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First *N*-alkyl heterolysis of tertiary benzamides in neutral conditions

Nicolas Auzeil,[a] Alain Tomas,[b] Maurice-Bernard Fleury[a] and Martine Largeron[a,]*

[a]*Laboratoire de Chimie Analytique et Electrochimie, associé au CNRS,*
Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4, Avenue de l'Observatoire,
75270 Paris Cedex 06, France
[b]*Laboratoire de Cristallographie et RMN Biologiques, associé au CNRS,*
Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4, Avenue de l'Observatoire,
75270 Paris Cedex 06, France

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Abstract

Tertiary benzamides **1**–**4** bearing a tricyclopropylmethyl substituent were synthesized and found to undergo rapid alkyl-nitrogen heterolysis at pH 7. X-Ray diffraction structural data for these amides revealed that their ability to give *N*-alkyl fission was not induced by the pyramidalization of the nitrogen atom, in contrast to what has been observed in the case of *N*-acyl cleavage (hydrolysis). © 2000 Elsevier Science Ltd. All rights reserved.

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A considerable effort has been expended to understand the mechanisms of hydrolysis of the amide bond, in both acidic and basic media.[1] The carbonyl oxygen atom of the amide group is universally believed to be the preferred site of protonation in planar amides. However, in the case of distorted amides, the strong pyramidalization of the nitrogen atom favors *N*-protonation, which is suggested to play a key role in enzyme-mediated hydrolysis of twisted amides.[2–7]

So far, little attention has been paid to the competitive *N*-alkyl fission of strained *N*-alkylamides, probably because of the drastic conditions of both temperature and pH necessary for the reaction, conditions which were considerably different from physiological ones.[8–10] However, we have recently shown that tertiary pyridinecarboxamides or related benzamides bearing a *tert*-butyl substituent, suffered a facile alkyl-nitrogen cleavage under unusually mild conditions (room temperature, dilute aqueous sulfuric acid solutions), subsequently to *O*-protonation of the amide group.[11] Replacing the *tert*-butyl substituent with the tricyclopropylmethyl group, we

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* Corresponding author. Fax: 33-1-43-29-05-92; e-mail: largeron@pharmacie.univ-paris5.fr

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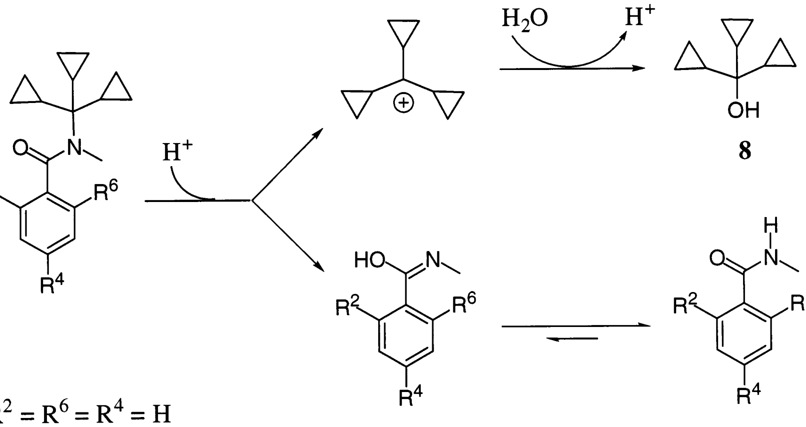
found that the amide portion became extremely sensitive towards *N*-alkyl heterolysis, so that it occurred even in the neutral pH region.

In this paper, we wish to report the first alkyl-nitrogen heterolysis in a neutral medium of tertiary benzamides bearing a tricyclopropylmethyl substituent. We provide both rate constants and activation parameters for *N*-alkyl fission, as well as X-ray diffraction structural data for benzamides **1**–**4**, in order to establish the relationship between the degree of amide distortion and the susceptibility towards *N*-alkyl heterolysis.

At pH 7 and 25°C, tertiary benzamides **1**–**3** afforded, in nearly quantitative yields, the corresponding secondary amides **5**–**7**, along with the tricyclopropylcarbinol **8**, by *N*-alkyl cleavage of the amide (Scheme 1). The kinetics was investigated using high-field ^{1}H NMR spectroscopy following a procedure previously reported.[11] The apparent first-order rate constant of the alkyl-nitrogen heterolysis was determined with **2**, in neutral medium. In the 5.0–7.5 pH range, the log k_{obs} vs pH profile was a straight line whose slope was 0.94, a result in agreement with a kinetic law of the type: $v = k_{obs}[\text{amide}] = k[\text{amide}][H_3O^+]$, which can be explained in terms of a full initial protonation of the amide oxygen atom.[12] Moreover, comparison of the rate constant values measured for compounds **1**–**3**, at pH 7 and 25°C, indicated that the reaction rate decreased in the presence of an electron-withdrawing substituent at the 4-position of the phenyl ring and, conversely, increased in the presence of an electron-donating substituent. Thus, a 15-fold decrease in k_{obs} was noted in passing from compound **1** ($k_{obs} = 35.3 \times 10^{-5}$ s^{-1}) to compound **2** ($k_{obs} = 2.3\ 10^{-5}$ s^{-1}), while the rate constant for *N*-alkyl heterolysis of compound **3** was too fast to be measured, under the same experimental conditions. Of particular note, introduction of methyl groups at the 2- and 6-positions of the phenyl ring blocked the alkyl-nitrogen heterolysis (compound **4**).



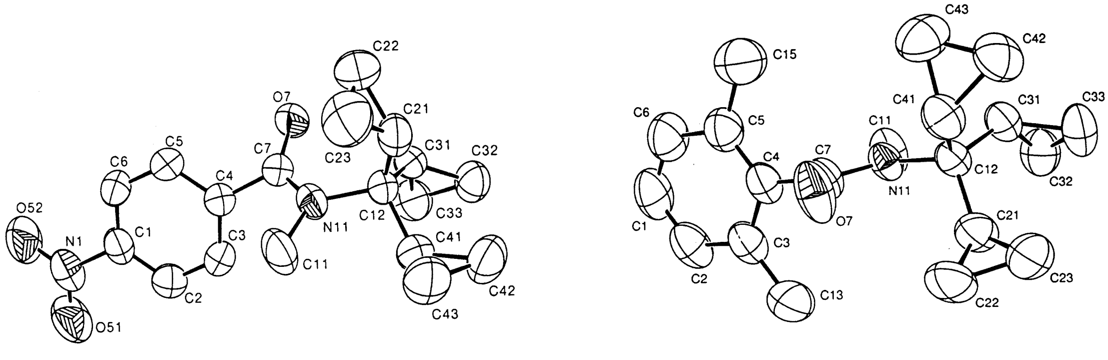
1 : R^2 = R^6 = R^4 = H
2 : R^2 = R^6 = H, R^4 = NO$_2$
3 : R^2 = R^6 = H, R^4 = OMe
4 : R^2 = R^6 = Me, R^4 = H

5 : R^2 = R^6 = R^4 = H
6 : R^2 = R^6 = H, R^4 = NO$_2$
7 : R^2 = R^6 = H, R^4 = OMe

Scheme 1.

Activation parameters[13] also supported the reaction scheme. The small positive $\Delta S^{\neq}$ value was as expected for a substrate exhibiting a unimolecular process.[10] It is known that distortion of an amide causes a shift from *O*- to *N*-protonation, which is accompanied by a marked decrease in the $\Delta H^{\neq}$ values, from 100 to 20 kJ mol^{-1}, while the $\Delta S^{\neq}$ values are generally large and negative (about −150 J mol^{-1} K^{-1}).[3,6,14] According to the data reported,[13] it could be deduced that the distortion caused by both the tricyclopropylmethyl and methyl substituents would not be sufficiently severe to provoke a shift from *O*- to *N*-protonation. This was further substantiated by the results of X-ray crystallographic study.

Benzamides **1**, **2** and **4** yielded crystals suitable for structure determination (Fig. 1). In contrast, we were unable to obtain satisfactory crystals of **3** for X-ray crystallographic analysis, due to its high reactivity which gave *N*-alkyl heterolysis on standing. While the most precise description of molecular distortion was obtained from the analysis of the atomic positions proposed by Dunitz and Winkler,[15] a qualitative feel for the distortion can be derived from the tilt and twist angles as defined by Brown.[5] We especially wanted to know whether the significant acceleration of *N*-alkyl heterolysis, observed with benzamides **1**–**3**, arose from twisting the *N*-lone pair out of conjugation, the tilting which was achieved on *N*-pyramidalization, or some combination of the two deformations. Selected bond distances and angles for benzamides **1**, **2** and **4** are collected in Table 1.[16] *N*-*p*-Nitrobenzoylpyrrolidine was added for comparison with benzamide **2**, as it was anticipated to have a planar amidic unit, or very nearly so.[17,18] X-Ray crystallographic data for 1-aza-2-adamantanone was also reported since this is the extreme case of a twisted amide, in which overlap of the lone pair of the nitrogen atom with the π system of the carbonyl group is prevented by the rigid geometry of the tricyclic compound.[19]



2 **4**

Figure 1. Perspective views of **2** and **4**. Atoms are represented by Gaussian ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. (Atom numbering is for crystallographic purposes only and does not correspond to naming of the compound)

Results reported in Table 1 indicate that, in all cases, benzamides contained a planar amidic unit, as characterized by summation of the three valence angles around N_{11} (roughly 360°) and by the low value found for the tilt angle which never exceeded 4°.[2,5] Moreover, the molecules displayed bond distances within normal limits for planar amides.[18] So, it could be deduced that the great reactivity of benzamides **1**–**3** did not correlate with *N*-pyramidalization. Interestingly, the difference between non-reactive benzamide **4** and highly reactive compounds **1**–**3** stemmed from changes in the twist angle, which markedly increased from 2 to roughly 20° (Table 1), a value which remains moderate when compared with that of 1-aza-2-adamantanone, the extreme case of twisted amide (90°). Whether such a twisting deformation was important in terms of increasing the susceptibility of benzamides **1**–**3** towards *N*-alkyl heterolysis was somewhat difficult to appreciate, as the distortion in these molecules also provoked a substantial torsion

Table 1
Selected structural parameters for benzamides **1**, **2** and **4**

	r (N_{11}–C_7) (Å)	Angle α[d] (°)	Angle around N_{11} (°)	Twist angle[e] (°)	Tilt angle[e] (°)
1[a]	1.355(3)	55.2(2)	359.5(2)	18.8(2)	3.4(2)
	1.356(3)	56.7(2)	360.3(2)	18.5(2)	4.1(2)
2	1.357(2)	50.2(2)	359.9(2)	20.0(2)	1.7(2)
4	1.354(3)	89.0(2)	359.7(2)	2.0(2)	2.6(2)
(*N*-*p*-Nitrobenzoyl)pyrrolidine[b]	1.337	–	359.3	6.1	3.7
1-aza-2-Adamantanone[c]	1.475	–	325.7	90.5	[f]

[a] Two crystallographically independent molecules in unit cell.

[b] Reference 18.

[c] Reference 19.

[d] Angle α between the plane of the amide and that of the phenyl ring.

[e] Reference 5.

[f] This value was not mentioned.

angle α between the amide plane and that of the phenyl ring (Table 1). Note, that according to kinetic results, α did not affect transmission of substituent effects at the 4-position of the phenyl ring, as orbitals twisted out of the plane in the ground state could become coplanar in the localized excited state.[20] In the case of non-reactive benzamide **4**, for which α was found to be maximal (89°), it could be conceivable that the steric crowding exerted by 2- and 6-methyl substituents forced the planar amidic unit out of the plane of the phenyl ring, even in the localized excited state.[21] Then, interruption of π-electron conjugation between the amidic portion and the phenyl ring would be responsible for the lack of reactivity observed. Consistent with this hypothesis, it could be remembered that, in the previously studied benzamide series,[11] *N*-cyclohexyl-*N*-*tert*-butylsalicylamide has been found to be the best candidate for *N*-alkyl heterolysis, due to intramolecular hydrogen bonding that rendered coplanar the N–C(O) moiety and the 2-hydroxyphenyl ring.

In summary, we have evidenced, in neutral medium, the first *N*-alkyl cleavage reaction of tertiary benzamides. Using X-ray crystallographic analysis, we have shown that the ability of these amides to give *N*-alkyl fission is not induced by *N*-pyramidalization, contrary to what is observed in the case of *N*-acyl cleavage (hydrolysis). It remains to be confirmed whether the propensity of *N*-tricyclopropylbenzamides to form the tricyclopropylium ion intermediate may account for their improved *N*-alkyl heterolysis, compared to that of *N*-*tert*-butyl analogues,[11] since the most stable carbonium ion shows the onset of *N*-alkyl cleavage in the lowest acidity. Further work to underpin this proposal is currently in progress in our laboratory.

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12. Found, in 0.2 mol L^{-1} aqueous citric buffered solutions containing 50% methanol, at 25°C, $10^5\ k_{obs}/s^{-1}$ (pH): 88.33 (5.3); 15.33 (6.0); 2.29 (7.0); 1.35 (7.4).
13. At pH 7, in 0.2 mol L^{-1} aqueous citric buffered solutions containing 50% methanol, the pseudo first order constants at 25, 35 and 45°C were converted to second order ones and plotted in the usual way according to the Eyring equation, to yield the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values. Found: $\Delta H^{\neq} = 59.2 \pm 1.5$ kJ mol^{-1} and $\Delta S^{\neq} = 1.7 \pm 1.0$ J mol^{-1} K^{-1}.
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16. X-Ray diffraction experiments of crystal were carried out on a Nonius CAD4 Enraf–Nonius diffractometer with Cu Kα ($\lambda = 1.5418$ Å) at 293 K. The structure was solved by direct methods and refined on F^2 using SHELX-97 software.[22] Non hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located from the difference Fourier map and then refined isotropically. **Crystal data for 1**. $C_{36}H_{46}N_2O_2$, $M_w = 508.74$, monoclinic, space group $P2_1/a$, $a = 14.582(1)$, $b = 10.250(1)$, $c = 22.054(2)$ Å, $\alpha = 90.00$, $\beta = 108.66(1)$, $\gamma = 90.00°$, $V = 3123.0(5)$ Å^3, $D_c = 1.082$ g cm^{-3}, $F(000) = 1108$, $\mu = 0.479$ mm^{-1}. 5300 reflections were measured. Final $wR_2 = 0.1834$, $R_1 = 0.0544$ (4001 reflections with $I > 2\sigma(I)$) and a goodness-of-fit = 1.072 for 500 refined parameters. The residual electron density shows no features up to 0.160 e Å^{-3} and down to −0.194 e Å^{-3}. **Crystal data for 2**. $C_{18}H_{22}N_2O_3$, $M_w = 314.38$, triclinic, space group $P\bar{1}$, $Z = 1$, $a = 7.652(1)$, $b = 10.335(1)$, $c = 10.925(1)$ Å, $\alpha = 109.16(2)$, $\beta = 92.04(2)$, $\gamma = 99.32(2)°$, $V = 801.7(2)$ Å^3, $D_c = 1.302$ g cm^{-3}, $F(000) = 336$, $\mu = 0.721$ mm^{-1}. 2743 reflections were measured. Final $wR_2 = 0.1126$, $R_1 = 0.0403$ (2509 reflections with $I > 2\sigma(I)$) and a goodness-of-fit = 1.028 for 279 refined parameters. The residual electron density shows no features up to 0.205 e Å^{-3} and down to −0.186 e Å^{-3}. **Crystal data for 4**. $C_{20}H_{27}NO$, $M_w = 297.43$, monoclinic, space group $P2_1/a$, $a = 13.472(2)$, $b = 7.692(3)$, $c = 17.059(6)$ Å, $\alpha = 90.00$, $\beta = 90.72\ (3)$, $\gamma = 90.00°$, $V = 1767(1)$ Å^3, $D_c = 1.118$ g cm^{-3}, $F(000) = 648$, $\mu = 0.519$ mm^{-1}. 2893 reflections were measured. Final $wR_2 = 0.2195$, $R_1 = 0.066$ (2284 reflections with $I > 2\sigma(I)$) and a goodness-of-fit = 1.108 for 285 refined parameters. The residual electron density shows no features up to 0.361 e Å^{-3} and down to −0.191 e Å^{-3}.
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