Polar Effects in Free-Radical Reactions. Carbamoylation and α-*N*-Amidoalkylation of Heteroaromatic Bases by Amides and Hydroxylamine-*O*-sulfonic Acid

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The decomposition by Fe(II) salt of hydroxylamine-*O*-sulfonic acid (HSA) in the presence of formamide, alkylformamides, and *N*-alkylacetamides provides the amino radical cation $\cdot^+NH_3$, which by hydrogen abstraction generates carbamoyl (ĊON<) and α-*N*-amidoalkyl (CONĊ<) radicals. Both kinds of radicals have a clear-cut nucleophilic character and selectively attack protonated heteroaromatic bases, such as 4-methylquinoline or quinoxaline, in the α position or are oxidized by Fe(III) salts. Redox chain mechanisms are involved. The importance of the polar effects in the hydrogen abstraction, aromatic substitution, and oxidation by Fe(III) salt is discussed.

Protonated heteroaromatic bases are very effective traps of nucleophilic carbon-centered radicals, due to the high rates of addition ensuing from polar effects.[1] Since this high reactivity is associated to a high positional and substrate selectivity, the reaction has often a twofold interest: it permits one to effectively trap and easily characterize nucleophilic radicals occurring in free-radical processes, bringing therefore significant evidences to the reaction mechanism. Moreover the high selectivity gives great synthetic interest to the functionalization of the heteroaromatic bases.[2] The very large variety of useful radicals (practically all the carbon-centered radicals without electron-withdrawing groups directly bonded or conjugated to the radical center) and heteroaromatic bases (all the bases with, at least, one α or γ free position) makes the reaction one of the most important among the heteroaromatic reactions.[2]

A simple and easily available source of amino radical cation is provided by the redox decomposition of hydroxylamine-*O*-sulfonic acid (HSA) (eq 1).[3] For its elec-

$$^+NH_3OSO_3^- + Fe^{2+} \rightarrow \cdot^+NH_3 + SO_4^{2-} + Fe^{3+} \quad (1)$$

trophilic character, $\cdot^+NH_3$ does not attack the protonated heteroaromatic bases, whereas it easily adds to electron-rich aromatic substrates and olefins.[3]

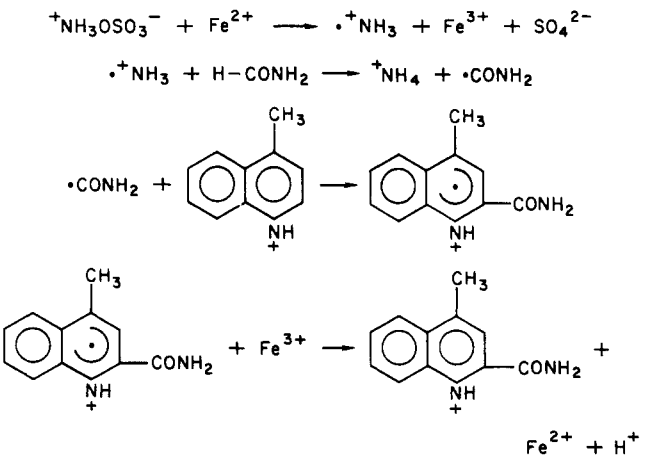
Polar effects also influence hydrogen abstraction by $\cdot^+NH_3$, the rates increasing with the electron availability of the C–H bonds (eq 2).[4] On the other hand the more

$$\geqslant CH \cdot^+NH_3 \leftrightarrow \geqslant C^+\text{---}\dot{H}\text{---}\ddot{N}H_3 \leftrightarrow \geqslant \dot{C}\text{---}H^+NH_3 \quad (2)$$

electron-rich the C-H bond, the more nucleophilic will generally be the corresponding carbon-centered radical.[4]

Formyl C–H bonds and α C–H bonds in *N*-alkylamides should be in general easily abstracted by the $\cdot^+NH_3$ radical for polar reasons, due to the contribution to the transition state of polar forms of the type of eq 2 and the relatively low C–H bond energies.[5]

Scheme I



Thus we have considered of interest to investigate the radical source described by eq 1 and 2 with amides in order to obtain information about the selectivity of the hydrogen abstraction and the synthetic potentiality of substitution of heteroaromatic bases.

Results and Discussion

When a small amount of Fe(II) salt is added to a solution of the protonated heteroatomatic base and HSA in $HCONH_2$:H_2O (10:1), the carbamoyl group ($CONH_2$) is selectively introduced in the position 2 of lepidine and quinoxaline. The conversions are better at 80 °C, but the reaction occurs significantly also at 20 °C. The reaction is quite clean; TLC and GLC analyses reveal only the presence of the amide and of the starting base and there are no traces of other side products. The yields are good (Table I) but they are not quantitative, probably because of losses during the separation procedure of the reaction products before the quantitative analysis. No significant reaction occurs in the absence of Fe(II) salt.

Hydrogen abstraction by $\cdot^+NH_3$ can, in principle, involve the C–H bond (eq 3) and/or the N–H bonds of formamide (eq 4).

$$\cdot^+NH_3 + H\text{–}CONH_2 \rightarrow {}^+NH_4 + \cdot CONH_2 \quad (3)$$

$$\cdot^+NH_3 + H\text{–}NHCHO \rightarrow {}^+NH_4 + \cdot NHCHO \quad (4)$$

The energy of the formyl C–H bond is lower than that of the N–H bond; moreover, the electron availability of the C–H bond is higher than that of the N–H bonds. Thus both factors contribute to a decrease the activation energy

(1) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960. Citterio, A.; Minisci, F.; Franchi, V. *J. Org. Chem.* **1980**, *45*, 4752.

(2) (a) Minisci, F. *Synthesis* **1973**, 1. (b) Minisci, F.; Porta, O. *Adv. Heterocycl. Chem.* **1974**, *16*, 123. (c) Minisci, F.; *Top. Curr. Chem.* **1976**, *62*, 1. (d) Minisci, F.; Porta, O. *Zh. Vses. Khim. Ova.* **1979**, *24*, 121; *Chim. Ind. (Milan)* **1980**, *62*, 769. (e) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27.

(3) Minisci, F.; Galli, R. *Tetrahedron Lett.* **1965**, 1679, 4663. Minisci, F.; Cecere, M.; Galli, R. *Chim. Ind. (Milan)* **1966**, *48*, 132. Minisci, F.; Bernardi, R.; Grippa, L.; Trabucchi, V. *Ibid.* **1966**, *48*, 24.

(4) Minisci, F.; Citterio, A. *Adv. Free-Radical Chem.* **1980**, *6*, 65.

(5) Reference 4, p 79.

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Table I. Carbamoylation of Lepidine and Quinoxaline by HSA in $HCONH_2$:H_2O (10:1)

heteroaromatic base	Fe(II)[a]	HSA:base (mole ratio)	T, °C	position of attack	convn,[b] %	yield,[c] %	material balance, %
lepidine	0.03	1	80	2	53	74	86
quinoxaline	0.03	1	20	2	29	78	94
quinoxaline	0.1	1	20	2	47	77	89

[a] Mole ratio of Fe(II) to heteroaromatic base. [b] Based on isolated unreacted heteroaromatic base. [c] Of isolated product, based on recovered heteroaromatic base.

Table II. Reaction of Lepidine and Quinoxaline with HSA in Dimethylformamide (DMF) at 20 °C

heteroaromatic base	Fe(II)[a]	HSA:base (mole ratio)	solvent DMF:H_2O	reactn prod (rel proportns)	convn,[b] %	yield,[c] %	material balance, %
lepidine	0.03	1	2:1	**3**(7) **4** (93)	40	92	97
lepidine	0.03	3	2:1	**3** (6) **4** (94)	74	81	86
quinoxaline	0.1	1	10:1	**5** (15) **6** (85)	50	80	80

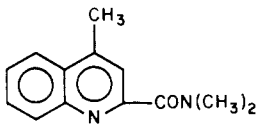
[a] Mole ratio of Fe(II) to base. [b] Based on isolated unreacted base. [c] Of isolated products, based on recovered base.

of reaction 3, which is much more favored than reaction 4; in any case the nitrogen-centered radical arising from eq 4 should not be involved in the reaction with the heterocyclic compound owing to its electrophilic character.

The redox chain mechanism of Scheme I explains, in our opinion, the results of Table I.

In terms of frontier orbital theory free radicals which have a high-energy SOMO interact strongly with the LUMO of a substrate and show nucleophilic properties.[6] The pyridinium cation has a low-energy LUMO[7] with the size of the orbital coefficients being the largest at position 4 and being larger at positions 2 and 6 than at positions 3 and 5. This rationalizes the selective substitution at position 2 since position 4 is not free.

When the reaction was carried out with dimethylformamide under the same conditions, two products were formed. They correspond to the introduction of the $\cdot CON(CH_3)_2$ (1) and $CHON(CH_3)CH_2\cdot$ (2) radicals at position 2 of lepidine (**3** and **4**) and quinoxaline (**5** and **6**).



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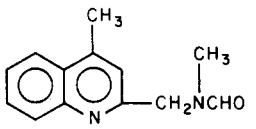

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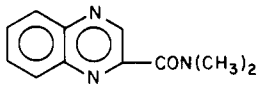

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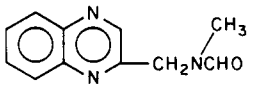

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The yields of isolated products are good, as shown in Table II; TLC and GLC analyses show that no other minor product is formed in detectable amounts and that the yields based on converted aromatic substrate, assuming losses during the separation, must be practically quantitative. The amino radical cation abstracts hydrogen atoms from both the formyl (eq 5) and methyl (eq 6) groups.

$$\cdot{}^{+}NH_3 + CHON(CH_3)_2 \rightarrow {}^{+}NH_4 + \cdot CON(CH_3)_2 \quad (5)$$

$$\cdot{}^{+}NH_3 + CHON(CH_3)_2 \rightarrow {}^{+}NH_4 + CHONCH_2\cdot \quad (6)$$

(CH3 on the CHONCH2· radical)

The compounds **4** and **6** greatly prevail over the compound **3** and **5** showing that reaction 6 is faster than reaction 5. The ratios **3**:**4** and **5**:**6** are affected by the fact that there are two redox chains in competition, one leading to aromatic substitution (Scheme I) and the other one involving oxidation of the radicals (eq 7 and 8). The latter redox chain is in part responsible for the low conversion of the heteroaromatic bases since it consumes HSA. In order to evaluate the effect of reactions 7 and 8 on the selectivity of the aromatic substitution, experiments were carried out with increasing amounts of Fe(III) salt. The results, reported in Table III, indicate that the reaction of radical **1** with the protonated heteroaromatic base is faster than its oxidation by Fe(III) salt by (eq 7), whereas the addition of the radical **2** to the protonated base and its oxidation by Fe(III) salt (eq 8) are competitive processes.

Table III. Effect of Fe(III) Salt Concentration on the Yields of 3 and 4 and on the 4:3 Ratio

Fe(III)[a]	4,[b] %	3,[b] %	4:3	convn, %
	83.7	6.3	13.3	40
0.01	62.1	11.9	5.2	21
0.03	51.1	21.9	2.3	11
0.05	46.5	25.5	1.8	9
0.07	47.2	32.8	1.4	7
0.13	35.0	52.5	0.7	4

[a] Mole ratio of Fe(III) to heteroaromatic base. [b] Yields of isolated product based on converted heteroaromatic base.

$$\cdot CON(CH_3)_2 + Fe^{3+} \rightarrow {}^{+}CON(CH_3)_2 + Fe^{2+} \quad (7)$$

(1; $+H_2O$ → $CO_2 + (CH_3)_2NH + H^+$)

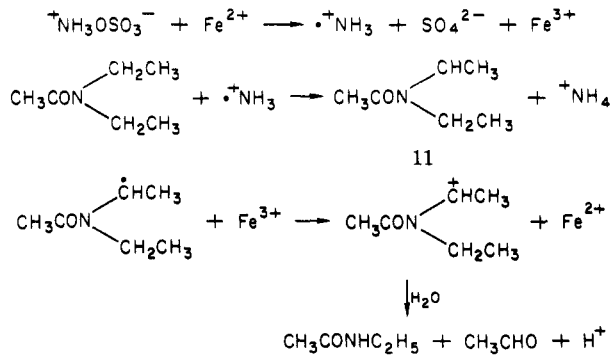
$$CHONCH_2\cdot + Fe^{3+} \rightarrow CHONCH_2^{+} + Fe^{2+} \quad (8)$$

(2; $+H_2O$ → $CHONHCH_3 + CH_2O + H^+$)

Thus three factors are involved in determining the ratio of carbamoylation and amidoalkylation: (i) the rates of formation of the radicals, (ii) their ease of oxidation by Fe(III), and (iii) their reactivity toward the heteroaromatic cation. At low concentration of Fe(III), factor ii can probably be neglected at first approximation, and the **3** to **4** (and **5** to **6**) ratios should depend on both factors i and iii. These two factors favor α-*N*-amidoalkylation since, mainly for polar reasons (or frontier orbital considerations) (i) the α C–H bond of *N*-alkylamides should be more reactive toward $\cdot{}^{+}NH_3$ than the formyl C–H bond (faster

(6) Reference 4, p 67.
(7) Hudson, R. F. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 36.

Scheme II



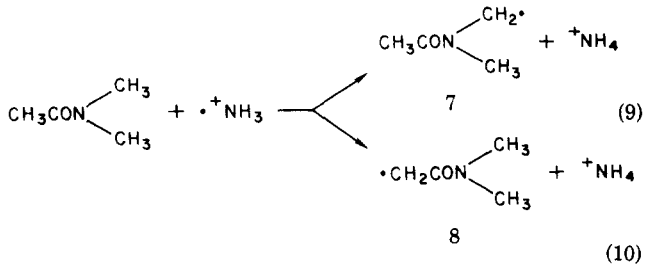
formation of radical **2**) and (ii) the α-*N*-amidoalkyl radical should be more nucleophilic (more reactive) toward heteroaromatic cations than the carbamoyl radical.

Both **1** and **2** are carbon-centered radicals with a nitrogen atom in α position and both have a clear-cut nucleophilic character; however, the polar effect of the nitrogen is opposite for the two radicals. Indeed we have previously[2c,d] shown the polar effects of α-alkoxy and amino groups on alkyl and acyl radicals. Thus α-alkoxy and α-*N*-amidoalkyl radicals (ROĊ< and -(-CO)NĊ<) are more nucleophilic than the corresponding unsubstituted alkyl radicals because they are π-type radicals. Acyl radicals are, on the contrary, σ-type radicals, and a clean reduction of nucleophilicity occurs with aminocarbonyl and alkoxycarbonyl radicals compared with acyl radicals.

The results of Table III further support this interpreration: radical **2** is more easily oxidized than radical **1** (reaction 8 is faster than reaction 7).

As the concentration of Fe(III) is increased, the **3** to **4** ratio increases (Table III) because the α-*N*-amidoalkyl radical is more easily oxidized than the carbamoyl radical. Furthermore the oxidation process becomes more and more important with respect to the substitution process as shown by the decrease of heteroaromatic base conversion. The absolute yields of **3** decrease only slightly (from 2.5% in the absence of Fe(III) to 2.1% in the presence of 13.4 mol % of Fe(III)), whereas the absolute yields of **4** dramatically decrease (Table III) (respectively from 35.5% to 1.4%).

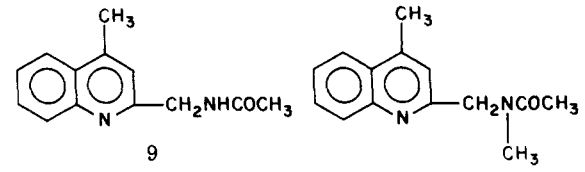
With *N*-methyl- and *N*,*N*-dimethylacetamide two different C–H bonds are present and could be involved in hydrogen abstraction by $\cdot^{+}NH_3$ (eq 9 and 10). Mainly for



(9)

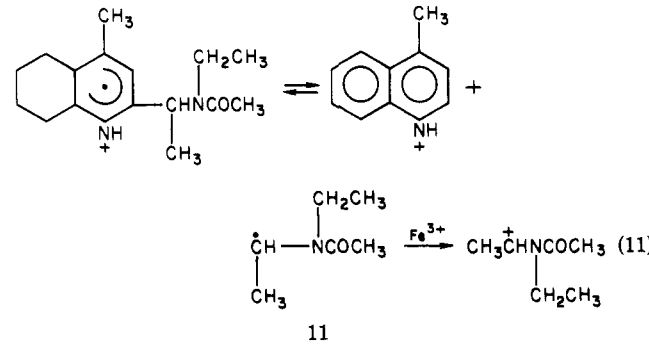
(10)

polar reasons, reaction 9 should prevail over reaction 10; in any case, always for polar effects, radical **8** arising from eq 10 should be unreactive toward the protonated base. Actually the only products obtained with lepidine and *N*-methyl- or *N*,*N*-dimethylacetamide (compounds **2** and **10**) arise from α-*N*-amidoalkyl radicals reacting at position 2 of the heterocyclic ring. With *N*,*N*-diethylacetamide and lepidine no attack on lepidine takes place and *N*-ethylacetamide is the only reaction product. We explain this result by the redox chain of Scheme II. The unsuccessful attack to the base of the radical **11**, contrary to the behavior of the radicals **2** and **7**, can be explained by two



9 **10**

effects: (i) The higher oxidizability by Fe(III) salt of the radical **11** compared to the radicals **2** and **7**. (ii) The increased reversibility of the addition to the heteroaromatic ring (eq 11).[1] The equilibrium is continuously shifted on



11

the right by the fast oxidation of the radical **11** by Fe(III) salt.

The isolated yields based on converted heteroaromatic bases are generally good; the actual yields are likely higher (practically quantitative) because in no case we have observed detectable amounts of side products.

The yields based on HSA are somewhat lower and they can be in part ascribed to the fast competitive hydrolysis of HSA (eq 12) in acidic aqueous medium.[8]

$$^{+}NH_3OSO_3^{-} + H_2O \rightarrow {}^{+}NH_3OH + HSO_4^{-} \quad (12)$$

Fe(II) salt does not effectively reduce the hydroxylammonium ion, contrary to HSA.

Experimental Section

All the reaction products were isolated by silica gel chromatography and identified by comparison IR, NMR, and MS) with authentic samples obtained previously by us by different procedures.[9]

Quantitative gas–liquid chromatographic analyses were performed with a Carlo Erba 4200 or a Dani 3600 instrument equipped with flame ionization detectors.

HSA (EGA) was used after iodometric titration (93–98%).

Reactions with Formamide. In a 25-mL flask, equipped with magnetic stirrer, were introduced the heteroaromatic base (4 mmol), concentrated H_2SO_4 (0.2 mL, 4 mmol) and $FeSO_4 \cdot 7H_2O$ (in the relative amounts reported in Table I) in 10 mL of formamide and 1 mL of water. The solution was flushed with N_2 for 5 min and placed in a thermostatic bath at the temperature reported in Table I. Then HSA (4 mmol) was added. After 2 h of stirring, 30 mL of water were added and the solution was basified at pH 10 with a 30% NH_4OH solution and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with water, dried, and quantitatively analyzed by GLC,[9] the results are reported in Table I.

Reactions with *N*,*N*-Dimethylformamide. A procedure similar to that described for formamide was used; 4 mmol of heteroaromatic base and 4 mmol of H_2SO_4 were dissolved in 7.5

(8) Specht, H. E.; Browne, A. W.; Scherk, K. W. *J. Am. Chem. Soc.* **1939**, *61*, 1083. Matsuguma, H. J.; Andrieth, L. F. *J. Inorg. Nucl. Chem.* **1959**, *12*, 189. Candlin, J. P.; Wilkins, R. G. *J. Am. Chem. Soc.* **1965**, *87*, 1490.

(9) Minisci, F.; Gardini, G.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, 15. Minisci, F.; Gardini, G.; Palla, G.; Arnone, A.; Galli, R. *Ibid.* **1971**, 59. Minisci, F.; Arnone, A.; Cecere, M.; Galli, R.; Perchinunno, M.; Porta, O. *Gazz. Chim. Ital.* **1973**, *103*, 13.

mL of solvent for lepidine and 11 mL of solvent for quinoxaline at 20 °C. The ratios of reagents, the composition of the solvent, the reaction products, the conversions, and the yields are reported in Table II. The results of Table III were obtained with an identical procedure using the amounts of $Fe_2(SO_4)_3$ reported in the table.

Reaction with *N*-Methylacetamide. Lepidine (4 mmol) 4 mmol of H_2SO_4, 4 mmol of HSA, and 0.12 mmol of $FeSO_4 \cdot 7H_2O$ were dissolved in 5 mL of *N*-methylacetamide and 2 mL of water at 20 °C. The mixture was stirred for 2 h at 20 °C, then diluted with 15 mL of water, basified by a 30% NH_4OH solution, and extracted with CH_2Cl_2 (4 × 10 mL). TLC and GLC analyses revealed the presence of only two products: lepidine (2.76 mmol) and IX (0.73 mmol); conversion 31%; yield based on converted lepidine 59%; the material balance is 87.3%.

Reaction with *N,N*-Dimethylacetamide. The procedure is similar to that used for *N*-methylacetamide starting with 4 mmol of lepidine. TLC and GLC analyses revealed only unreacted lepidine (2.6 mmol) and X (0.93 mmol) and no other product: conversion 35%; yield based on converted lepidine 66%; the material balance is 88.3%.

Reaction with *N,N*-Diethylacetamide. The same procedure used for *N,N*-dimethylacetamide was utilized for *N,N*-diethylacetamide. Unreacted lepidine (91%) was recovered; TLC and GLC analyses did not reveal traces of products of substitution of lepidine; GLC analyses of the solvent revealed the presence of N-ethylacetamide (1.96 mmol) (49% based on HSA).

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Registry No. Lepidine, 491-35-0; quinoxaline, 91-19-0.

Synthesis, Stability, Structure, Reactivity, and Chemistry of *N*-Alkylbenzoazetinones

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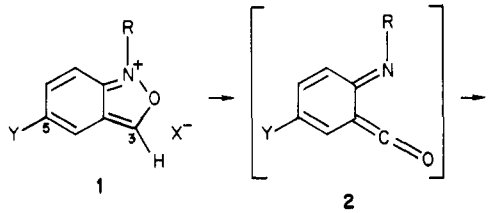
On treatment with triethylamine, 3-unsubstituted anthranilium salts 1 ring open and then recyclize to *N*-alkylbenzoazetinones **3**. When the alkyl group is tertiary, **3** is stable and the X-ray crystal structure of one such derivative, *N*-1′-adamantylbenzoazetinone (**3g**), requires a planar antiaromatic formulation with some bond localization in the benzo moiety. Ring-cleavage products are obtained in the rapid reaction of the β-lactams **3** with nucleophiles such as alcohols (→ **10a–e**), amines (→ **10f,g**), water (→ **11a,c**), benzoate (→ **12**), and azide (→ **14**). When heated, the acyl azides **14** undergo Curtius rearrangement followed by ring closure to benzimidazolones **17**.

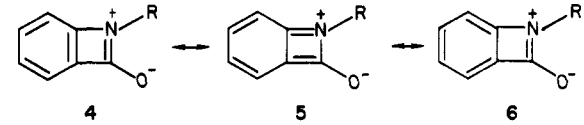
Several years ago, a simple and facile synthesis of *N*-alkylbenzoazetinones **3** was outlined in a preliminary report from this laboratory.[1] The isolation and characterization of the first stable compound **3f** with this ring system also was described.[1] Prior to this report, benzoazetinones had been proposed as short-lived, impossible-to-isolate reaction intermediates in the photolysis of benzotriazinones.[2] Subsequently, other less efficient and practical routes to **3** including isolable derivatives have been published.[3,4]



1 **2** **3**

a, R = methyl; Y = H; X = BF_4
b, R = methyl; Y = H X = CF_3SO_3
c, R = ethyl; Y = H; X = BF_4
d, R = ethyl; Y = H; X = FSO_3
e, R = isopropyl; Y = H; X = BF_4
f, R = *tert*-butyl; Y = H; X = ClO_4
g, R = 1-adamantyl; Y = H; X = ClO_4
h, R = *tert*-butyl; Y = Br; X = ClO_4
i, R = 1-adamantyl; Y = Br; X = ClO_4

Theoretical interest in **3** derives from its relationship to benzocyclobutadiene.[5] In so far as **3** is an amide and canonical structures such as **4–6** contribute to a resonance-stabilized hybrid structure, then **3** is a benzocyclobutadiene analogue and thus a formal violation of Hückel's $4n + 2$ rule. However, **3** is a rare molecule with an option.



4 **5** **6**

(1) Olofson, R. A.; Vander Meer, R. K.; Stournas, S. *J. Am. Chem. Soc.* **1971**, *93*, 1543.

(2) Burgess, E. M.; Milne, G. *Tetrahedron Lett.* **1966**, 93. Ege, G. *Chem. Ber.* **1968**, *101*, 3079. Ege, G.; Pasedach, F. *Ibid.* **1968**, *101*, 3089.

(3) See, for example: Bashir, N.; Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. 1* **1973**, 868 and references therein.

(4) Although discussed in other terms by Kametani, the synthetically useful dehydrative thermolysis of anthranilic acids also must involve **3** as an intermediate: Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186; **1977**, *99*, 2306.

(5) Vollhardt, K. P. C. *Top. Curr. Chem.* **1975**, *59*, 113. Gheorghiu, M. D.; Filip, R. *Rev. Roum. Chim.* **1976**, *21*, 1189; **1974**, *19*, 859. Hoffmann, R. *Chem. Commun.* **1969**, 240. Gheorghiu, M. D.; Hoffmann, R. *Rev. Roum. Chim.* **1969**, *14*, 781. Gompper, R.; Seybold, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 824 and references therein.

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