

Electron transfer vs. heterolytic reactions. Behaviour of *N*-benzyl aziridine towards (aqua)_xCu^{II} and batho₂Cu^{II} ions

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Dedicated to the memory of Professor Costin D. Nenitzescu (1902-1970)

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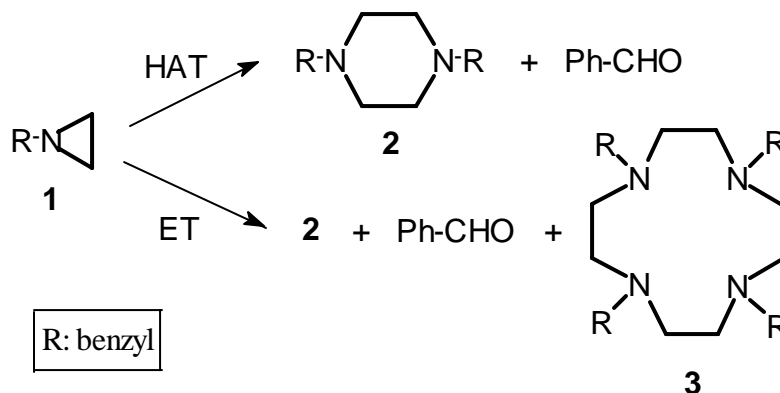
Abstract

Treatment of *N*-benzylaziridine (**1**) with (aqua)_xCu²⁺ yields tetrabenzylcyclen **3** by a metal-assisted heterolytic (HETERO) pathway. Conversely, **1** is oxidised by the batho₂Cu^{II} ion (batho: 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline disulfonate) to afford benzaldehyde, dibenzylpiperazine **2** and **3**, according to an electron-transfer mechanism (ET). Actually, evidence is presented for a competition between the ET and HETERO routes leading to **3**. This competition is modulated by the pH of the solution, and experimental conditions are found where the contribution of the ET route unambiguously prevails.

Keywords: Electron transfer, radical cations, cyclen, heterolytic reactions, aziridines

Introduction

In our investigations of the biomimetic and enzymatic oxidative *N*-dealkylation of tertiary amines,^{1,2} the reactivity features of *N*-benzylaziridine (**1**) emerged as being informative in case of competing oxidation mechanisms, because **1** gave different reaction products depending on the mechanism involved. For example, 1,4-dibenzylpiperazine **2** (i.e., a dimer) resulted in a *bona fide* hydrogen atom transfer (HAT) reaction, while 1,4,7,10-tetrabenzylcyclen **3** (i.e., a tetramer), in addition to **2**, was obtained in a *bona fide* electron transfer (ET) oxidation (Scheme 1).² In both cases, variable amounts of benzaldehyde also resulted. Formation of **3** from any oxidation reaction with **1** can therefore be taken as unambiguous evidence for the incursion of an ET oxidation mechanism.



Scheme 1

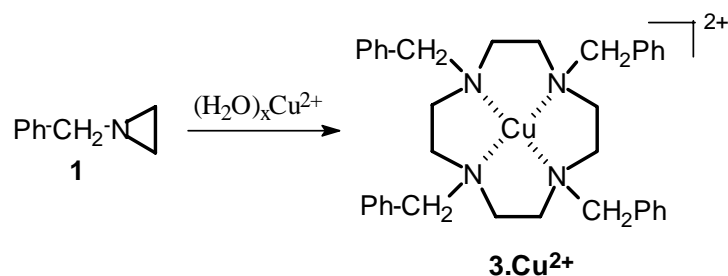
However, both oxidation products **2** and **3** can also result from an acid-catalysed heterolytic mechanism (HETERO).³⁻⁵ Consequently, extreme care must be taken with aziridine **1**, in order to circumvent or strictly quantify the contribution of the heterolytic pathway *vs.* any ET/HAT route.³ This appeared to be the case in the present investigation.

As a continuation of our studies^{2,3} on the behaviour of **1** in oxidation reactions,⁶ we have addressed our attention towards a new one-electron oxidant, namely batho₂Cu²⁺ (shortened as B₂Cu²⁺), where batho (B) stands for 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline disulfonate. This complex ion was recently described as a model of electron-transfer enzymes of the family of the “blue” copper oxidases.^{7,8} It has a relatively high oxidation potential, suitable for the oxidation of aliphatic tertiary amines,^{7a-b,8} but aziridine derivatives were not considered as substrates till now. The results of our investigation on the oxidation of **1** with batho₂Cu²⁺ are here reported. For appropriate comparison, experiments were also performed with the (aqua)_xCu²⁺ ion.

Results and Discussion

1. Reaction of **1 with (aqua)_xCu²⁺** A clean reaction occurred when excess aziridine **1** was added to an unbuffered aqueous acetonitrile or methanol solution of a Cu^{II} salt (either chloride, sulphate, nitrate, or acetate). The homogeneous solution gradually developed a blue colour ($\lambda_{\text{max}} = 610 \text{ nm}$ for **1** + CuCl₂) and gave only **3** (and unreacted **1**) after the usual work-up. Thus, starting from [1]₀ = 20 mM and [CuCl₂]₀ = 2 mM, tetramer **3** was obtained in about 18 % yield with respect to [1]₀ after two days at room temperature. No conversion of Cu^{II} into Cu^I ions could be detected during the reaction. These data are consistent with the formation of a 3.Cu²⁺ species during our experiments (Scheme 2). We have confirmed this by preparing 3.Cu²⁺ from an

authentic sample of **3** and CuCl_2 ,⁹ and found identical spectroscopic features. Conversely, a solution of **3** and CuCl remained colourless.



Scheme 2

Blank experiments, run under the above conditions but without Cu^{II} salts, showed a partial transformation of aziridine **1** into a complex reaction mixture, from which tetramer **3** was identified. Starting from $[\mathbf{1}]_0 = 20 \text{ mM}$, the highest attainable yield of **3** was 7% with respect to $[\mathbf{1}]_0$, that is significantly lower than that obtained in the presence of CuCl_2 (see above).

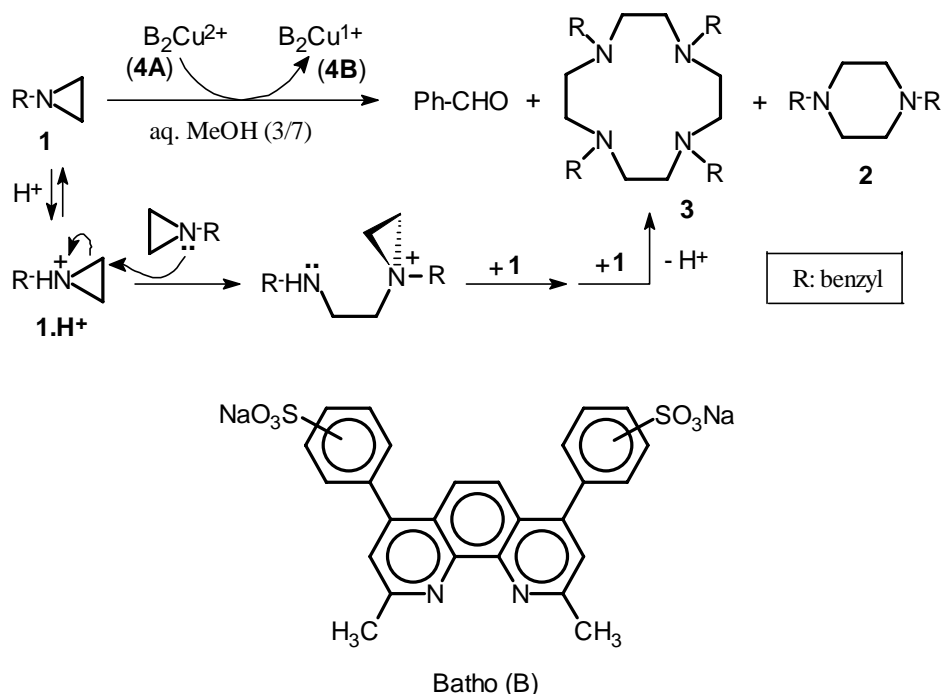
This transformation of **1** into **3** in aqueous acetonitrile or methanol solution containing $(\text{aqua})_x\text{Cu}^{2+}$ ions is *not* an oxidation reaction, because no Cu^{I} species have been detected. By consequence, a heterolytic mechanism can be suggested here, with the Cu^{II} salt acting as a Lewis acid. Because the outcome of the reaction was more simple with the Cu^{II} salt, and the yield of **3** higher than in the blank experiments, it is conceivable that the cupric cation assists the “tetramerization” of **1**, possibly by complexation of the various reaction intermediates at the nitrogen lone pair. To our knowledge, this is the *first* example of a metal-assisted transformation of **1** into **3**.¹⁰ Because several cyclen-based complexes similar to $\mathbf{3}\cdot\text{Cu}^{2+}$ are (or proposed to be) used as carriers for highly selective extraction and transport of nucleosides and nucleotides,¹¹ or as magnetic resonance imaging (MRI) substances in cancer radioimmunotherapy,¹² our Cu^{2+} -catalysed transformation of **1** into $\mathbf{3}\cdot\text{Cu}^{2+}$ might represent, after optimization, a valuable synthetic approach to such compounds.¹³

2. Reaction of **1** with B_2Cu^{2+}

2a. Product analysis. Excess *N*-benzylaziridine (**1**) reacted at 25°C with B_2Cu^{2+} (**4A**) in buffered ($\text{KH}_2\text{PO}_4/\text{KOH}$) methanol/water (3/7; v/v) mixture to afford benzaldehyde, dimer **2**, tetramer **3**, and other unidentified compounds (top of Scheme 3). The pH value was varied from 8 to 11. Depending on the reaction conditions, the three identified reaction products made up to 90 % of reacted **1**. Simultaneously, the corresponding batho copper(I) complex (B_2Cu^{1+} ; **4B**) was also produced, supporting an ET oxidation mechanism. The different behaviour of $(\text{aqua})_x\text{Cu}^{2+}$ and B_2Cu^{2+} towards **1** can be easily explained by considering the respective oxidation potentials. Indeed, the former species is a weaker oxidant than the latter ($E_0 = 0.167$ and 0.62 V , respectively, vs. NHE)¹⁴ and therefore is not able to oxidize aliphatic tertiary amines.

Several blank experiments were performed with **1** in the same pH range as that mentioned for the **1** + **4A** reaction, but without **4A** (i.e., pure HETERO conditions). As expected from the

results presented above in Section 1, the final reaction mixtures did contain tetramer **3**, but not dimer **2**. Formation of **3** should take place through cation **1.H⁺** (bottom of Scheme 3), a well-known reactive species towards ring opening by nucleophiles.¹⁵ A possible explanation for the lack of **2** under these conditions has already been given.³



Scheme 3

Comparison of these data with those obtained from the **1** + **4A** reaction shows that dimer **2** and benzaldehyde are the unambiguous reaction products of the ET route, while tetramer **3** could possibly result from both the ET and HETERO routes. The crucial question then arises for the reaction **1** + **4A**: how much does the contribution of the HETERO pathway add to the suggested ET route? We assumed that the extent of the ET route could be assessed from the comparison of the yields of **3** obtained with and without **4A**.

Starting from $[1]_0 = 0.03$ M, the same concentration of the kinetic experiments to be reported below, a detailed search revealed that $[1]_0/[B]/[Cu^{2+}]_0 = 1/3.3/1$ and $pH = 8-11$ could be experimental conditions suitable for running product analysis. In this cases, substrate **1** was consumed more rapidly than Cu^{2+} , although the $1/1 [1]_0/[Cu^{2+}]_0$ ratio was twice the generally accepted¹⁶ stoichiometric value (i.e., 1:2). On the other hand, blank and oxidation experiments showed both the HETERO and ET rates decreasing with increasing pH value. A convenient reaction time was found for $pH = 9$, and the related results are presented in Table 1. Under these particular conditions, only about 60% of $[Cu^{2+}]_0$ was reduced to $[Cu^{1+}]$ for a complete consumption of **1**. This was taken as the end-time of the reaction. For a 40% of this time span,

Table 1 shows that no heterolytic contribution to the formation of **3** can be appraised; conversely, for 80% of this time span, 88% of the experimentally found **3** was formed by the ET route. Similar results were obtained at higher pH values. It emerges that the HETERO route competes with the ET one *only* for relatively long reaction times. In other words, under these experimental conditions, the ET route appears to be the major (or the unique) operating mechanism leading to **3**.

Table 1. Product analysis for the **1** + **4A** reaction^a

| Reaction Product | Micromoles obtained ^b | | ET yields (%) ^e |
|--|----------------------------------|-------------------------------|----------------------------|
| | no 4A ^{a,c} | with 4A ^{a,d} | |
| <i>At 40 % of reaction^f</i> | | | |
| 1 (recovd.) | 363 | 240 | - |
| 2 | - | 8.4 | 9.3 |
| 3 | < 0.5 | 21.6 | 24.0 |
| PhCHO | - | 13.3 | 29.6 |
| <i>At 80 % of reaction^f</i> | | | |
| 1 (recovd.) | 312 | 45 | - |
| 2 | - | 15.1 | 8.4 |
| 3 | 6.2 | 51.7 | 25.3 |
| PhCHO | - | 29.2 | 32.4 |

^a General conditions: 375 μmol of **1** ($[\mathbf{1}]_0 = 0.03 \text{ M}$), $[\text{buffer}] = 0.1 \text{ M}$, pH 9.0, 25°C, MeOH/H₂O (3/7, v/v) as solvent. - ^b Mean values ($\pm 10\%$), corrected for work-up loss. - ^c HETERO conditions; same reaction times as in ET experiments. - ^d ET conditions: as before, but also $[\text{Cu}^{2+}]_0 = 0.03$ and $[\text{B}]_0 = 0.1 \text{ M}$. - ^e Calculated with respect to the **4B** formed (see also Section 2c). Error: 10%. The contribution of the ET route was obtained by subtracting the value of the blank experiment from that obtained in the presence of **4A**. - ^f Calculated as $[\mathbf{4B}]/[\mathbf{4B}]_{\text{final}} (\%)$, where $[\mathbf{4B}]_{\text{final}} = 0.6 [\text{Cu}^{2+}]_0$.

Interestingly, the ET yields (Table 1, last column) were practically invariant with respect to the reaction time. This suggests that benzaldehyde did not result from further oxidation of **2** and/or **3** by **4A**.¹⁷ Where this the case, the yields of **2** and **3** should decrease at longer reaction times, and that of benzaldehyde should increase, in contrast to what is observed.

2b. Kinetic analysis. Kinetic experiments were performed with a large excess of substrate (*pseudo*-first order conditions: $[\mathbf{1}]_0/[\mathbf{4A}]_0 = 100\text{-}300$) and at pH values in the 7-11 range. The progress of the reaction was followed by monitoring spectrophotometrically the formation of **4B** at 478 nm (λ_{max}). Blank experiments were also made in all cases. Although the experimental ET rates (i.e., $\mathbf{4A} \Rightarrow \mathbf{4B}$) were enhanced with respect to those observed previously under preparative conditions, substrate **1** was mainly consumed *via* the HETERO route, because of the relatively

lower value of $[4\mathbf{A}]_0$ with respect to that of $[1]_0$. However, for $\text{pH} > 8$, this consumption of $\mathbf{1}$ resulted to be no more than 10% of $[1]_0$ for reaction times of interest (i.e., ~ 3 half-lives of $\mathbf{4A}$). Moreover, this 10 % variation of $[1]$ was of the same order of magnitude of the error affecting the ET rate determination. Accordingly, one can consider $[1] \cong [1]_0$ under these conditions, the fundamental requisite of a *pseudo*-first order reaction being therefore fulfilled. It must be pointed out that, at $\text{pH} < 8$, the relative high velocity of the HETERO consumption of $\mathbf{1}$ precluded any ET rate determination.

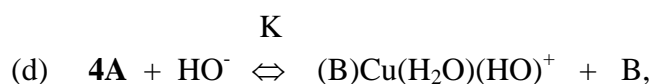
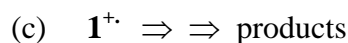
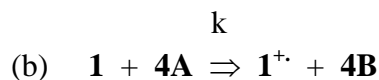
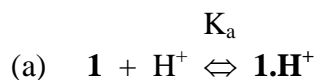
Products $\mathbf{2}$ and $\mathbf{3}$ are poorly soluble in the reaction mixture, and therefore tend to precipitate with time at the concentration adopted. For the sake of more precise kinetic evaluations, aliquots of the reaction mixture (at pH 8.8 and 9.4) were extracted with chloroform or ether, and the resulting clear water solution submitted to UV observation. Plots of the natural logarithms of $(A_t - A_0)/(A_\infty - A_0)$ vs. time, where A_0 and A_∞ have the common meaning of the absorbancies at the initial and "infinity" times, respectively, gave straight lines until 70-80% of reaction. The slope of the plots provided the *pseudo*-first-order rate constants, k_{exp} . At the same time, on keeping constant the pH value, a linear dependence of k_{exp} with the amine concentration was observed. It follows that the ET-reaction is first-order in both $[4\mathbf{A}]$ and $[1]$, as expected.^{7a,8} As no significant differences were observed between the k_{exp} values determined in this way (with extraction; ~ 3 half-lives) and those obtained directly on the somewhat cloudy reaction mixture (no extraction; ~ 1 half-live), the more easy direct method was adopted to determine k_{exp} at other pH values. At $\text{pH} > 10$, the low k_{exp} value (e.g., half-live > 20 h) forced us to follow the reaction until 0.5 half-live time. Values of k_{exp} are presented in Table 2.

Table 2. Kinetic data for the oxidation of *N*-benzylaziridine ($\mathbf{1}$) and *N,N*-dimethylbenzylamine ($\mathbf{5}$) with the copper(II) complex $\mathbf{4A}^a$

| Amine | Constant | Experimental values | | | | |
|----------|---|----------------------------------|------|------|------|------|
| 1 | pH | 8.0 | 8.5 | 8.8 | 9.4 | 10.1 |
| | $10^4 * k_{\text{exp}} (\text{s}^{-1})$ | 2.62 | 1.88 | 1.45 | 0.70 | 0.10 |
| | $k (\text{M}^{-1}\text{s}^{-1})^b$ | mean value: 0.038 ($\pm 15\%$) | | | | |
| | pK_a^c | 8.1 | | | | |
| 5 | pH | 7.3 | 8.3 | 9.3 | 9.9 | 10.6 |
| | $10^4 * k_{\text{exp}} (\text{s}^{-1})$ | 1.33 | 3.98 | 3.63 | 1.45 | 0.44 |
| | $k (\text{M}^{-1}\text{s}^{-1})^b$ | mean value: 0.47 ($\pm 15\%$) | | | | |
| | pK_a^c | 9.06 | | | | |

^a Reaction conditions: $[\text{amine}]_0 = 0.03 \text{ M}$, $[\text{Cu}^{2+}]_0 = 0.15 \text{ mM}$, $[\text{B}]_0 = 1.5 \text{ mM}$, $[\text{buffer}] = 0.1 \text{ M}$, 25°C , $\text{MeOH}/\text{H}_2\text{O}$ (3/7, v/v) as solvent. ^b Determined from Equation (1), by using $K=2000$ and $[\text{HO}^-]=10^{-14.22}/[\text{H}^+]$. ^c Kinetic value calculated from Equation (1).

As indicated elsewhere,⁸ the ET oxidation of a tertiary amine like **1** by means of **4A** follows the sequence (a) - (d):



where K_a , k , and K are the acidity constant of $\mathbf{1.H}^+$, the second-order rate constant of the ET rate-determining step (b), and the equilibrium constant of (d), respectively. Step (c) is a composite one and involves all the subsequent transformations of $\mathbf{1}^{\cdot+}$ (faster than step (b)) leading to the reaction products; it will be detailed in Section 2c.

At high pH, k_{exp} decreases because of the partial conversion of **4A** into an inert species, namely $(\text{B})\text{Cu}(\text{H}_2\text{O})(\text{HO})^+$ (see step (d)).⁸ The same slowing down effect should be observed in more acidic conditions, when increasing amounts of the free base **1** are converted into the non oxidizable cation $\mathbf{1.H}^+$ (see step (a)). Summing it up, the overall effect of pH should determine a bell-like profile for the k_{exp} variation, if the pH range could extend on *both* sides of the $\text{p}K_a$ value of the amine.^{7a,8} Unfortunately, this is not the case for aziridine **1**, due to the incursion of the HETERO route discussed before (too fast at $\text{pH} < 8$). No such complications arose in the case of the acyclic similar compound *N,N*-dimethylbenzylamine (**5**).⁸ We repeated the oxidation of **5** ($\text{p}K_a$ 9.00)⁸ with **4A** under our conditions, and the expected bell-like profile of k_{exp} vs. pH was indeed observed (Table 2). Comparison of the k_{exp} /pH variation for **1** and **5** (Table 2) would indicate that the unknown $\text{p}K_a$ of **1** is close to 8.

Taking into account the proposed ET-mechanism (steps (a)-(d)), the corresponding reaction rate is given by Equation (1),

$$(1) \quad \frac{d[\mathbf{4B}]}{dt} = -\frac{d[\mathbf{4A}]}{dt} = k_{\text{exp}} [\mathbf{4A}]_t = 0.5 k [\text{amine}]_0 \left\{ \frac{K_a}{K_a + [\text{H}^+]} \right\} \{ D - (D^2 - 4 [\text{B}]_t [\text{Cu}^{2+}]_t + 4 [\text{Cu}^{2+}]_t^2)^{1/2} \},$$

$$\text{where } [\text{B}]_t = 2 [\mathbf{4A}] + [(\text{B})\text{Cu}(\text{H}_2\text{O})(\text{HO})^+] + [\text{B}],$$

$$[\text{Cu}^{2+}]_t = [\mathbf{4A}] + [(\text{B})\text{Cu}(\text{H}_2\text{O})(\text{HO})^+], \text{ and}$$

$$D = [\text{B}]_t + K [\text{HO}^-].$$

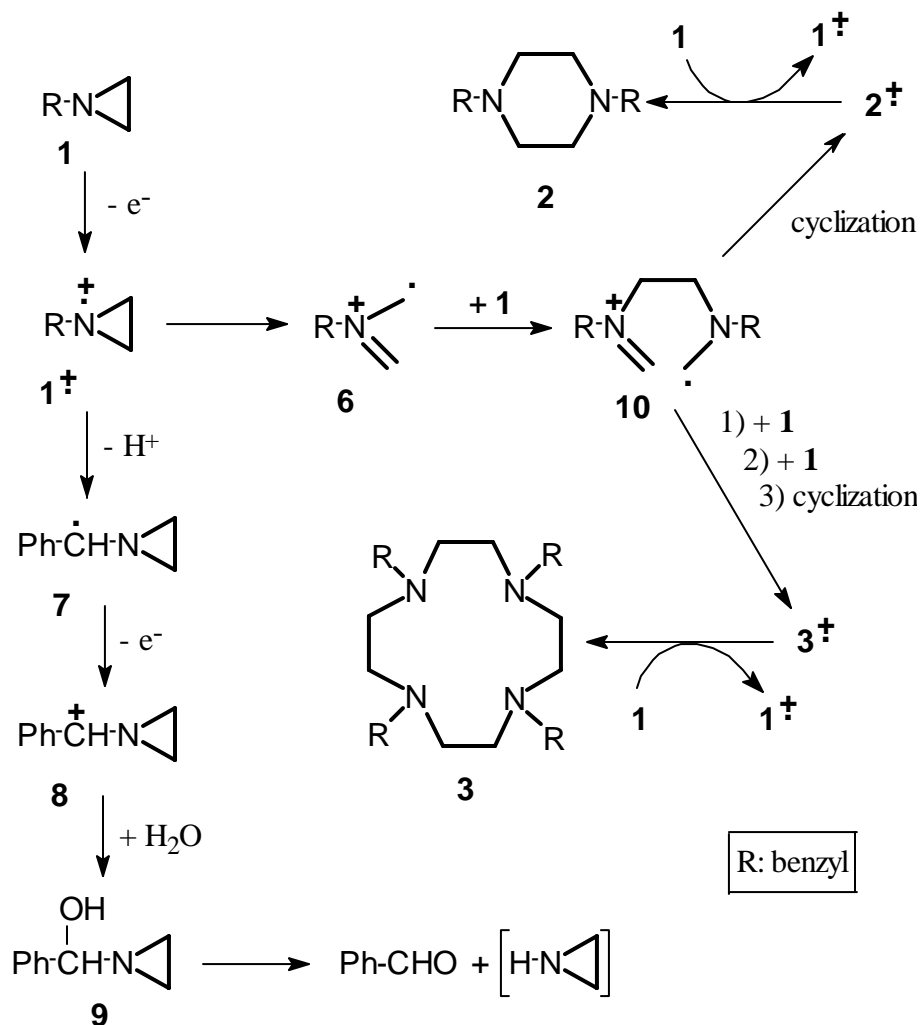
Actually, for **5** as the substrate, every molecule of reacted amine requires the consumption of two molecules of oxidant,¹⁶ by consequence, the correct second-order rate constant (k_{corr}) is twice the

value of our k . A similar reasoning can not be extended to the oxidation of **1**, because of the slightly different mechanism involved (see Section 2c). Therefore, we decided to compare only k values.

Our Equation (1) is identical to that given in the literature,⁸ with the only exception of the initial factor of the right member (2, instead of our 0.5). In order to solve this discrepancy, we calculated the rate constant k for the oxidation of **5** according to Equation (1), by using our k_{exp}/pH data (Table 2) and the recommended values of $K = 2000$,⁸ $\text{pK}_a = 9.00$,⁸ and $[\text{HO}^-] = 10^{14.22}/[\text{H}^+]$.¹⁸ The obtained value ($k = 0.47 \text{ M}^{-1} \text{ s}^{-1}$; Table 2) is just *four* times greater than that of the literature ($0.12 \text{ M}^{-1} \text{ s}^{-1}$). This means that the Authors⁸ did not calculate a truly corrected rate constant. However, the computed pK_a (9.06; Table 2) is in accord with the literature.⁸

By an identical procedure, and employing the k_{exp}/pH data for the oxidation of **1** (Table 2), a value of $k = 0.038 (\pm 15\%) \text{ M}^{-1} \text{ s}^{-1}$ was obtained at 25°C, that is about *one tenth* of the corresponding value belonging to **5**. This lower value might reflect to some extent the more difficult electron abstraction from the nitrogen lone-pair of **1** in the rate-determining step.¹⁹ At the same time, the kinetic value of pK_a (8.1; Table 2) calculated in the usual way⁸ from our kinetic data is well in keeping with the thermodynamic pK_a value (7.86)²⁰ of *N*-methylaziridine, a compound very similar to **1**.

2c. ET Reaction mechanism. The oxidation of aziridine **1** with the copper complex **4A** may be rationalised as depicted in Scheme 4.^{2,3} The reaction starts by a one-electron transfer from **1** to **4A**. The resulting radical cation $\mathbf{1}^{\cdot+}$ may be involved in two concurrent reactions: (i) fast cleavage of the C-C bond of the aziridine ring²¹ to yield **6**, and (ii) proton abstraction (by a base) to give a benzylic radical (**7**). In case (ii), the final reaction product is benzaldehyde (plus aziridine), as a result of the steps $\mathbf{7} \Rightarrow \mathbf{8} \Rightarrow \mathbf{9}$; this sequence is the generally accepted one for the ET oxidation of amines.¹⁶ Accordingly, the formation of benzaldehyde requires two equivalents of **4A**. In case (i), the ring-opened radical cation **6** might be attacked by **1** in a $\text{S}_{\text{H}}2$ -type reaction.²² The resulting acyclic dimeric radical cation (**10**) can undergo cyclization to $\mathbf{2}^{\cdot+}$ or, in competition, stepwise addition of two molecules of **1** to give $\mathbf{3}^{\cdot+}$, after another cyclization reaction.²³ When **1** is in large excess with respect to $\mathbf{2}^{\cdot+}$ and $\mathbf{3}^{\cdot+}$, which is actually our case, both radical cations $\mathbf{2}^{\cdot+}$ and $\mathbf{3}^{\cdot+}$ can separately react with **1** to yield the neutral species **2** and **3**, respectively, thereby regenerating $\mathbf{1}^{\cdot+}$ without consumption of additional oxidant.² In this way, formation of **2** and **3** requires only one equivalent of **4A**.



Scheme 4

According to the depicted sequence $1^+ \Rightarrow 7 \Rightarrow 8 \Rightarrow 9$, both 2^+ and 3^+ could be deprotonated and subsequently oxidised. If the proton is abstracted from their benzylic position, benzaldehyde would be formed.³ Therefore, benzaldehyde might in principle result from all three radical cations 1^+ , 2^+ , and 3^+ . Because for any amine (i.e., **1**, **2**, or **3**) the rate-determining step is (b), the separate contributions to benzaldehyde formation could be rationalised if the respective k 's and product analyses were known. Unfortunately, both **2** and **3** are highly insoluble in aqueous methanol, even at the low concentration level required by the UV-VIS method. This did not allow us to perform oxidation of **2** or **3** at the same conditions adopted for **1**. However, judging from the respective yields listed in Table 1, production of benzaldehyde from 2^+ and/or 3^+ seems unlikely, as pointed out before. The low solubility of **2** and **3** in the reaction solvent is likely to prevent any further reaction of these two compounds. The insolubility of **3** might also be invoked to explain the lack of $3 \cdot \text{Cu}^{2+}$ in the reaction mixture, despite its presumably higher

constant of formation²⁴ with respect to that of **4A** (from **B** and Cu^{2+}): the attainment of equilibrium $\mathbf{3} + \text{B}_2\text{Cu}^{2+} \rightleftharpoons \mathbf{3}\cdot\text{Cu}^{2+} + 2 \text{B}$ probably requires a time far longer than that used in our experiments.

Conclusions

While tetrabenzylcyclen **3** resulted from *N*-benzylaziridine (**1**) and $(\text{aqua})_x\text{Cu}^{2+}$ by a Cu^{2+} -assisted heterolytic (HETERO) pathway, experimental conditions were found where an ET mechanism competes and predominates for the conversion of **1** into **3**, dibenzylpiperazine **2**, and benzaldehyde in the presence of the batho₂Cu²⁺ (**4A**) oxidant. In fact, in the pH range of 8 to 11 and for $[\mathbf{1}]_0/[\mathbf{4A}]_0 = 1/1$, the HETERO route appears to be largely suppressed. A kinetic analysis run under *pseudo*-first order conditions allowed the determination of the rate constant for the ET reaction of **1** with **4A** as $0.038 \text{ M}^{-1}\text{s}^{-1}$ at 25°C. Under the same conditions, the reaction of **4A** with the acyclic similar substrate *N,N*-dimethylbenzylamine (**5**) gave a higher rate constant ($0.47 \text{ M}^{-1}\text{s}^{-1}$), in keeping with an easier electron abstraction from the nitrogen lone-pair of **5** than from the lone-pair of the strained three-membered ring of **1**. Substrate *N*-benzylaziridine confirms once more to be a reliable mechanistic tool, enabling to discriminate among different reactive pathways and to assess their relative importance.

Experimental Section

General Procedures. GC analyses were carried out with a HRGC 5300 Mega Series instrument (FID detector), and a SE-52 (methylphenylsilicone polymer) fused silica capillary column (25 m x 0.32 mm), operating between 50 and 240°C with a 10°C/min programmed temperature increase, under hydrogen as the carrier gas; suitable response factors of pure samples of **1** and benzaldehyde were determined with respect to benzophenone. GC-MS analyses were performed at 70 eV with a HP 5972 MSD, coupled to a HP 5890 series II+ apparatus, fitted with a methylsilicone capillary column (30 m x 0.25 mm). A Varian Gemini A 300A spectrometer was used to record the ¹H-NMR spectra at 300 MHz (TMS as internal standard). UV-VIS analyses were made with a Carl Zeiss Specord spectrophotometer equipped with a temperature-controlled cell compartment, while pH measurements were run on a E 436 Metrohm Herisau instrument.

Materials. Compounds **1**,³ **2**,²⁵ and **3**,^{5a} were prepared according to the literature and their ¹H-NMR characteristics reported previously.³ *N,N*-Dimethylbenzylamine (**5**) and the disodium salt of batho were used as received (Aldrich). Reagent grade methanol (Chimopar) and acetonitrile (Merck) were employed as solvents. Water was distilled twice.

Reaction of **1 with (aqua)_xCu²⁺: Formation of **3**.Cu²⁺**

A solution of a Cu^{II} salt (chloride, sulphate, nitrate, or acetate; 1 ÷ 2 mM) was prepared in MeCN/H₂O (1/1) or MeOH/H₂O (3/7; v/v). Addition of a known amount of **1** (0.01 ÷ 0.02 M) caused the development of a blue colour in the homogeneous solution. This process can be conveniently followed spectrophotometrically at $\lambda_{\text{max}} \sim 610$ nm. After completion of the reaction, the mixture was treated with concentrated alkali, excess KCN added in order to remove **3** from its copper complex, and the heterogeneous, colourless mixture extracted several times with ether. The ethereal layers were collected, dried over Na₂SO₄, and quantitatively transferred in a graduated flask. An aliquot was used to determine the amount of **1** by GC analysis with benzophenone as the internal standard (no benzaldehyde was found) and the remaining ethereal solution was evaporated *in vacuo*. The residue was taken up in CDCl₃, a known quantity of nitromethane added (as the internal standard for integral measurement), and analysed by ¹H-NMR to quantify the amount of **3**. Only the peaks of **1** (unreacted) and **3** were observed. The identification was made by adding pure samples of the compounds to the above mentioned CDCl₃ solution.

General procedures for reaction of **1 with B₂Cu²⁺ (**4A**)**

Separate solutions of KH₂PO₄, KOH, CuCl₂.2H₂O, and **1** were prepared in methanol/water (3/7; v/v). The last solution was made just before use. Mixing of appropriate volumes of the above solutions gave three types of reaction mixtures, i.e., for product analysis, kinetic measurements, and blank experiments, respectively. In all cases [KH₂PO₄] was kept constant at 0.1 M, and the pH maintained within the 7-11 range by varying [KOH]. The experimental pH values were converted to operational ones by subtraction of 0.04 pH unit, due to composition of the mixed solvent employed.²⁶

(i) Product analysis. Typical procedure

The concentrations adopted for this reaction solution were: [B]₀ = 0.1, [Cu²⁺]₀ = 0.03, [**1**]₀ = 0.03 M; the pH was set at 9.0. A 1 mL-aliquot of this solution was stored in the dark at 25°C (thermostat). The formation of **4B** was followed by taking aliquots (4 µL) at proper times; these samples were diluted 200 times with methanol/water, and the absorbance at 478 nm measured. After a certain time, [**4B**] remained practically constant (i.e., [**4B**]_{final}), within a reasonable time of observation. This preliminary analysis allowed to determine the rate of production of **4B** under these conditions. Accordingly, a 12.5 mL-aliquot of an identical (freshly prepared) solution was kept at 25°C for a time sufficient for a 40% formation of **4B** (with respect to its final value); it was then diluted with 5 mL of a 20% aqueous KOH solution, 100 mg of KCN added, and the whole mixture extracted with 3 x 3 mL of ether. The ethereal layers were worked-up as indicated before for the formation of **3**.Cu²⁺. The same procedure was followed with a second 12.5 mL-sample, analysed after an 80% formation of **4B**. The experimentally found

amounts of the reaction products were corrected for the work-up loss using synthetic mixtures. Identification and quantification of the reaction products were made by $^1\text{H-NMR}^{27}$ and GC-MS.

(ii) Kinetic measurements. The concentrations adopted for this reaction solution were: $[\text{B}]_0 = 1.5 \text{ mM}$, $[\text{Cu}^{2+}]_0 = 0.15 \text{ mM}$, $[\text{1}]_0 = 0.3 \text{ M}$. Analogous solutions were prepared when substrate **5**, instead of **1**, was investigated. *Method A (no extraction)*. A sample of the reaction solution (at the desired pH value) was placed in the thermostated cell of the UV instrument and the rising of **[4B]** monitored as in (i). The “infinity” value A_∞ was obtained by adding of solid $\text{Na}_2\text{S}_2\text{O}_4$. Usually, when working with **1**, precipitation of reaction products occurred after 1-2 half-lives, and the absorbance reading was discontinued. With **5** as the starting amine, no precipitation was observed at all. *Method B (with extraction)*. Aliquots (1.5 mL) were taken at appropriate times from an initial 20 mL-solution containing **1**; each aliquot was extracted with chloroform or ether (peroxide-free), and the aqueous layer analysed by UV. The kinetic data were handled as indicated.⁸

(iii) Blank experiments. This reaction solution had $[\text{1}]_0 = 0.03 \text{ M}$. The desired pH value was set, and the solution kept at 25°C in a thermostat. After a reaction time equal to that in experiments (i) or (ii), the solution was worked-up as indicated before (addition of KCN was omitted) and analysed by GC and $^1\text{H-NMR}$.

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