Stereoelectronic Inhibition of Deprotonation in the Radical Cation of *N*-Benzylpiperidine: a Contribution to the Debate on the Mechanism of *N*-Dealkylation of Tertiary Amines

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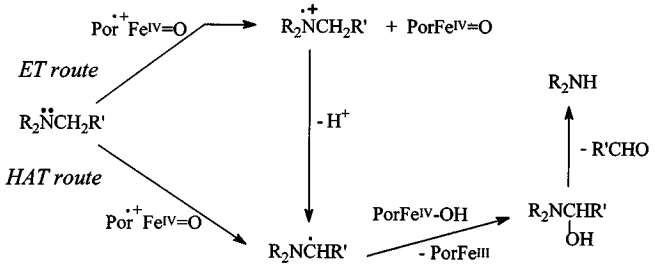
Evidence for a stereoelectronic inhibition of deprotonation of the radical cation of *N*-benzylpiperidine is presented. This stereoelectronic effect, which is due to the cyclic structure of the precursor, provides a tool to differentiate hydrogen-atom- versus electron-transfer routes in the biomimetic oxidative *N*-dealkylation of tertiary amines: the electron-transfer route appears to be the operating mechanism.

The oxidative *N*-dealkylation of amines is one of the most important reactions catalyzed by monoxygenase enzymes such as cytochrome P450.[1] Metalloporphyrin model compounds can bring about this reaction as well.[2] A dichotomy of mechanistic pathways is in principle possible with tertiary amines (see Scheme 1, where $Por^{\bullet+}Fe^{IV}=O$ represents the perferryl group): either an *e*lectron-*t*ransfer (ET) or a *h*ydrogen-*a*tom-*t*ransfer (HAT) route can be envisioned as responsible for the enzymatic or biomimetic *N*-dealkylation.

Scheme 1



Electron transfer from the amine lone pair to the perferryl group (Scheme 1; *ET route)* of the enzyme gives a nitrogen-centered radical cation; deprotonation of the latter from C_α forms an α-aminoalkyl radical and $PorFe^{IV}-OH$. The radical then undergoes fast recombination with $PorFe^{IV}-OH$ (*rebound*) to produce an unstable carbinol amine; the latter decomposes into a secondary amine and an aldehyde as the final products. In the other possible pathway (Scheme 1, *HAT route*), the α-aminoalkyl radical is directly formed from the precursor by a hydrogen-atom-transfer event, followed by rebound with $PorFe^{IV}-OH$.[1][2]

The ET pathway has received so far the more general consensus, both for enzymatic and biomimetic *N*-dealkylations. This is based on various experimental evidence,[3] but mainly on intramolecular H/D isotope effect determinations.[4] However, the reliability of this mechanistic probe has been seriously questioned, and it has been suggested that the correct use of this probe would rather lead to conclude that the cytochrome P450 induced *N*-dealkylation of tertiary amines occurs by the HAT mechanism.[5]

We have found that *N*-benzylpiperidine (**1**) is a substrate capable to aid in solving this mechanistic conundrum, at least for biomimetic processes, since a significant difference in the composition of the products mixture results under HAT or ET reaction conditions.

Products analysis of the oxidation reactions of the various substrates investigated here were performed by GC and GC/MS methods, and the results are reported in Table 1, together with some representative blank experiments.

Results and Discussion

Reaction of a substrate with *t*BuO•, produced from *t*BuOOH and tetraphenylporphyriniron(III) chloride [FeTPP], is widely considered as an example of a bona-fide HAT process.[6][7] Under these conditions we find that *N*-benzylpiperidine (**1**) undergoes hydrogen-atom abstraction from both the benzylic and piperidine-ring α-methylene groups. This is followed by rebound with $PorFe^{IV}-OH$ (see Scheme 1), giving benzaldehyde and 1-benzyl-2-piperidone (**2**; Scheme 2) (Table 1, entry 1), with a k_{benzyl}/k_{alkyl} relative

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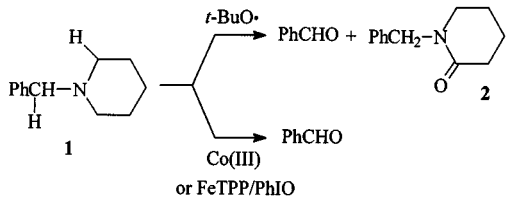
Table 1. Summary of the oxidative *N*-dealkylation reactions: conditions and yields

Entry	Substrate	Reaction conditions[a]	Yields (%)[b] Substrate (recovd.)	Max.[c]	PhCHO	Other(s)
1		*t*BuOOH/FeTPP	73	10	2.6	**2**, 1.0
2		*t*BuOOH[d]	94	10	–	–
3	1	CoIIIW	50	50	15	**2**, 0
4		PhIO/FeTPP	65	10	2.1	**2**, 0
5		PhIO[d]	88	10	–	–
6		FeTPP[d]	93	–	–	–
7		*t*BuOOH/FeTPP	90	10	–	–
8	2	CoIIIW	95	50	–	–
9		PhIO/FeTPP	96	10	–	–
10		*t*BuOOH/FeTPP	83	10	4.5	**4**, 6.3
11	3	CoIIIW	68	50	20	**4**, 16
12		PhIO/FeTPP	77	10	3.5	**4**, 2.0
13		*t*BuOOH/FeTPP	65	10	–	[e]
14	5	CoIIIW	85	50	–	–
15		PhIO/FeTPP	89	10	–	–
16		*t*BuOOH/FeTPP	67	10	–	**7**, 1.2
17	6	CoIIIW	88	50	–	**7**, 16[f]
18		PhIO/FeTPP	90	10	–	**7**, 2.5

[a] See also the Experimental Section. – [b] With respect to the initial amount of substrate. Unknown side-reactions, such as polymerization, might explain the low mass balance in some cases. – [c] Maximum attainable yield of oxidation products, calculated on the basis of substrate/oxidant molar ratio and oxidation stoichiometry. – [d] Blank experiment. – [e] Minor amounts (< 1%) of 1-benzyl-2-pyrrolidinone and of a dimeric product (*m*/*z*: 290). – [f] Benzidine-type dimeric products are also formed in very low yields.

reactivity of 5, taking into account the number of equivalent positions. 1-Benzyl-2-piperidone (**2**) indeed represents a product of further functionalization of a possible carbinol amine intermediate, rather than being a true product of dealkylation, as PhCHO is. In contrast to this outcome of the HAT route, only PhCHO is produced from **1** under the bona fide ET reaction conditions provided by a Co^{III} salt, i.e., potassium 12-tungstocobaltate [$Co^{III}W$] (entry 3), a well-known one-electron oxidant.[8] Under these conditions, the nitrogen-centered radical cation is expected to deprotonate to the α-aminoalkyl radical, which is further oxidized by a second molecule of $Co^{III}W$ into a carbocation and product(s) therefrom.[8] Finally, under biomimetic oxidative conditions,[1][7] that is, with PhIO as the oxidant and FeTPP as the catalyst, we obtain only PhCHO (entry 4). A strong similarity of the result of the biomimetic reaction with that of the bona fide ET reaction thus emerges.

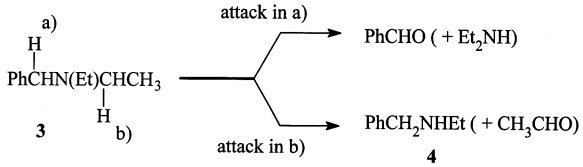
Scheme 2



Control experiments showed that **1** does not react with *t*BuOOH in the absence of FeTPP, nor under biomimetic conditions when only PhIO or only FeTPP are used (entries 2, 5, and 6). In addition, compound **2** showed to be stable under all conditions employed (entries 7–9).

It is useful to compare these reactions of **1** with the corresponding reactions carried out on the open-chain *N*,*N*-diethylbenzylamine model compound (**3**, Scheme 3).

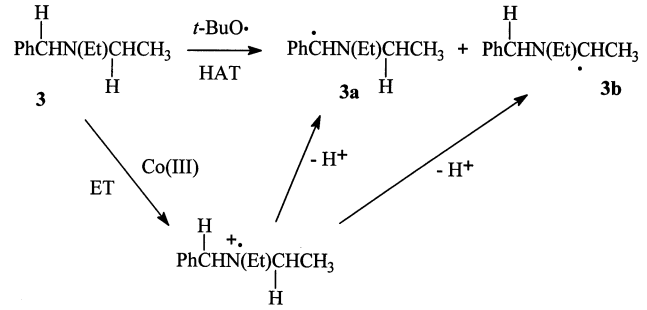
Scheme 3



Two *N*-dealkylation products, i.e., PhCHO and *N*-ethylbenzylamine (**4**), resulting from attack at the benzylic and alkylic positions of **3**, respectively, were found under all the three above reaction conditions (Table 1, entries 10–12). From the HAT (i.e., *t*BuOOH/FeTPP) a k_{benzyl}/k_{alkyl} ratio of 1.4 was obtained, while the ET process [i.e., $Co^{III}W$] gave 2.6, and the biomimetic reaction (i.e., PhIO/FeTPP) gave 3.5. Although these values of regioselectivity are not different enough as to make a precise assessment about the intervening mechanism for the biomimetic case, it is important to stress that with the open-chain precursor **3** there is firm evidence of formation of reaction products arising from attack at both kinds of *N*-methylene groups present in the molecule. This is a significant difference with respect to the outcome of the reactions with the cyclic precursor **1**. Reaction at both kinds of methylene positions of an *N*,*N*-dialkylbenzylamine such as **3** is not unprecedented[7][9] nor strange for HAT or ET processes, since no major differ-

ences in stability for the two intermediate radicals of this precursor can be foreseen (see Scheme 4).

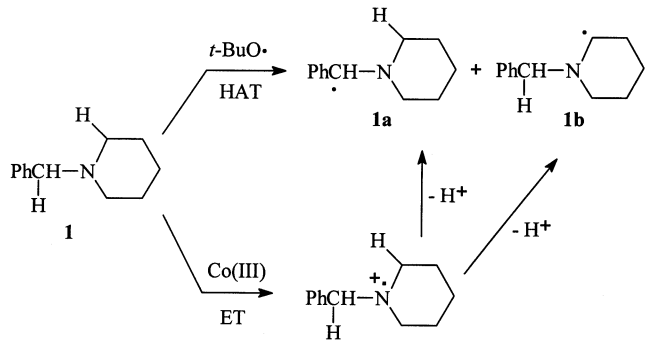
Scheme 4



In fact, calculations of the heats of formation of radicals **3a** and **3b** by MNDO (29.2 and 36.3 kcal/mol, respectively), give the benzylic radical **3a** as being more stable than **3b** by 7.1 kcal/mol. A similar difference (5.0 kcal/mol) is obtained by using the AM1 method. The difference is not so high as to compel one to expect products from **3a** only (i.e., PhCHO) and not from **3b** (i.e., **4**) as well. Thus, these calculations support the experimental findings of k_{benzyl}/k_{alkyl} ratios larger than 1 with substrate **3**, regardless the experimental conditions (HAT or ET) followed.

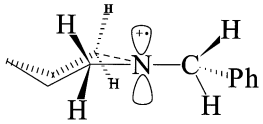
Calculations of the heats of formation for radicals **1a** and **1b** (see Scheme 5) consistently give the benzylic radical **1a** more stable than **1b**, by 5.4 kcal/mol (MNDO) or 4.4 kcal/mol (AM1). However, and more importantly, the difference in stability of **1a** and **1b** is comparable with that of the radicals **3a** and **3b** above. Accordingly, these calculations would once again support the expectation for k_{benzyl}/k_{alkyl} ratios not much larger than 1 also for substrate **1**; conversely, they find experimental support only for reaction of **1** under HAT conditions (i.e., $k_{benzyl}/k_{alkyl} = 5$); no products from **1b** (i.e., **2**) appear instead under ET or biomimetic conditions. This is the puzzling difference with the case of the open-chain substrate **3**.

Scheme 5



We have interpreted this difference as due to stereoelectronic effects that would operate at the stage of the nitrogen-centered radical cation in the *ET route*. The stereoelectronic effects appear to play an important role in the biomimetic reaction of **1** as well. The reason behind the different results between the HAT and ET dealkylations of **1**, which makes this substrate to be more telling than **3** from a mechanistic viewpoint, is possibly that the nitrogen-centered radical cation of **1** undergoes a strong structural rearrangement.[10] A planar nitrogen-centered structure would result, where all the α-C−H bonds of the piperidine ring are staggered with respect to the radical cation site. In fact, the PM3-computed geometry of the radical cation of **1** clearly shows that the nitrogen atom and the three α-C atoms lie in the same plane (Figure 1), with a dihedral angle of 32° between the *unpaired orbital−nitrogen−α-piperidine carbon* plane and the *nitrogen−α-piperidine carbon−hydrogen* plane. Conversely, the C−H bonds of the exocyclic benzylic group of **1** can be eclipsed to the nitrogen-centered radical cation, due to the unhindered rotation around the CH_2-N bond. The eclipsed arrangement would make possible an electronic assistance to the loss of the exocyclic α-protons. Consequently, loss of H^+ can occur from the benzylic position, leading ultimately to PhCHO, but *not* from the α-C−H bonds of the piperidine ring. In the HAT process of **1**, on the contrary, the relevance of the stereoelectronic effect in the abstraction of hydrogen atom is less stringent, since the geometry of the nitrogen atom is not perturbed, and at least one C−H bond for each α-methylene group of the ring is eclipsed with the nitrogen lone pair. Therefore, a hydrogen atom can be removed from both the benzylic and the ring-methylene groups, even with different rates, and therefore both the products from **1a** and **1b** are obtained, as also suggested by our calculations. In the case of the open-chain substrate **3**, on the contrary, the ET route is not afflicted by stereoelectronic restrictions to the correct alignment of the unpaired orbital of the nitrogen-centered radical cation with the C−H bonds and, consequently, both PhCHO and $PhCH_2NHEt$ are produced. This interpretation can be considered as an extension of the stereoelectronic argument previously invoked for explaining the lower reactivity of piperidine vs. open-chain tertiary amines in HAT processes with the *t*BuO• radical.[11]

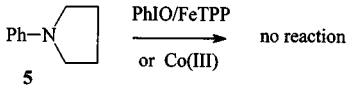
Figure 1



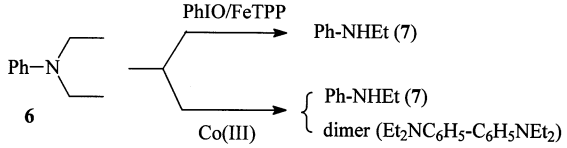
In order to obtain support to our interpretation, we then investigated the behaviour of *N*-phenylpyrrolidine (**5**), which lacks the *N*-benzylic methylene group (Scheme 6). Following the formation of the nitrogen-centered radical cation, a stereoelectronic inhibition of deprotonation from the α-C−H bonds of the pyrrolidine ring, analogous to that suggested to hold in **1**, was expected to severely depress the reactivity of **5** in an ET route. In fact, **5** does not react appreciably with $Co^{III}W$, nor with PhIO/FeTPP, while it reacts under HAT conditions (see Experimental Section), although with low conversion (Table 1, entries 13−15). This lack of reactivity of **5** represent a strong contrast with the normal behaviour of non-cyclic dialkylanilines, which are substrates easier to oxidize than trialkylamines such as **1** or

3.[9] For example, *N,N*-diethylaniline (**6**) is known to react under bona fide ET conditions,[9][12] and we indeed find the *N*-dealkylation product **7** from reaction with $Co^{III}W$ (Scheme 7), accompanied by benzidine-type dimeric products (detected and identified by GC-MS) (Table 1, entry 17). In addition, compound **6** does react under HAT conditions, affording the *N*-dealkylation product **7**, as it does also under biomimetic conditions (entries 16 and 18, respectively).

Scheme 6



Scheme 7



In conclusion, use of suitable *N*-cycloalkyl derivatives of amines allows to differentiate the stereoelectronic requirements of HAT vs. ET routes in the biomimetic *N*-dealkylation reaction. In the ET route, an eclipsed arrangement of a C–H bond to be broken with respect to the unpaired orbital of the nitrogen-centered radical cation appears to be the necessary requirement that makes loss of H^+ possible. Whenever this alignment is prevented, for example due to the conformational restriction imposed by a cyclic structure, either the formation of the nitrogen-centered radical cation might become reversible, and no reaction takes place at all (as in **5**), or other reactive paths of the radical cation take over, such as deprotonation from another available C–H bond which is unaffected by stereoelectronic restrictions (such as the benzylic protons in **1**). Within this scenario, the similar behaviour of the biomimetic and of the bona fide ET reactions of *N*-benzylpiperidine allows to suggest the ET route as being the operating mechanism in the biomimetic case.[13] The lack of reactivity of **5** is also in favour of this conclusion. It can be added that, in the absence of the steric restriction imposed by a cyclic structure, the difference in reaction products, or in intramolecular selectivity between alike reaction sites, would be significantly lower between the HAT or the ET routes of Scheme 1 (see the case of **3** and **6**), and this might explain the present debate on the mechanism of the biomimetic *N*-dealkylation reaction.

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Experimental Section

General: Gas-chromatographic analyses were carried out with a VARIAN Star 3400 instrument, fitted with a OV3 (5% phenylsilicone in methylsilicone) 10 m × 0.53 mm wide-bore capillary column; the yield values (typical errors, ± 4%) were calculated with respect to an internal standard, suitable response factors being determined on pure samples. – GC-MS analyses were carried out with an HP 5972 MSD, coupled to an HP 5890 series II+ GC, fitted with a methylsilicone 30 m × 0.25 mm capillary column. – Semiempirical calculations were carried out with a PC, by employing a MOPAC[14]package.

Materials: N,N-Diethylaniline (**6**), *N*-ethylaniline (**7**), *N*-ethylbenzylamine (**4**), *t*BuOOH (70% in H_2O), 1-benzyl-2-pyrrolidinone, and 2-piperidone (viz. δ-valerolactam) were commercial Aldrich samples, as it was also tetraphenylporphyiriniron(III) chloride [FeTPP]. A sample of *N*-phenylpyrrolidine (**5**) was already available in the laboratory.[15] Iodosobenzene was prepared from iodobenzene diacetate, as described.[16] The Co^{III} salt, i.e., $K_5[Co^{III}W_{12}O_{40}]\cdot 11\ H_2O$, was synthesised as previously reported.[8a][17]

N-Benzylpiperidine (**1**) was synthesised from excess piperidine and benzyl chloride in boiling benzene; bp 107–108°C at 5 Torr (ref.[18] bp 122°C at 15 Torr). *N,N-Diethylbenzylamine* (**3**) was similarly obtained from diethylamine and benzyl chloride; bp 109–111°C at 33 Torr (ref.[19] bp 96–98°C at 17 Torr). Products yields were in the 80–90% range.

1-Benzyl-2-piperidone (**2**) was obtained in a 86% yield from reaction of 2-piperidone with benzyl chloride in boiling benzene containing K_2CO_3 and $Bu_4N^+HSO_4^-$, as described;[20] bp 105–106°C at 0.5 Torr (ref.[21] bp 156°C at 4 Torr).

Reaction Conditions: a) Oxidations with 12-tungstocobaltate(III) (i.e., $Co^{III}W$)[8b] were conducted in 2 ml of a 5:1 (by weight) CH_3CN/H_2O deareated mixed solvent containing 50 μmol $Co^{III}W$, 0.3 mmol AcOK and 50 μmol of substrate, for 60 min at room temperature under argon. The blue color of the starting mixture had faded. Addition of the internal standard (acetophenone), work-up with $CHCl_3$, and concentration to a small volume preceded gas-chromatographic analyses. A control experiment showed that recovery of both reactant and product(s) from the water work-up is within experimental errors (≥ 95%). – b) Oxidations with the HAT agent *t*BuO•[7] were conducted in deaerated benzene (2 ml) employing 1.75 mmol of substrate, 175 μmol of *t*BuOOH and 17.5 μmol of tetraphenylporphyriniron(III) chloride, with stirring under argon for 1 h. Addition of the internal standard and direct injection (no work-up) of the reaction solution for GC quantitative analysis followed. Occasionally, water was added and the mixture was extracted with $CHCl_3$, in order to have work-up conditions comparable with those of procedure a): no major differences in distribution and yield of products were obtained. Under HAT conditions, compound **5** gave evidence of minor conversions (< 1%) to 1-benzyl-2-pyrrolidinone, identified by comparison with a pure sample, and to a dimeric product (*m/z*: 290), whose structure was not investigated any further. – c) Under biomimetic conditions,[7][22] the substrate (1.8 mmol), PhIO (180 μmol), and FeTPP catalyst (18 μmol) in benzene (2 ml) were stirred at room temperature under argon for 1 h. Gas-chromatographic analysis (as above) followed.

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[13] This conclusion appears to be supported by preliminary oxidation experiments catalyzed by *Horseradish Peroxidase* (HRP) in the presence of H_2O_2. Compound **1** gives PhCHO as the only detectable oxidation product, and no **2** is found. Under the same conditions, substrate **3** gives instead both PhCHO and **4**, with a k_{benzyl}/k_{alkyl} of about 40.
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