane. If planarity is imposed, a C_s structure is obtained which shows an imaginary frequency of 100i cm^{-1}. The frequency is an internal rotation of the methyl group of the atom C13. The energy difference between this transition structure and the minimum energy structure is 0.99 kcal/mol at the HF/3-21G level of theory. When the energy is recalculated at the HF/6-31G** and MP2/6-31G* levels, the C_1 structure is still more stable by 1.33 kcal/mol and 1.50 kcal/mol, respectively. From these energy data, the potential energy barrier between the two conformers (C_1 structures) is small enough to assume an equilibrium between them that leads to an averaged planar geometry (eq 1) if the temperature effects are considered.



The charges on heavy atoms for the nonplanar structure are also presented in Figure 1. As expected, the hydrogen atoms showed positive charges ranging from

Table 1. Optimized Geometrical Parameters for 7a[a]

bond lengths (3-21G)		bond angles (3-21G)			
C1–C2	1.409	C1–C2–C3	120.8	C12–C12a–C12b	116.3
C2–C3	1.356	C2–C3–C3a	120.6	C12a–C12b–C6a	121.3
C3–C3a	1.416	C3–C3a–C4	122.2	C12b–C6a–N7	116.8
C3a–C4	1.419	C3a–C4–C5	120.0	C6a–N7–C7a	121.7
C4–C5	1.352	C4–C5–C6	121.2	C6–C6a–C12b	119.5
C5–C6	1.413	C5–C6–C6a	120.4	C6a–C12b–C3a	120.0
C6–C6a	1.359	C6–C6a–N7	123.7	C12b–C3a–C4	118.9
C6a–N7	1.435	C6a–N7–C7a	121.7	C3–C3a–C12b	118.6
N7–C7a	1.337	C7a–N7–C13	117.9	C3a–C12b–C12a	118.6
C7a–C8	1.430	N7–C7a–C8	122.2	C12b–C12a–C1	121.8
C8–C9	1.344	C7a–C8–C9	120.9	C12a–C1–C2	119.2
C9–C10	1.444	C8–C9–C10	117.9	N11–N12–C12a	113.9
C10–N11	1.282	C9–C10–C11	121.2	N12–C12a–C1	121.9
N11–N12	1.337	C7a–C12–C12a	122.6	C14–C9–C8	122.0
N12–C12a	1.434	C10–C11–C12	119.9	C14–C9–C10	120.2
N12–C7a	1.335	C8–C7a–C12	116.6	C15–C10–C9	121.2
C12a–C12b	1.410	C11–C12–C7a	123.5	C15–C10–N11	117.6
C12a–C1	1.355				
N7–C13	1.486				
C9–C14	1.505				
C10–C15	1.504				

[a] Bond lengths are in angstroms and bond angles in degrees.

0.163 to 0.224. All three nitrogen atoms show a negative charge, with the N7 which is in out of plane arrangement the most negative. The carbon atoms α-bonded to the nitrogens show a positive charge, with the C7a which is the most positive carbon atom linked to the most negative N7 atom. The rest of the carbon atoms show either essentially neutral or negative charges. This charge distribution is supported by the resonance structure **7a-(II)** (eq 2).

7a(I) **7a(II)**

Both geometrical and electronic considerations support the fact that the heterocyclic ring of the perimidinium moiety (ring N7–C7a–N12–C12a–C12b–C6a) has, as it happens in perimidine itself, nonaromatic character, and the interaction of the N7 nitrogen lone pair and the pyridazinium ring is strongly reduced as a consequence of the out-of-plane position of N7. In Figure 2, the HOMO, LUMO, and next HOMO (HOMO − 1) and their energy levels are presented for the cation **7a** (C_s structure). Only atomic orbitals with coefficients larger than 0.1 are depicted. Both HOMO and HOMO − 1 show nonbonding interactions between the N7 atom and whichever of the ring moieties (pyridazinium and naphthalene). The bonding interactions between the N7 and the whole cation are found in the first and second occupied molecular orbitals (MO) of the π-system. The first π-occupied MO ($\epsilon_1 = -0.824\ 53$ au) shows coefficients of 0.35, 0.35, and 0.44 for the N7, C7a, and N12 atoms, respectively. The second π-occupied MO ($\epsilon_2 = -0.640\ 37$ au) shows a bonding interaction between the N7 atom and the naphthalene moiety. The other MOs show essentially either nonbonding interactions ($\epsilon_3 = -0.639\ 36$ au, $\epsilon_4 = -0.585\ 21$ au, and $\epsilon_5 = -0.518\ 23$ au) or even antibonding interactions ($\epsilon_6 = -0.518\ 23$ au) with respect to the pyridazinium moiety, and $\epsilon_7 = -0.491\ 63$ au with respect to the naphthalene moiety.

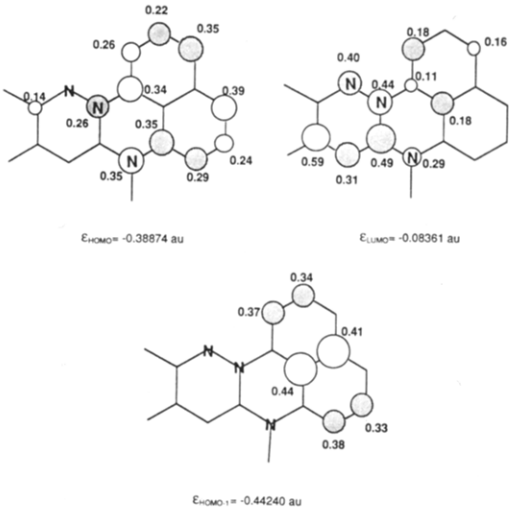


Figure 2. HOMO, LUMO, and HOMO − 1 MO of the cation **7a** with the orbital energies and the renormalized HF/6-31G*//HF/3-21G MO coefficients.

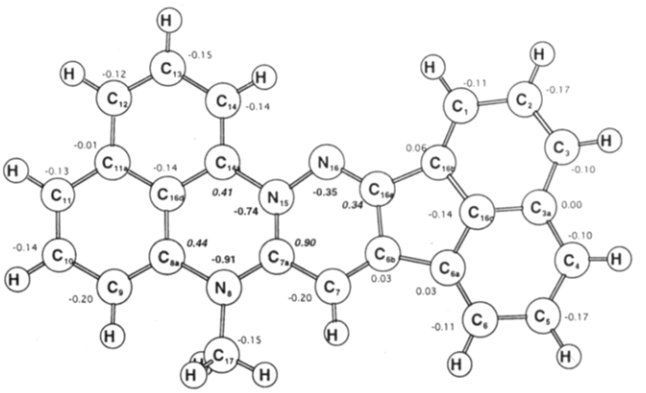


Figure 3. Optimized geometry and atomic charges for compound **9a** obtained at the HF/6-31G** level.

The geometry of cation **9a** is presented in Figure 3, and the calculated geometrical parameters obtained are listed in Table 2. Cation **9a** presents a stronger aromatic character than cation **7a** due to the fused acenaphtho moiety at carbon atoms C6b and C16b. Geometrical optimizations of cation **9a** have been restricted to C_s

Table 2. Optimized Geometrical Parameters for 9a[a]

bond lengths (3-21G)		bond angles (3-21G)			
C1–C2	1.409	C1–C2–C3	122.1	C8–C8a–C16d	117.6
C2–C3	1.356	C2–C3–C3a	120.4	C8a–C11d–C14a	120.8
C3–C3a	1.416	C3–C3a–C4	127.5	C7–C7a–N15	117.5
C3a–C4	1.419	C3a–C4–C5	120.6	C7a–N15–N16	124.2
C4–C5	1.352	C4–C3a–C16c	116.2	N15–N16–C16a	117.7
C5–C6	1.413	C4–C5–C6	122.0	C6b–C16a–N16	122.8
C6–C6a	1.359	C5–C6–C6a	118.3	C7–C6b–C16a	118.6
C6a–C6b	1.461	C6–C6a–C6b	134.7	N16–C16a–C16b	129.1
C6b–C7	1.341	C6a–C6b–C7	134.0	C1–C16b–C16a	134.9
C7–C7a	1.435	C6b–C7–C7a	119.1	C16a–C16b–C16c	105.3
C7a–N8	1.341	C7–C7a–N8	122.7	C6a–C16c–C16b	113.2
N8–C8a	1.430	C7a–N8–C8a	122.2	C6b–C6a–C16c	105.9
C8a–C9	1.360	C17–N8–C8a	115.2	C6a–C6b–C16a	107.4
C9–C10	1.413	C7a–N8–C17	122.6	C6b–C16a–C16b	108.1
C10–C11	1.353	N8–C8a–C9	122.5	C1–C16b–C16c	119.8
C11–C11a	1.417	C8a–C9–C10	120.0	C2–C1–C16b	118.1
C11a–C12	1.415	C9–C10–C11	121.2	C3a–C16c–C16b	123.3
C12–C13	1.357	C10–C11–C11a	120.1	C3–C3a–C16c	116.3
C13–C14	1.409	C11–C11a–C16d	118.8	C6–C6a–C16c	116.3
C14–C14a	1.356	C8a–C16d–C11a	120.0	C6a–C16c–C3	123.5
N15–N16	1.390	C9–C8a–C16d	119.9		
N16–C16a	1.270	C11–C11a–C12	122.5		
C16a–C16b	1.469	C16d–C11a–C12	120.4		
C16b–C16c	1.408	C11a–C12–C13	120.0		
C6a–C16c	1.413	C12–C13–C14	121.0		
C3a–C16c	1.381	C13–C14–C14a	119.2		
C1–C16b	1.357	C14–C14a–C16d	121.4		
C6b–C16a	1.461	C14a–C16d–C11a	119.2		
C7a–C15	1.347	C14a–N15–N16	122.1		
N8–C25	1.480	C14a–C15–C16	112.6		
C8a–C16d	1.415	C7a–C15–C14a	123.1		
C11a–C16d	1.404	C16d–C14a–N15	116.5		
C14a–C16d	1.407	C8–C7a–N15	119.8		

[a] Bond lengths are in Angstroms and bond angles in degrees.

symmetry due to the similarities between the planar and the nonplanar electronic structures found for cation **7a**. In order to compare both cations, the HF/6-31G** wave functions have also been obtained. In Figure 2, the charges on the heavy atoms of cation **9a** are presented. No meaningful differences with respect to cation **7a** were obtained. The electronic structure of cation **9a** shows properties similar to that of cation **7a**, the stronger aromatic character of the acenaphtho moiety not being seen to affect the electronic structure of the perimidinium cation.

The MOs of the π-system of cation **9a** are closely related to those previously presented for **7a**. For instance, the HOMO, LUMO, and HOMO − 2 are essentially the same MOs as the HOMO, LUMO, and HOMO − 1 of cation **7a**. The energy levels of the HOMO, LUMO, and HOMO − 2 are −0.8973, −0.379 96, and −0.435 12 au, respectively. The HOMO − 1, which has an energy of −0.409 05, is a MO of the acenaphtho moiety.

In conclusion, the Westphal synthesis has been succesfully applied to N–C perimidinium substrates, yielding pyridazino[2,3-*a*]perimidinium derivatives **7** and **9** and, in one case, to a C–C substrate, yielding pyrido-[2,3-*a*]perimidin-15-ium salt **10**. The unusual structure of the fused perimidinium derivatives, in which an electron-donating nitrogen is linked to a positively charged pyridazinium ring, has been studied by the use of ab initio geometric optimization. From these results, the interaction between the nitrogen lone pair of electrons and the pyridazinium ring was seen to be extremely reduced, showing an out-of-plane position for the nitrogen in the lowest energy conformers.

Experimental Section

All melting points were measured in open capillay tubes and are uncorrected. Infrared spectra were recorded as KBr pellets, and spectral bands are reported in cm^{-1}. NMR spectra were recorded at 300 MHz, and the chemical shifts are expressed in parts per million downfield from tetramethylsilane, with multiplicity, coupling constants in hertz, and the number of protons. The chemical shifts of the protons of the mesitylenesulfonate anion at δ 6.66 (s, 2H), 2.45 (s, 6H), and 2.11 (s, 3H) ppm are omitted for clarity in the ^1H NMR spectra of the corresponding salts. Elemental analyses were perfomed in the microanalytical laboratory of the university. The calculations were performed on a Supercomputer FUJITSU VP 2400. All chemicals were of reagent grade and were used without further purification.

The following compounds were prepared by known literature procedures: 1*H*-2-methylperimidine (3), mp 216–117 °C (lit.[18] mp 215–216 °C); 1,2-dimethylperimidine (4a), mp 130–131 °C (lit.[19,21] mp 130–131 °C); ethyl 2-methylperimidine-1-acetate (4b), mp 132–133 °C (lit.[19] mp 132–133 °C); 3-(2-methylperimidine)-1-propionitrile (4c), mp 145–146 °C (lit.[19] mp 145–146 °C); 3-amino-1,2-dimethylperimidin-3-ium mesitylenesulfonate (5a), mp 234–236 °C (lit.[20] mp 236–237 °C).

General Procedure for the Preparation of Salts 5. A solution of MSH (1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise under an argon atmosphere to an ice-cooled solution of **4** (1 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 1 h and cooled, and the precipitated crystals formed were collected by filtration, washed with ethyl ether, and recrystallized to give pure products.

3-Amino-1-[(ethoxycarbonyl)methyl]-2-methylperimidin-3-ium mesitylenesulfonate (5b): yellow powder from EtOH/Et_2O (80%); mp 193–195 °C; IR (KBr) 3290, 3161, 2978,

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2936, 1738, 1655, 1590, 1554, 1490, 1174, 1085 cm^{-1}; ^1H NMR (DMSO-d_6) 7.7–7.6 (m, 3H), 7.50 (t, J = 8.0, 1H), 7.37 (d, J = 7.5, 1H), 6.98 (d, J = 7.5, 1H), 6.20 (bs, NH_2), 5.14 (s, 2H), 4.25 (q, J = 7.1, 2H), 2.86 (s, 3H), 1.25 (t, J = 7.1, 3H). Anal. Calcd for $C_{25}H_{29}N_3O_5S$: C, 62.08; H, 6.06; N, 8.69. Found: C, 61.90; H, 6.26; N, 8.53.

3-Amino-1-(cyanoethyl)-2-methylperimidin-1-ium mesitylenesulfonate (5c): yellow powder from EtOH/EtOAc (74%); mp 181–183 °C; IR (KBr) 3265, 3160, 2933, 2252, 1738, 1649, 1605, 1588, 1489, 1376, 1247, 1175, 1084 cm^{-1}; ^1H NMR (DMSO-d_6) 7.64 (d, J = 8.6, 2H), 7.56 (t, J = 8.0, 1H), 7.51 (t, J = 8.0, 1H), 7.31 (d, J = 7.7, 1H), 7.21 (d, J = 7.7, 1H), 6.11 (bs, NH_2), 4.49 (t, J = 7.0, 2H), 3.27 (s, 3H), 3.10 (t, J = 7.0, 2H). Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.34; H, 5.94; N, 12.19.

3-[(Ethoxycarbonyl)methyl]-1,2-dimethylperimidin-3-ium Iodide (6). To a suspension of **4b** (0.43 g, 1.6 mmol) in dry ethyl acetate (5 mL) was added iodomethane (4.3 mL, 69.1 mmol) under an argon atmosphere. The reaction mixture was heated at reflux for 8 h and cooled to room temperature and the precipitate collected by filtration, washed with acetone, and recrystallized from EtOH/Et_2O to give the salt **6** (73%) as a yellow powder: mp 195–199 °C; IR (KBr) 2986, 2868, 1743, 1641, 1588, 1564, 1493, 1378, 1274, 1261, 1028 cm^{-1}; ^1H NMR (DMSO-d_6) 7.7–7.4 (m, 5H), 7.26 (d, J = 8.1, 1H), 5.18 (s, 2H), 4.25 (q, J = 7.1, 2H), 3.65 (s, 3H), 2.76 (s, 3H), 1.27 (t, J = 7.1, 3H). Anal. Calcd for $C_{17}H_{19}IN_3O_2$: C, 49.76; H, 4.68; N, 6.83. Found: C, 49.52; H, 4.92; N, 7.23.

General Procedure for the Condensation of Salts 5 and 6 with 1,2-Dicarbonyl Compounds. Method A. An equimolar mixture of the corresponding salt (10 mmol) and the dicarbonyl derivative and anhydrous sodium acetate (0.82 g, 10 mmol) were suspended in dry acetone (15 mL). The mixture was heated at reflux for the time indicated below, and the precipitate was collected by filtration, washed with water and acetone, and recrystallized from a suitable solvent to yield analytical grade compounds.

Method B: The same amounts of salt and dicarbonyl compounds used in the method A were heated at reflux in ethanol (12 mL) in the presence of triethylamine (1.01 g, 10 mmol). The solvent was evaporated under reduced pressure, and the oily residue was triturated with ethyl ether. The solid formed was collected, washed with ethyl ether, and recrystallized, yielding pure condensation products.

7,9,10-Trimethylpyridazino[2,3-*a*]perimidin-12-ium mesitylenesulfonate (7a): prepared by method B (6 h) in 80% yield; brown prisms from EtOH/Et_2O; mp 225–227 °C dec; IR (KBr) 2970, 1642, 1587, 1537, 1490, 1191, 1084 cm^{-1}; ^1H NMR (DMSO-d_6) 8.22 (s, 1H), 7.88 (d, J = 7.6, 1H), 7.78 (d, J = 8.0, 1H), 7.6–7.5 (m, 3H), 7.14 (d, J = 7.1, 1H), 3.57 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H). Anal. Calcd for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.61. Found: C, 65.39; H, 5.87; N, 9.51.

9,10-Diethyl-7-methylpyridazino[2,3-*a*]perimidin-12-ium mesitylenesulfonate (7b): prepared by method B (20 h) in 60% yield; brown prisms from EtOH; mp 296–298 °C dec; IR (KBr) 2976, 2935, 1643, 1624, 1601, 1583, 1488, 1457, 1375, 1187, 1084 cm^{-1}; ^1H NMR (DMSO-d_6) 8.19 (s, 1H), 7.99 (d, J = 7.3, 1H), 7.86 (d, J = 8.1, 1H), 7.7–7.5 (m, 3H), 7.24 (d, J = 7.1, 1H), 3.75 (s, 3H), 3.6 (m, 4H), 1.50–1.40 (m, 6H). Anal. Calcd for $C_{28}H_{31}N_3O_3S{\cdot}H_2O$: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.34; H, 6.34; N, 8.11.

7-Methyl-9,10-diphenylpyridazino[2,3-*a*]perimidin-12-ium mesitylenesulfonate (7c): prepared by method A (7 h) in 90% yield; red needles from EtOH/H_2O; mp 281–283 °C; IR (KBr) 3054, 2978, 2928, 1640, 1620, 1578, 1539, 1482, 1450, 1372, 1191, 1082 cm^{-1}; ^1H NMR (DMSO-d_6) 8.37 (s, 1H), 7.97 (d, J = 7.9, 1H), 7.87 (d, J = 8.3, 1H), 7.7–7.3 (m, 13H), 7.27 (d, J = 7.8, 1H), 3.76 (s, 3H). Anal. Calcd for $C_{36}H_{31}N_3O_3S$: C, 73.81; H, 5.35; N, 7.18. Found: C, 73.72; H, 5.50; N, 7.18.

10-Methylphenanthro[9′,10′-5,6]pyridazino[2,3-*a*]perimidin-17-ium mesitylenesulfonate (8a): prepared by method A (8 h) in 70% yield; dark red needles from EtOH/H_2O; mp 291–193 °C; IR (KBr) 2927, 1641, 1615, 1599, 1576, 1529, 1495, 1192, 1083 cm^{-1}; ^1H NMR (DMSO-d_6) 9.10 (d, J = 7.2, 1H), 8.8–8.7 (m, 2H), 8.69 (d, J = 8.8, 1H), 8.64 (d, J = 8.1, 1H) 8.31 (d, J = 7.8, 1H), 8.0–7.5 (m, 8H), 7.24 (d, J = 7.1, 1H), 3.86 (s, 3H). Anal. Calcd for $C_{36}H_{29}N_3O_3S$: C, 74.07; H, 5.02; N, 7.20. Found: C, 74.30; H, 5.12; N, 7.17.

10-[(Ethoxycabonyl)methyl]phenanthro[9′,10′-5,6]pyridazino[2,3-*a*]perimidin-17-ium mesitylenesulfonate (8b): prepared by method B (24 h) in 35% yield; dark red needles from EtOH/H_2O; mp 162–165 °C dec; IR (KBr) 2929, 1739, 1645, 1601, 1575, 1524, 1475, 1445, 1373, 1210, 1082 cm^{-1}; ^1H NMR (DMSO-d_6) 9.1–8.9 (m, 3H), 8.8–8.7 (m, 2H), 8.44 (d, J = 7.3, 1H), 8.0–7.3 (m, 8H), 6.95 (d, J = 7.2, 1H), 5.40 (s, 2H), 4.30 (q, J = 7.3, 2H), 1.33 (t, J = 7.3, 3H). Anal. Calcd for $C_{39}H_{33}N_3O_5S$: C, 71.43; H, 5.08; N, 6.41. Found: C, 71.68; H, 4.75; N, 6.08.

8-Methylacenaphtho[1′,2′-5,6]pyridazino[2,3-*a*]perimidin-15-ium mesitylenesulfonate (9a): prepared by method A (8 h) in 90% yield; brown needles from EtOH/H_2O; mp 277–279 °C; IR (KBr) 2971, 1641, 1538, 1494, 1440, 1373, 1244, 1189, 1084 cm^{-1}; ^1H NMR (DMSO-d_6) 9.04 (s, 1H), 8.62 (d, J = 7.1, 1H), 8.44 (d, J = 7.1, 1H), 8.33 (d, J = 7.9, 1H), 8.26 (d, J = 8.2, 1H), 8.08 (d, J = 7.8, 1H), 8.0–7.9 (m, 2H), 7.78 (d, J = 8.2, 1H), 7.7–7.5 (m, 3H), 7.22 (d, J = 7.3, 1H), 3.76 (s, 3H). Anal. Calcd for $C_{34}H_{27}N_3O_3S{\cdot}H_2O$: C, 70.93; H, 4.93; N, 7.30. Found: C, 71.39; H, 4.93; N, 7.18.

8-[(Ethoxycarbonyl)methyl]acenaphtho[1′,2′-5,6]pyridazino[2,3-*a*]perimidin-15-ium mesitylenesulfonate (9b): prepared by method A (14 h) in 69% yield; dark red needles from EtOH/DME; mp 245–247 °C; IR (KBr) 3058, 2978, 1739, 1644, 1568, 1531, 1493, 1483, 1211, 1014 cm^{-1}; ^1H NMR (DMSO-d_6) 9.09 (s, 1H), 8.64 (d, J = 7.1, 1H), 8.58 (d, J = 6.8, 1H), 8.46 (d, J = 8.3, 1H), 8.39 (d, J = 8.3, 1H), 8.28 (d, J = 7.8, 1H), 8.1–7.9 (m, 2H), 7.86 (d, J = 7.8, 1H), 7.7–7.6 (m, 2H), 7.59 (t, J = 8.0, 1H), 7.03 (d, J = 7.8, 1H), 5.8 (s, 2H), 4.35 (q, J = 7.3, 2H), 1.33 (t, J = 7.1, 3H). Anal. Calcd for $C_{37}H_{31}N_3O_5S$: C, 70.56; H, 4.97; N, 6.67. Found: C, 70.31; H, 5.10; N, 6.47.

8-(Cyanoethyl)acenaphto[1′,2′-5,6]pyridazino[2,3-*a*]perimidin-15-ium mesitylenesulfonate (9c): prepared by method A (1 h) in 44% yield; brown prisms from EtOH/Et_2O; mp 235–240 °C; IR (KBr) 3070, 2928, 2250, 1642, 1569, 1527, 1493, 1483, 1453, 1189, 1085 cm^{-1}; ^1H NMR (DMSO-d_6) 9.16 (s, 1H), 8.71 (d, J = 7.0, 1H), 8.51 (d, J = 7.0, 1H), 8.46 (d, J = 8.1, 1H), 8.40 (d, J = 8.4, 1H), 8.24 (d, J = 7.7, 1H), 8.07 (d, J = 7.9, 1H), 8.01 (t, J = 7.7, 1H), 7.85 (d, J = 8.1, 1H), 7.70 (t, J = 8.2, 1H), 7.68 (d, J = 8.4, 1H), 7,61 (d, J = 7.9, 1H), 7.46 (d, J = 7.7, 1H), 4.79 (t, J = 7.0, 2H), 3.18 (t, J = 7.0, 2H). Anal. Calcd for $C_{36}H_{28}N_4O_3S$: C, 72.46; H, 4.73; N, 9.39. Found: C, 72.12; H, 4.87; N, 9.16.

16-(Ethoxycarbonyl)-8-methylacenaphtho[1′,2′-5,6]pyrido[2,3-*a*]perimidin-15-ium iodide (10): prepared by method B (24 h) in 36% yield; brown prisms from EtOH/CH_2Cl_2; mp >350 °C; IR (KBr) 2981, 1768, 1736, 1638, 1563, 1535, 1484, 1427, 1377, 1283, 1218, 1129, 1010 cm^{-1}; ^1H NMR (DMSO-d_6) 8.76 (s, 1H), 8.39 (d, J = 7.0, 1H), 8.3–8.2 (m, 2H), 8.19–7.9 (m, 3H), 7.8–7.6 (m, 3H), 7.4–7.3 (m, 3H), 4.41 (q, J = 7.2, 2H), 3.33 (s, 3H), 1.06 (t, J = 7.2, 3H). Anal. Calcd for $C_{29}H_{21}IN_2O_2$: C, 62.60; H, 3.80; N, 5.03. Found: C, 62.53; H, 4.15; N, 5.38.

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