products were isolated by addition of an equivalent volume of water to the reaction mixture followed by extraction into hexane. After drying over magnesium sulfate and removal of the hexane under reduced pressure, the product was purified by vacuum distillation. All of the toluenes were >99% pure by GC analysis.

The redox potentials were measured using the photomodulation voltammetry technique that has been described elsewhere.[6] All measurements were made at a gold minigrid working electrode in acetonitrile containing di-*tert*-butyl peroxide (0.5 M), the substituted toluene (0.3–0.5 M), and tetrabutylammonium perchlorate (0.1 M) as supporting electrolyte. Potentials are reported with respect to the saturated calomel electrode (SCE) as the reference.

Calculational Methods. The various radicals were calculated using the AM1 molecular orbital method and the half electron approximation. This procedure generally gives better energetic results than the alternative UHF procedure for radicals.[20,21] The geometries of the radicals were completely optimized in all internal coordinates. The radicals were first optimized using the MMX molecular mechanics method as incorporated into the PCMODEL program.[22] This geometry was then used as the starting point for the AM1 calculations. Vertical potentials are based on single-point calculations of the ions in the optimized geometry of the radical. All calculations were performed on a Ulysses Systems workstation or an Ogivar Technologies System 386/33 microcomputer.

Acknowledgment. We gratefully acknowledge Dr. D. Griller (NRCC) for helpful discussions.

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Synthesis and Correlation of Electronic Structures and NMR Properties of 10c-Azoniafluoranthene and 12d-Azoniaperylene

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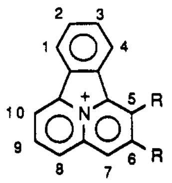
The synthesis of 10b-azoniafluoranthene (**1a**) and 12d-azoniaperylene (**2**) is described. MNDO calculations and ^{1}H, ^{13}C, and ^{15}N NMR data demonstrate that the positive charge in the two cations is delocalized off the nitrogen on the peripheral framework. Also, the fluoranthene derivative **1a** supports an additional ring current not observed in **2**. The two cations are reversibly reduced to the neutral radicals, whose EPR spectra in solution are reported and analyzed.

Introduction

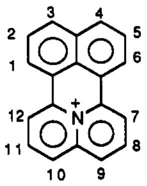
Cation radical salts of aromatic hydrocarbons (naphthalene, fluoranthene, etc.) crystallize upon electrochemical oxidation in simple salts like (fluoranthene)$_2$PF$_6$.[2] In these conducting solids, motional narrowing combined with one-dimensional effects results in the observation of extremely narrow solid-state EPR signals.[3] The salts are, however, rather unstable,[4] a feature that prevents several applications of these materials.[5]

We decided to investigate isoelectronic azonia cations of fluoranthene and perylene and targeted 10c-azoniafluoranthene (**1a**)[6] and 12d-azoniaperylene (**2**). In these cations the nitrogen atom is substituted into positions where a minimal effect on the electronic properties of the corresponding radicaloid species is expected (vide infra). Also, light atom substitution was chosen to minimize spin-orbit coupling effects.

By preserving the geometry of the parent arenes, it was expected that conducting solids exhibiting similar properties could be derived from **1a** and **2**. In addition, it was anticipated that the overall chemical stability might also be enhanced, since the salts would now be obtained by reduction rather than by oxidation.



R = H **1a**
R = Me **1b**



2

The cations **1a** and **2** are reminiscent of the well-known cyclazine compounds that have been the object of considerable interest in the past 30 years.[7] The first cyclic π-electron system bridged by a central nitrogen atom, cycl[2.2.3]azine (**3**), was reported by Boekelheide et al.[8] Further compounds in this series became available by the work of Leaver et al.,[7] who reported the highly symmetric cycl[3.3.3]azine (**4**) and several fused derivatives. These compounds, as well as, more recently, several aza derivatives,[8b] were thoroughly studied by means of theoretical calculations and spectroscopic methods (UV–vis, XPS,

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(1) (a) Paris. (b) København.

(2) Enkelmann, V. *Adv. Chem. Ser.* **1988**, *217*, 177.

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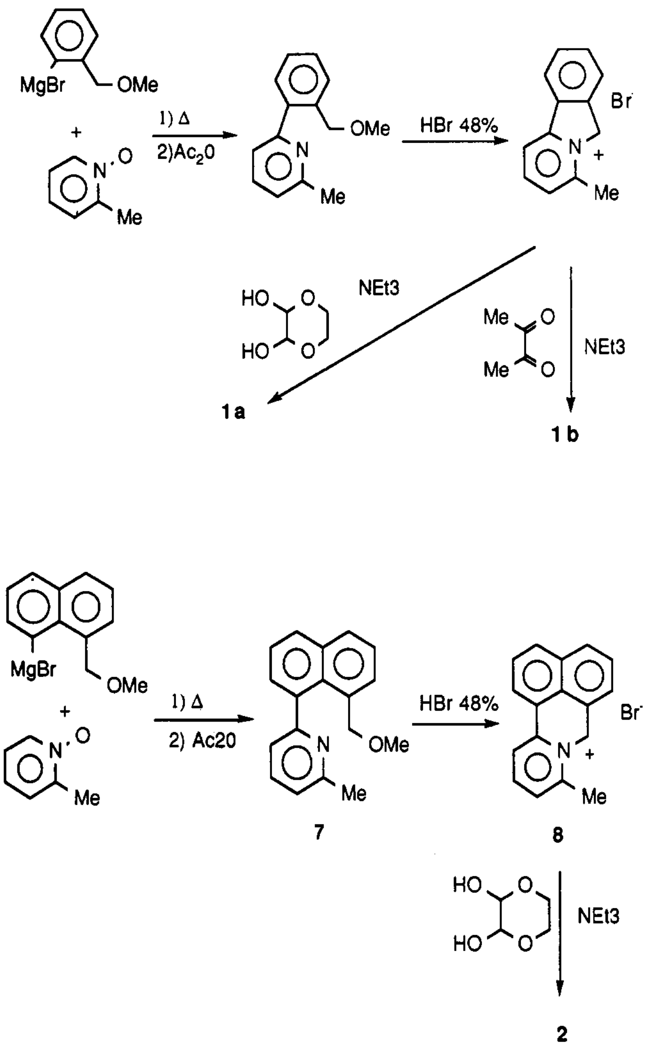
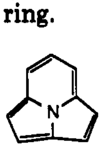
0022-3263/91/1956-4858$02.50/0

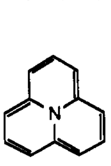
Scheme I



NMR, EPR) and compared with the isoelectronic hydrocarbon analogues. In those series of compounds, only one cationic cyclazine was described, pyrrolo[2,1,5-*de*]quinolizinium (**5**),[9] isoelectronic with acenaphthylene. From NMR studies it was inferred that the positive charge of the nitrogen is partially delocalized on the 11-carbon peripheral ring.



3



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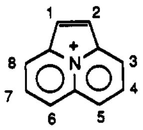

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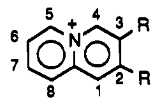

R = H **6a**
R = Me **6b**

In the present work, we report the ready access to a series of cationic cyclazines. Their electronic properties and the extent of delocalization are investigated by comparison of MO calculations and ^{1}H, ^{13}C, and ^{15}N NMR data. Reduction of the cationic species affords the neutral radicals **1a**$^\bullet$ and **2**$^\bullet$, which are characterized by EPR in solution. The two cations are also compared with the acenaphthylene derivative **5** as well as with the quinolizinium cation **6a**, since this heterocycle is a constituent of the cations **1a**, **2**, and **5**, yet with the nitrogen atom in a bridgehead *peripheral* position.

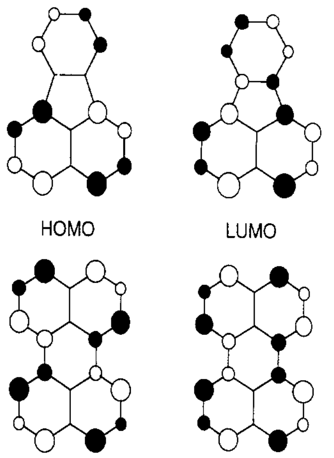

Figure 1. Atomic coefficients in the HOMO and the LUMO of fluoranthene and perylene. The radii of circles are approximately proportional to the coefficients of the considered molecular orbital on each atom.

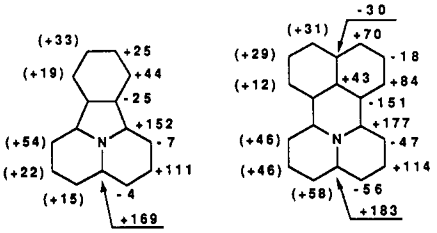

Figure 2. Net total ($\sigma + \pi$) atomic charge shifts (me) upon nitrogen introduction. A positive sign indicates an increased positive charge. The charge shifts at the hydrogen atoms are in parentheses. Note that the net charge shift is +1, as expected.

Synthesis. **1a** was obtained in three steps starting from picoline *N*-oxide (Scheme I), as described earlier.[6] Use of butanedione in the last condensation step yields 5,6-dimethylazoniafluoranthene (**1b**) in good yield. **1b** was synthesized in order to facilitate NMR assignments of **1a** by introducting substituents.

A similar synthetic procedure was followed for the perylenic analogue **2**. 1-Bromo-8-(methoxymethyl)naphthalene was obtained by methylation of 1-bromo-8-(hydroxymethyl)naphthalene by a classical procedure.[10] The intermediate salt **8** presents two potentially nucleophilic sites for reaction with α-dioxo compounds. Reaction in the presence of a base with the glyoxal equivalent, 2,3-dihydroxy-1,4-dioxane, yields the azoniaperylene **2**.

MNDO. Calculations of the MNDO type[11] have been conducted on **1a** and **2** as well as on the corresponding arenes fluoranthene and perylene. As expected (Figure 1), the presence of a node in the frontier orbitals (HOMO and LUMO) at the positions of nitrogen substitution results in identical electron density distribution in the parent arenes and their cationic analogues **1a** and **2** in these orbitals. Therefore, there is no electronic density on the nitrogen atom in the LUMO of **1a** and **2**. Thus, the coupling of the π-electron spin of the radicaloid reduced neutral forms **1a**$^\bullet$ and **2**$^\bullet$ with the nitrogen atom nucleus

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(9) Farquhar, D.; Gough, T. T.; Leaver, D.; Miller, J. F.; Dick, J. W.; Jessep, M. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2553.

(10) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

(11) The MNDO method was employed using MOPAC (Version 5.0).

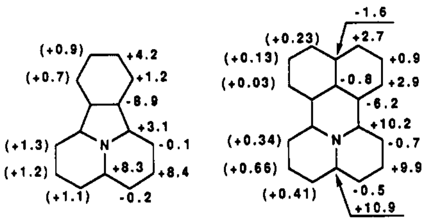

Figure 3. The NMR chemical shifts of **1a** and **2** minus the shifts on the same atoms in the corresponding arenes (in ppm). A positive sign indicates a low-field shift. ^1H chemical shift variations are given in parentheses, ^{13}C chemical shift variations without parenthesis.

should be very weak, as demonstrated later in this paper.

The total ($\sigma + \pi$) atomic charges were calculated for the arenes and the cations **1a** and **2**. Of particular note is the slight negative charge supported by the nitrogen, whose valence electron density amounts to 5.0989 in **1a** and 5.0973 in **2**. Thus, the positive charge in the cations is fully delocalized onto the peripheral framework. The net positive charge can be broken down into individual components at each atom by substracting the corresponding atomic charge in the arene from that in the cation (Figure 2). Note that each hydrogen atom experiences an increased positive charge upon nitrogen substitution in the arene framework. This holds for the protons of the quinolizinium moities as well as for those of the benzene and naphthalene units in **1a** and **2**. Similar trends are observed in the charge shifts on the carbon positions, which are largest in the positions α and γ to the nitrogen and still of a significant amount in the benzene and naphthalene moities. Note also that the positive charge appears to be more concentrated around the nitrogen atom in **2** since the atomic charge shifts are larger in the α-positions of this cation than in **1a**.

Examination of the bond-order variations upon nitrogen substitution shows a decrease from averaged values of 1.24 (C–C bond to the internal carbon in the arenes) to 1.10 (C–N bond in the cations) in the two systems. Of particular importance are the variations of the carbon–carbon bonds connecting the quinolizinium, benzene, and naphthalene moities. In **1a**, the observed increase of the C_{4a}–C_{4b} bond order (from 1.018 to 1.041, +2.2%) is to be correlated with the shortening of this bond, as observed in the crystal structure determination of **1a**.[12] Conversely, a small decrease of the C_{6a}–C_{6b} bond order (−0.5%) is predicted in **2**.

These results point toward a similar crude description for the two cations. The positive charge is delocalized off the nitrogen atom onto the peripheral framework, not only in the α- and γ-positions but also in the benzene and napthalene moities of **1a** and **2**.

^1H and ^{13}C NMR. The ^1H NMR data (Table I) confirm to some extent the previous observations. The protons of the two cations are strongly deshielded (low-field shift) when compared to the arenes, and their chemical shifts lie well in the usual range for protons of heteroaromatic cations. This deshielding affects every proton in the cations (Figure 3), albeit to a larger extent in the nitrogen vicinity. Note also that this occurs to a lesser extent in **2** (mean δ^1H variation, 0.3 ppm) than in **1a** (mean δ^1H variation, 1.04 ppm).

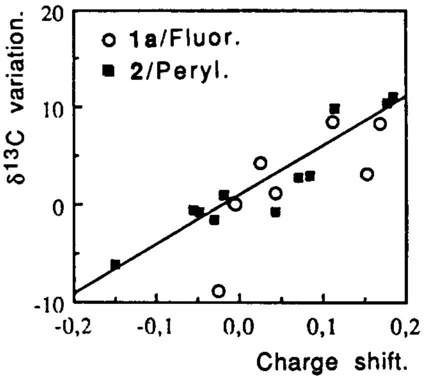

Figure 4. Correlation between the ^{13}C shift variations from the arene to the isoelectronic cation (in ppm) and the total calculated charge differences, upon nitrogen introduction in the arene framework, at each carbon atom.

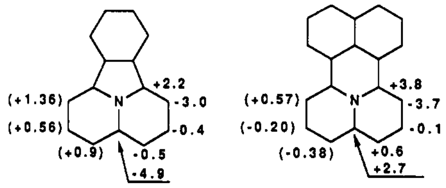

Figure 5. The NMR chemical shifts of **1a** and **2** minus the NMR shifts on the same positions in the quinolizinium **6a** (in ppm). A positive sign indicates a low-field shift: in parentheses, ^1H shift variations; without parentheses, ^{13}C shift variations.

The changes in ^{13}C NMR chemical shifts upon nitrogen introduction are shown in Figure 3. Clearly, the observation of a large deshielding of the α- and γ-positions is in agreement with the calculated increased positive charge at these positions, as commonly observed in conjugated hydrocarbons.[13,14] The deshielding is, however, more pronounced at each of the α- and γ-positions of **2** than in **1a**, for which two of the α-positions are only slightly deshielded (+3.1 ppm). This relationship between charge calculations and ^{13}C NMR data can be extended to every carbon atom. Actually, an excellent correlation is observed between the atomic charge changes upon nitrogen introduction and the differences in ^{13}C chemical shifts on the same atoms (Figure 4). By contrast, note that in individual molecules, the calculated atomic charges (π or total), and the ^{13}C shifts do not correlate as well owing to differences in ring sizes and to the presence of quaternary atoms.[13] By plotting now, at each position, the charge changes versus the shift differences between the neutral arene and its isoelectronic azonia analogue, a very satisfactory linear fit is obtained indicating that the former perturbating effects have been compensated. However, two data points corresponding to the C_{4a} and C_{4b} positions in **1a** lie strikingly off the fit. This indicates that these two positions experience an additional electronic perturbation not taken into account in the calculations. Note also that the linear fit for the fluoranthene system excluding these two points gives a R value of 0.96 instead of 0.76 if all positions are considered, while a R value of 0.94 was obtained for **2** by taking into account every carbon atom.

The ^1H and ^{13}C chemical shifts of the two cations are also compared, in Figure 4, with the values at the same positions in the quinolizinium **6a**. Again, there appear to be significant differences between **1a** and **2**. A large deshielding of every proton is observed in **1a** (average δ^1H variation, 0.94 ppm), while the average ^1H shift variation

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[12] Boubekeur, K.; Fourmigué, M.; Batail, P. *Acta Crystallogr.* **1989**, *C45*, 1636.

[13] Jones, A. J.; Alger, T. D.; Grant, D. M.; Litchman, W. M. *J. Am. Chem. Soc.* **1970**, *92*, 2386.

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Table I. ^1H and ^{13}C NMR Data of 1a, 2, and 6a and Selected Reference Compounds[a]

	fluoranthene					1a				
pos	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$
1	8.06	158.1	s.o.	s.o.	121.9	8.93	165.5	s.o.	s.o.	123.1
2	7.43	160.1	7.2 (d)	s.o.	127.8	8.13	163.9	7.1 (d)	s.o.	132.0
4a					138.7					129.8
4b					136.2					139.3
5	8.14	160.8	8.5 (d)	7.0	120.8	9.48	175.0	8.8 (d)	7.6	120.9
6	7.72	159.7	(s)	8.3	128.3	8.96	171.8	(s)	7.6	136.7
7	7.97	162.5	6.5/3.5 (dd)		126.6	9.10	175.8	6.5/3.1 (dd)		126.6
7a					129.6					137.9
10c					131.5				see Table II	
	perylene					2				
pos	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$
1	8.35	158.0	8.0 (d)	7.5	120.9	8.38	163.0	8.2 (d)	7.7	123.8
2	7.54	162.4	(s)	8.2	127.1	7.67	164.6	(s)	8.3	128.0
3	7.79	163.5	s.o.		128.2	8.02	165.3	s.o.		130.9
3a					134.6					133.0
6a					130.6					124.4
6b					130.6					140.9
7	8.35	158.0	8.0 (d)	7.5	120.9	8.69	170.4	s.o.	s.o.	120.2
8	7.54	162.4	(s)	8.2	127.1	8.20	172.5	(s)	s.o.	137.0
9	7.79	163.5	s.o.		128.2	8.20	176.1	7.1/3.6 (dd)		127.7
9a					134.6					145.5
12c					128.1					127.3
	naphthalene					6a				
pos	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$	δ^1H	$^1J_{C-H}$	$^3J_{C-H}$	$^3J_{H-H}$	$\delta^{13}C$
1	7.91	157.6	s.o.	s.o.	127.7	8.58	173.5	7.5/3.5 (dd)		127.1
2	7.51	159.5	8.5 (d)	s.o.	125.9	8.40	173.5	6.8 (d)	s.o.	137.1
3	7.51	159.5	8.5 (d)	s.o.	125.9	8.12	173.5	8.5 (d)	s.o.	123.9
4	7.91	157.6	s.o.	s.o.	127.7	9.35	190.0	unr	s.o.	137.1
8a					133.0					142.8

[a] In DMSO-d_6 solutions. Assignments of chemical shifts for close-lying peaks marked with the same symbol may be reversed: unr = unresolved; s.o. = second-order splitting pattern; s, d, dd, and m refer to peak multiplicity as singlet, doublet, double doublet, and multiplet, respectively.

in 2 is zero. Concerning the ^{13}C shifts and hence the differences in the localization of the positive charge, we note an important upfield shielding of the C_{7a} α-position in **1a**, i.e., a more delocalized charge than in the quinolizinium and an opposite smaller deshielding of this position (C_{9a}) in **2**.

The analysis of all these NMR data demonstrate that the positive charge is delocalized off the nitrogen atom onto the peripheral framework, in agreement with the MNDO calculations. This holds not only in the vicinity of the nitrogen atom but also in the benzene and naphthalene moities of the cations. However, the charge appears to be more delocalized in **1a** than in **2**. To the extent that this effect actually occurs, the heterocycles will become more like an annulenylium ion, σ-bonded to an internal neutral nitrogen atom, as previously proposed for the acenaphthylene analogue **5**.[9]

Extra Ring Current in the 10c-Azoniafluoranthene (1a). This hypothesis and the differences noted between **1a** and **2** can be rationalized if one simply adds the number of π-electrons involved in every possible path of conjugation in the cations and their hydrocarbon analogues.[15] In the fluoranthene molecule, we have a potentially antiaromatic system with 16 π-electrons. As a consequence, the separation into two weakly coupled benzene and naphthalene aromatic subsystems is preferred, with 10 and 6 π-electrons, respectively. Clearly, a delocalized 15 π-electron ($4n + 3$; $n = 3$) conjugation path with an inner carbon atom acting as a small perturbation is not favored. The situation is actually the opposite in the isoelectronic cation **1a**. Our results do indeed demonstrate that two electrons are localized onto the central nitrogen atom, while a 14 ($4n + 2$; $n = 3$) π-electron Hückeloid conjugation path is stabilized. The large deshielding of all the protons, the smoother charge alternation, the increased C_{4a}–C_{4b} bond order, and the corresponding bond shortening are all convincing evidences for an additional diatropic ring current in **1a**. The latter is likely to be at the origin of the C_{4a} and C_{4b} anomalous ^{13}C chemical shifts, although such ring current effects on ^{13}C chemical shifts are not very well documented yet.[13] A similar pattern holds for the acenaphthylene derivative **5**, with a Hückeloid path of conjugation of 10 π-electrons. This is in full agreement with the reported ^1H and ^{13}C NMR data for this salt.[9]

Table II. ^{15}N NMR Chemical Shifts in 1a, 2, 5, and 6a and ^{13}C NMR Chemical Shifts of the Same Internal Positions in the Corresponding Arenes

	6a	5	1a	2
$\delta^{15}N$	207.1[a]	184.4[a]	195.2[b]	199.6[b]
	naphthalene	acenaphthene	fluoranthene	perylene
$\delta^{13}C$	136.0[c]	127.8[a]	132.0[c]	128.1[c]

[a] From ref 9, at 36.5 MHz in $(CD_3)_2SO$, δ/ppm relative to NH_3. [b] At 30.4 MHz; measured in $(CD_3)_2SO$ relative to external NO_3^- and referenced to NH_3 by addition of 376 ppm. [c] See Table I.

Likewise, the potentially antiaromatic 20 π-electron system of the perylene molecule breaks down into a pattern of two weakly coupled aromatic naphthalene moities, each with a Hückeloid number of 10 π-electrons. In the isoelectronic cation **2**, a peripheral path of conjugation, similar to that observed in **1a** or **5**, would lead to a 17 π-electron nonaromatic system with the nitrogen (two electrons) and the second internal carbon (C_{12c}, one electron) acting as perturbations. Instead, our NMR data for **2** favor a description analogous to that of the perylene, i.e., two weakly

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(15) Minsky, A.; Meyer, A. Y.; Hafner, K.; Rabinovitz, M. *J. Am. Chem. Soc.* **1983**, *105*, 3975.

coupled quinolizinium and naphthalene Hückeloid 10 π-electron moities.

Conclusion Supported by the ^{15}N NMR Data. These conclusions, supported by the ^1H and ^{13}C NMR data, are also corroborated by the ^{15}N NMR data (Table II). Taking the ^{15}N chemical shift of the quinolizinium **6a** as a reference, the three cations **5**, **1a**, and **2** experience an upfield shielding of the nitrogen. This may be attributed to a higher electronic density on this atom and/or an increased aromatic ring current. However, in the arenes, a comparable upfield shielding of the carbon atoms at the *same* internal positions is observed, when compared with the naphthalene ^{13}C shift at the C_{8a} position. This indicates that the geometry of the framework has indeed an influence on the shielding of this internal position. Clearly, one needs to separate, in the upfield shielding of the nitrogen in the cations, when compared to **6a**, the contribution of some additional ring current due to the introduction of the nitrogen from the contribution of the framework (deduced from the arene series). In these series, compared to the naphthalene ^{13}C shift at the bridgehead atom C_{8a}, an upfield shielding of 6, 2.9, and 5.8% is observed at the internal carbons of the acenaphthylene, fluoranthene, and perylene, respectively. Similar trends would be expected for the ^{15}N shifts, in the analogous cationic series, if the framework were the only contribution to the upfield shielding at these internal positions. However, compared to the quinolizinium ^{15}N shift, an upfield shielding of 11, 5.7, and 3.6% is observed in **5**, **1a**, and **2**, respectively. Clearly, the ^{15}N shift variations in **5** and **1a** are nearly twice as large as the ^{13}C shift variations observed in the acenaphthylene and the fluoranthene on the same position. The situation in the perylenic analogue **2** is exactly the opposite with the ^{15}N shift variation, which amounts to half that observed in the perylene.

From these complementary ^{15}N NMR studies, we can now conclude that **1a**, when compared with the quinolizinium and the fluoranthene, does support some additional ring current, while the perylenic derivative **2** behaves much more like an quinolizinium σ-bonded to a naphthalene fragment.

Electrochemical Properties. Cyclic voltammetry experiments performed in acetonitrile demonstrate that the cations **1a** and **2** are reversibly reduced at $E_{1/2} = -0.95$ V and -1.08 V/SCE, respectively. This contrasts with the well-documented situation for the simplest pyridinium-like salts (*N*-alkylpyridinium, -quinolinium, and -acridinium and also quinolizinium **6a** or acridizinium) for which reduction is irreversible. This nonreversible character has been attributed to the rapid formation of dimers, unless the cation carries an electron-attracting substituent at the position of highest electronic density in the LUMO, usually α or γ to the nitrogen.[16] In **1a** and **2**, the spin density is to a larger extent delocalized over the entire molecule, as in the fluoranthene or perylene anion radicals. This might provide a rationale for the observed reversibility of the reduction of **1a** and **2**, when compared with other unsubstituted pyridinium-like cations. The reduction of **1a** and **2** occurs at somewhat rather negative potentials comparable to those for pyridinium or quinolizinium salts. This is in fact in agreement with the observation that the LUMOs of the arenes were only slightly modified by the introduction of the nitrogen.

EPR. Since the reduction of **1a** and **2** is reversible, we have investigated the EPR spectra of the neutral radicals **1a$^\bullet$** and **2$^\bullet$** in solution. These are isoelectronic with the corresponding fluoranthene and perylene anion radicals. EPR spectra were obtained by direct electrolysis of an acenonitrile solution (TBA PF_6 0.1 M) of the cation as PF_6^- salt in a flat quartz cell within the EPR spectrometer. The spectrum of **1a$^\bullet$** (Figure 6) shows five equally spaced, rather broad lines with an apparent hyperfine splitting (a_H) of 5.17 G. A well-resolved spectrum was obtained for **2$^\bullet$**

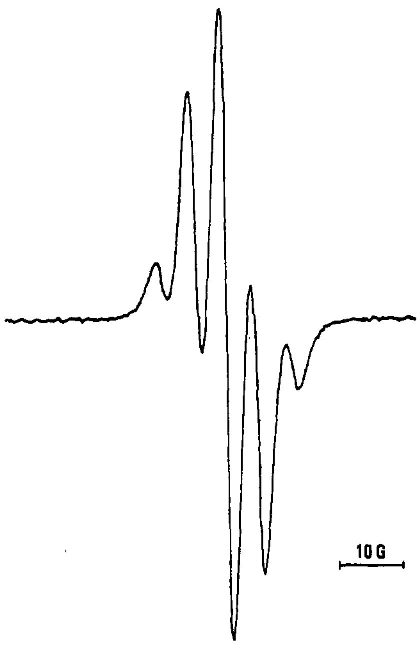

Figure 6. EPR spectrum of **1a$^\bullet$** in CH_3CN solution.

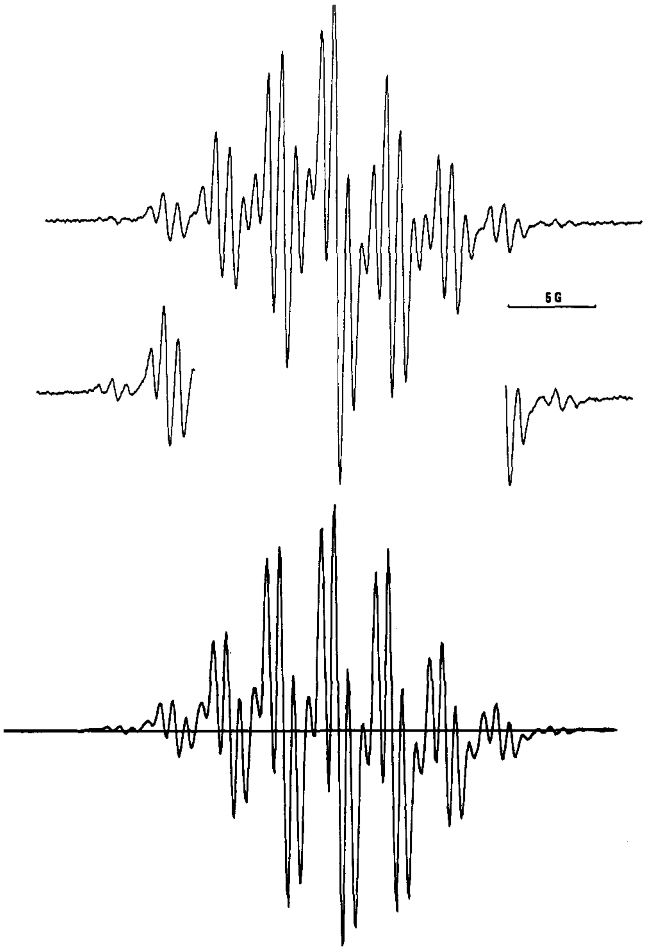

Figure 7. EPR spectrum of **2$^\bullet$** in CH_3CN solution (top) and the corresponding simulation (bottom, see text).

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Table III. ESR Hyperfine Splitting Constants (in G) of 1a$^{\bullet}$, 2$^{\bullet}$, and Selected Referenced Radical Anions

fluoranthene anion[a]	1a$^{\bullet}$	perylene anion[b]	2$^{\bullet}$
a_{H_2}, 1.20		a_{H_2}, 0.46	0.73
a_{H_5}, 3.93		a_{H_1}, 3.08	3.10
a_{H_7}, 5.24	5.17	a_{H_3}, 3.53	3.20

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(Figure 7). The spectrum could be simulated with three coupling constants $a_{Ha} = 3.20$ G, $a_{Hb} = 3.10$ G, $a_{Hc} = 0.73$ G. From the similitude of the LUMO's of the cations and the corresponding arenes, one expects similar hyperfine splitting constants for **1a**$^{\bullet}$ and **2**$^{\bullet}$ and the isoelectronic fluoranthene and perylene anion radicals, as indicated in Table III. Note that the symmetry breakdown from the perylene to its cationic analogue **2** has only a limited influence on the LUMO of **2**, since the EPR spectrum of **2**$^{\bullet}$ can be satisfactorily simulated with only three hyperfine coupling constants.

Conclusion

The substitution of a nitrogen in the central positions of fluoranthene and perylene leads to a novel series of cationic cyclazine derivatives. Extensive NMR studies demonstrate that the positive charge of the nitrogen is actually delocalized over the carbon framework. The fluoranthene derivative **1a** can be described as an aromatic 14 π-electron conjugated system with the neutral central nitrogen acting as a perturbation. By contrast, data on the perylenic derivative **2** are consistent with two slightly interacting quinolizinium and naphthalene 10 π-electrons fragments.

Experimental Section

For the reference compounds fluoranthene,[13,17-19] perylene,[20-22] and quinolizinium perchlorate **6a**,[9] some NMR data have previously been reported. However, for the purpose of this paper it was necessary to redetermine these data to obtain consistency of experimental conditions. Especially the ^{1}H chemical shifts were found to be quite sensitive to changes in solvent and concentration.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 250 instrument at 5.9 T in DMSO-d_6 solutions at 27 °C with a concentration of 0.5% for ^{1}H and 10% for ^{13}C NMR spectra. The ^{1}H and ^{13}C spectra were determined with 0.3 and 0.6 Hz/point, respectively. The coupling constants given were obtained from a first-order analysis.

The assignments given in Table I are based on chemical shift substituent effects together with the following considerations: in the heterocyclic molecules larger $^1J_{CH}$ values are measured for carbon atoms in the nitrogen containing ring (170–176 Hz). Carbon atoms in the peri position (e.g., C-7 in **1a** and C-9 in **2**) that showed ^{1}H-coupled ^{13}C signals amenable to first-order analysis appear as double doublets by coupling with one cisoid and one transoid vicinal protons. Second-order effects in the ^{1}H coupled ^{13}C spectra are seen for the carbon atoms at position 1 in the fluoranthene skeletons and position 3 in the perylene skeleton and were used for assignments. Selectively ^{1}H decoupled ^{13}C spectra were applied in assignments when appropriate. NMR spectra of the dimethyl-substituted derivatives **1b** and **6b** were obtained to support the assignments.

Except for the data of perylene in ref 20 the assignments given agree with previous analysis (see the previous text), when due allowance is taken for solvent and concentration effects. The ^{1}H NMR assignment of perylene in Table I agrees with refs 21 and 22. Selective ^{1}H decouplings were used to confirm the connections to the ^{13}C assignments given.

5,6-Dimethyl-10c-azoniafluoranthene Hexafluorophosphate (1b). A solution of 4-methyl-6*H*-benz[*a*]indolizinium bromide **6**[6] (6.5 g; 25 mmol) and butanedione (2.5 mL; 25 mmol) in EtOH (150 mL) is treated with NEt_3 (3.5 mL; 25 mmol) and refluxed during 2 h. The cooled solution is concentrated and the precipitated bromide washed and recrystallized from EtOH (4.1 g; 52%), mp > 320 °C. Anal. Calcd for $C_{17}H_{14}NBr$: C, 65.39; H, 4.52; N, 4.48. Found: C, 68.86; H, 4.43; N, 4.55. Metathesis with HPF_6 yields the hexafluorophosphate, recrystallized from acetonitrile/ethyl acetate, mp > 320 °C; λ_{max} (EtOH) 225 (4.57), 248 (4.46), 273 (4.54), 342 (3.78), 358 (3.9), 377 (3.84); δ^1H 8.9 (H_1, H_4, H_7, H_8, H_9), 8.12 (H_2, H_3), 9.37 (H_{10}); δ^{13}C 122.8 (C_1), 131.9 (C_2), 130.9 (C_3), 124.6 (C_4), 129.1 (C_{4a}), 135.1 (C_{4b}), 135.4 (C_5), 149.4 (C_6), 125.4 (C_7), 135.7 (C_{7a}), 125.2 (C_8), 135.4 (C_9), 119.1 (C_{10}), 137.5 (C_{10a}), 129.3 (C_{10b}), 15.4 (Me), 20.5 (Me). Anal. Calcd for $C_{17}H_{10}NPF_6$: C, 54.12; H, 3.74; N, 3.71. Found: C, 53.67; H, 3.63; N, 3.66.

1-Bromo-8-(methoxymethyl)naphthalene. KOH (47.3 g; 0.84 mol) crushed to pulver is dissolved in DMSO (400 mL). 8-Bromo-1-naphthylmethanol[23] (50 g; 0.21 mol) is then poured into the solution, and immediately thereafter MeI (26.1 mL; 0.42 mol) is added. The reaction is slightly exothermic. After 30 min of stirring, 200 mL of water are added and the resulting solution extracted three times with CH_2Cl_2. The combined organic phases are washed twice with water, dried ($MgSO_4$), and vacuum evaporated. The reaction is repeated two more times and the combined oils distilled, (158 g; 90%) bp 160–165 °C (4 mmHg); δ_H ($CDCl_3$) 3.4 (3 H, s, Me), 5.25 (2 H, s, CH_2), 7.05–7.85 (6 H, m, Ar). Anal. Calcd for $C_{12}H_{11}OBr$ (MW 251): C, 57.4; H, 4.41. Found (M^+ 251): C, 5.80; H, 4.32.

2-[8-(Methoxymethyl)-1-naphthyl]-6-methylpyridine (7). A Grignard reagent is prepared from 1-bromo-8-(methoxymethyl)naphthalene in dry THF with Mg (4.86 g; 0.2 mol) and EtBr (3.8 mL; 0.05 mol) by pouring a solution of the two halogenides in dry THF (100 mL) on Mg at such a speed that the solution is gently boiling. After addition is finished, reflux is maintained for 1 h. The solution is then cooled to 10 °C, and a solution of picoline *N*-oxide (19.6 g; 0.18 mol) in dry THF is poured dropwise. After being stirred overnight, the cooled solution is treated with water until a white gummy precipitate appears. The THF solution is decanted and the precipitate extracted with CH_2Cl_2. The combined organic phases are washed with NaOH (0.1 N), HCl (0.1 N), and H_2O and then dried ($MgSO_4$) and evaporated. The orange oil is refluxed 3 h in Ac_2O (150 mL) and then cooled, vacuum evaporated, treated with NaOH (0.1 N, 200 mL), and extracted with toluene. Extraction with HCl (2 N) and basification yields a brown oil that is chromatographed on silica gel (toluene/ethyl acetate (2:3)). **7** is obtained as a light yellow oil (6.3 g; 10%): δ_H ($CDCl_3$) 2.6 (3 H, s, Me-Py), 2.9 (3 H, s, OMe), 4.05 (2 H, s, CH_2), 7.0–7.9 (9 H, m, Ar). Anal. Calcd for $C_{18}H_{17}NO$ (MW 263): C, 82.09; H, 6.51; N, 5.32. Found (M^+ 263): C, 81.89; H, 6.53; N, 5.25.

7*H*-9-Methylnaphtho[1,8a,8-*ab*]quinolizinium Bromide (8). A solution of **7** (6.3 g; 0.024 mol) in a mixture of HBr 48% (100 mL) and AcOH (100 mL) is refluxed 3 h. After being cooled, the solution is vacuum evaporated. The solid is purified by dissolution in EtOH and precipitation with ethyl acetate (5.5 g; 55%) mp > 260 °C. Ethanolic solutions show a blue fluorescence: δ_H (CF_3CO_2D) 3.07 (3 H, s, Me), 6.05 (2 H, s, CH_2), 7.6–8.65 (9 H, m, Ar); λ_{max} (EtOH) 282 (4.05), 380 (4.0). Anal. Calcd for $C_{17}H_{14}NBr$: C, 65.82; H, 5.52; N, 4.51. Found: C, 64.60; H, 4.68; N, 4.40.

12d-Azoniaperylene Bromide (2). A solution of **8** (1.27 g; 4.1 mmol) and 2,3-dihydroxy-1,4-dioxane (0.5 g; 4.1 mmol) in EtOH (50 mL) is treated with NEt_3 (0.57 mL; 4.1 mmol) and the refluxed 2 h. After cooling and vacuum evaporation, the solid is triturated with ethyl acetate and filtrated. It can be purified

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by dissolving in the minimum amount of EtOH and precipitation by ethyl acetate addition (0.76 g; 55%): mp 220 °C dec. Anal. Calcd for $C_{19}H_{12}NBrH_2O$: C, 64.78; H, 4.00; N, 3.97. Found: C, 63.60; H, 3.84; N, 4.07. Metathesis with HPF_6 (70%) yields the hexafluorophosphate, recrystallized from $EtOH/CH_3CN$: λ_{max} (EtOH) 260 (4.03), 274 (3.99), 410 (sh, 3.75), 448 (3.82), 460 (sh, 3.55). Anal. Calcd for $C_{19}H_{12}NPF_6$: C, 57.15; H, 3.03; N, 3.51. Found: C, 56.97; H, 3.05; N, 3.52.

2,3-Dimethylquinolizinium Hexafluorophosphate (6b). It has been prepared following ref 24: ^{1}H δ 9.21 (H$_1$), 8.37 (H$_4$), 8.38 (H$_5$), 8.25 (H$_6$), 7.99 (H$_7$), 9.13 (H$_8$); ^{13}C δ 135.1 (C$_1$), 134.7 (C$_2$), 150 (C$_3$), 125.2 (C$_4$), 140.8 (C$_{4a}$), 125.8 (C$_5$), 135.7 (C$_6$), 122.8 (C$_7$), 134 (C$_8$).

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The First Total Synthesis of OPC-15161

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The first total synthesis of OPC-15161, a novel inhibitor of superoxide generation by guinea pig macrophages, has been accomplished via a convergent and efficient route exploiting the coupling of the fully functionalized pyrazine part with the indolyl group. 2-(Hydroxyimino)-4-methylpentanoic acid and ethyl aminocyanoacetate were condensed with DCC to afford the amide 3, which was converted to pyrazinone *N*-oxide 4 via intramolecular cyclization between the oxime and cyano groups. O-Benzylation of 4 followed by reduction of the ethoxycarbonyl group by DIBALH gave the aminopyrazine alcohol 7. The aryl chloride 8 was obtained by the direct substitutive deamination using isoamyl nitrite and copper salts. After protection of the hydroxyl group, the methoxy group was introduced at the 5-position via treatment of 2,5-bis(benzyloxy)pyrazine 4-oxide 10 with methoxide to afford 11. The methoxy compound 11 was converted to benzylic iodide 14 via deprotection, mesylation, and iodination. The functionalized pyrazine skeleton 14 was coupled with the zinc salt of indole to produce 17, which upon catalytic hydrogenolysis afforded OPC-15161.

Introduction

A new pyrazinone OPC-15161 (1) was isolated by Nakano et al. as a major degradation product of the natural compound OPC-15160, which was obtained from a fermentation broth of the fungus *Thielavia minor* OFR-1561.[1] OPC-15160 and OPC-15161 are novel inhibitors against superoxide anion generation by guinea pig macrophages, and the latter compound is 5 times more active than the parent OPC-15160. These compounds are therapeutically promising since recent studies suggest that inhibitors of superoxide generation are effective in protecting against tissue damage in vitro and in vivo in models of ischemia or inflammation.[2] The structure of OPC-15161 was established by X-ray crystallographic analysis to be 6-(1*H*-indol-3-ylmethyl)-3-isobutyl-5-methoxy-2(1*H*)-pyrazinone 4-oxide.[1] In addition to its therapeutic potential, OPC-15161 is of chemical interest in that it possesses a hitherto unknown highly functionalized skeleton. From a synthetic point of view, construction of such a highly functionalized pyrazine is challenging. Herein, we report the first total synthesis of OPC-15161.

OPC-15161 embodies a functionalized pyrazine ring and an indolyl group. Synthesis of indolyl derivatives often suffer from their instability, and this consideration led us to couple a correctly functionalized pyrazine moiety with indolylmetal at a late stage of the total synthesis to furnish OPC-15161 (Scheme I).

Scheme I

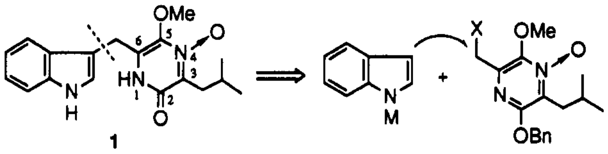

Table I. Substitutive Deamination of the Aminopyrazine Alcohol 7[a]

run	$CuCl_2/7$	CuCl/7	yield of 8,[b] %	yield of 15,[b] %
1	5	0	48	19
2	0	5	13	13
3	3	2	75	10

[a] Reactions were performed in acetonitrile at rt using 3 equiv of isoamyl nitrite. [b] Isolated yields by chromatography.

Synthesis of the Pyrazine Skeleton

The framework of the pyrazine moiety is a cyclodipeptide. To prepare this heterocycle, 2-(hydroxyimino)-4-methylpentanoic acid (2) and ethyl aminocyanoacetate[3] were condensed using DCC to afford the amide 3 (Scheme II). Following the procedure reported by Taylor et al.,[4] 3 was converted to the pyrazinone *N*-

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