Aqueous Radicals

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Alkyl Radical Generation in Water under Ambient Conditions—A New Look at the Guareschi Reaction of 1897**

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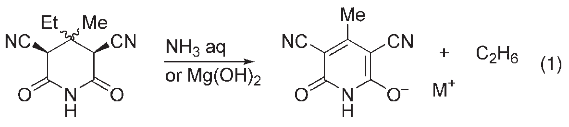
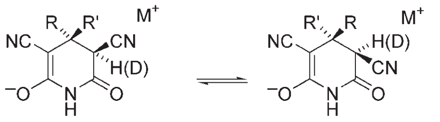
In memory of Arthur J. Birch

In a series of papers initially published between 1897 and 1901, I. Guareschi (Turin) and his colleagues reported the synthesis of 4,4′-dialkyl-3,5-dicyanoglutarimides by the condensation of ketones other than acetone with ethyl cyanoacetate in ethanolic ammonia.[1,2] The reaction has frequently been used subsequently as a route to functional quaternary centers,[3] and because glutarimides have shown potential as drugs.[4] In Guareschi's work, these otherwise unremarkable compounds demonstrated a remarkable property. The imide **1a**, on neutralization with alkaline ammonia or $Mg(OH)_2$, gave pyridone **2** with evolution of ethane [Eq. (1)]. Likewise, hydrocarbons RH (R = Et, Pr, *n*Bu, *n*-C_6H_{13}, $Me_2C{=}CH\text{-}CH_2CH_2$, *n*-$C_9H_{19}$) were formed starting with glutarimides derived from ketones RCOMe. This aspect of Guareschi's work appears to have been at best neglected, at worst forgotten.



1a **2**



3, $M^+ = NH_4^+$ (isolated salt) or Na^+ (buffer)

1, **3** :**a**-**h**, R' = Me, **i**, R' = Et; **a**, R = Et, **b**, R = CH_2Ph, **c**, R = $CH_2(4\text{-}MeOC_6H_4)$, **d**, R = $CH_2(4\text{-}ClC_6H_4)$, **e**, R = $CH_2{=}CH(CH_2)_4$, **f**, R = **c**-$C_3H_5CH_2$, **g**, R = *i*Pr, **h**,**i** R = *n*Pr

We began by verifying a simple case. Imide **1a** was isolated as the ammonium salt **3a** according to the original procedure,[1] and both species characterized by ^1H and ^{13}C NMR spectroscopy.[5] In $[D_6]$DMSO, the imide **1a** exists predominantly as a mixture of the two *syn*-CN diastereomers, one of which was further characterized by X-ray analysis. Salt **3a** exists in D_2O mainly as two diastereomers with the enolate structure drawn in the formula. A minor $(\approx 10\%)$ more symmetrical component is also present. Under these conditions, NH and CHCN protons were completely exchanged for deuterons. On dissolution of salt **3a** in D_2O buffered to pH 7.2, 8.0, and 9.1, respectively, a slow, clearly visible evolution of C_2H_5D (EI MS: *m*/*z* 31.0535; calcd 31.0532) was observed, and formation of the aromatic product **2** occurred concurrently. The ethyl homologue of **2** was not detected. After reaction in H_2O (pH 8 buffer, 40°C, 4 h, sealed vial) ethane was detected in the head-space with $<1{:}1000$ parts of butane. The fastest reaction occurred at pH 8.0; in all three cases both ethane evolution and product formation ceased before the reaction was complete. In addition to the ethane, a significant amount of EtOD $(\leq 20\%)$ was consistently observed when the reaction was carried out in D_2O.

In order to elucidate the mechanism of alkane elimination, a series of analogues was prepared. In some cases it proved convenient to isolate the imide (**1c**, **1d**, **1g**, **1h**), and in others the ammonium salt was more easily accessible (**3a**, **3b**, **3e**, **3f**, **3i**). They could be interconverted (NH_3(g) or P_2O_5 in vacuum) and were used as prepared, normally in deuterated buffer solution. The benzylimide salt **3b** was subjected to the conditions described above. Formation of product **2** occurred over several days, but benzyl alcohol was the main product along with some benzaldehyde; C_7H_7D was not detected after extraction into $CDCl_3$. Reaction in 10%-enriched $^{17}OH_2$ demonstrated that the oxygen atom of the benzyl alcohol did not arise from water (*m*/*z* 109/108 = 0.06, calculated for the absence of ^{17}O incorporation: 0.07). Further, an Ar-degassed solution of **3b** showed little decomposition after several days; after bubbling through this solution O_2 for 5 min

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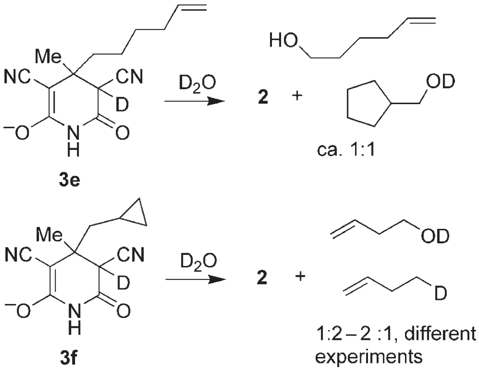
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

the reaction proceeded normally.[6] All of this suggested an alkyl radical intermediate. Cyclic voltammetry experiments in H_2O/0.1 M $NaClO_4$ revealed an irreversible one-electron oxidation at 0.80 V, pH 6.89. A similar peak was observed in CH_3CN. In H_2O, the corresponding peak at 0.75 V broadened in more basic solution and at pH 9.64, the highest value used, a second broad oxidation peak centered at 0.50 V was seen.

With the substituted-benzyl derivatives **3c** and **3d**, comparable rates of product formation were observed at 25 °C. This process corresponded to a first-order rate constant (k_1) for the decomposition of **3c** of $2.2\times10^{-6}\,s^{-1}$ and for that of **3d** of $2.7\times10^{-6}\,s^{-1}$. The relative reactivities were confirmed by an internal competition experiment. An induction period was observed, but absent when Ba^{2+} rather than NH_4^+ was the cation. When decomposition of **3c** was taken to 80% completion, the product was a mixture of 4-methoxybenzaldehyde (45%) and 4-methoxybenzyl alcohol (55%). This is consistent with benzyl radical generation, and its capture by dissolved oxygen. Hence the products arise via a benzylic hydroperoxide.

Imide salt **3e** was prepared from oct-7-en-2-one in 34% yield.[7a] Reaction in buffered D_2O resulted in slow formation of a 47:53 mixture of hex-5-en-1-ol and cyclopentylmethanol together with pyridone **2** (Scheme 1). Formation of the alcohols was verified by NMR comparison with authentic samples. Extraction into $CDCl_3$ confirmed the absence of both cyclohexanol and C_6 hydrocarbons. The alcohol ratio in the product was consistent, both over time and between experiments.



Scheme 1. Radical rearrangements in the fragmentation of imides **3**.

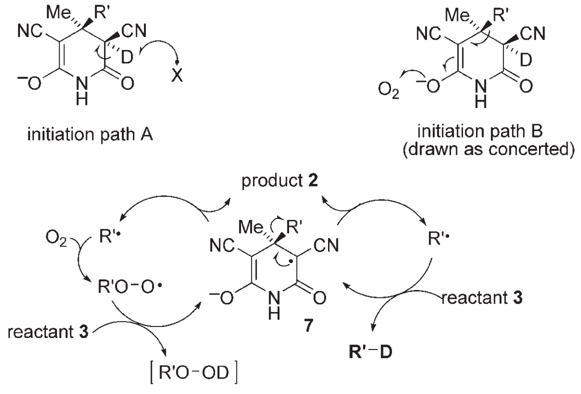
Compound **3f** was prepared from the corresponding ketone in 41% yield.[7b] Monitoring its decomposition by NMR spectroscopy in buffered D_2O showed that but-3-en-1-ol was formed, but in lower amount than pyridone **2**. On extraction with $CDCl_3$ the remaining C_4 product was found to be [4-^{2}H]but-1-ene (Scheme 1; δ(4-CH_2) = 0.95 ppm, $J_{H,D}$ = 1.2 Hz). No additional products were detectable. For comparison, S_N1 hydrolysis of cyclopropylmethyl mesylate (**4**) at pH 8.0 gave a mixture of cyclobutanol and cyclopropylmethanol together with traces of but-3-en-1-ol (49.5:48.5:2).[8] These results demonstrate the intermediacy of an alkyl radical in the Guareschi reaction and indicate that it possesses a lifetime of > 1 μs under the reaction conditions. This follows from a comparison with the rate constants for cyclization of the 5-hexenyl radical ($k_1 = 1\times10^5\,s^{-1}$) and for ring-opening of the cyclopropylmethyl radical ($k_1 = 1.3\times10^8\,s^{-1}$).[9]

The *i*Pr derivative **3g** was prepared by a two-step synthesis via the Knoevenagel product, following Cope et al.[10] As expected, alkyl cleavage was much faster for **3g** than for the *n*Pr analogue **3h**. *i*PrOOH (**5**; δ(C*H*O) = 4.20 ppm) was the major oxygenated product, confirmed by in situ NMR comparison with authenic **5**,[11] which reacted slowly with NaI to give *i*PrOH. In contrast to the benzylglutarimide **3b**, derivative **3g** is reactive in degassed solutions under standard conditions, indicating mechanistic differences between the routes to hydrocarbon and alcohol product.

One intriguing claim in Guareschi's original work is that imide salt **3i** derived from hexan-3-one gave exclusively ethane on aromatization in water.[1] We observed, however, the formation of both [D_1]ethane and [D_1]propane (EI MS), with a stronger signal from the former. Monitoring by NMR showed that ethanol and propanol were both formed in a ratio of 69:31. In accordance, the pyridones **2** with *n*Pr and Et instead of Me as substituent at position 4 were formed in a ratio of 70:30. Hydrocarbon formation was the minor process (RD:ROH ca. 1:2). The observed selectivity towards ethyl cleavage may originate from the different hydrophobicity and differential solvation of ethyl and propyl radicals, since their gas-phase stabilities are the same.[12]

The decomposition of glutarimides in buffered D_2O is suppressed by the stable spin trap 4-hydroxy-TEMPO **6**. In its absence, the *i*Pr species **3g** reacted completely after 21 h at 60 °C. In the presence of one equivalent of **6**, 27% decomposition was observed under the same conditions. Similar observations were made using the hexenyl derivative **3e**. Reactions run in the presence of azobisisobutyronitrile (AIBN; added in [D_6]DMSO) showed an enhanced rate of decomposition, however.

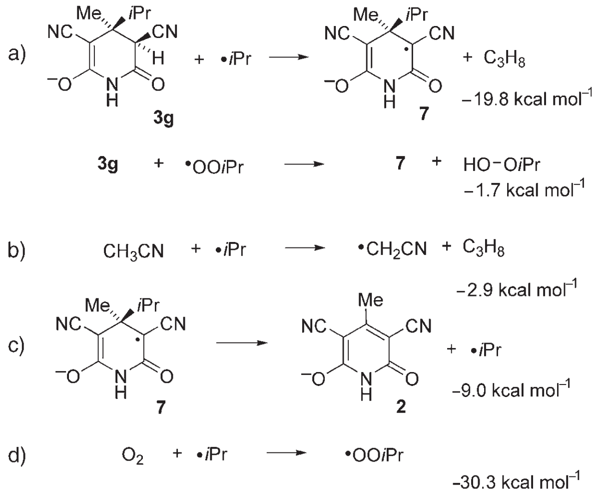
A mechanistic postulate consistent with these observations is shown in Scheme 2. In path A reaction is initiated by D abstraction, most likely by oxygen, and a stabilized radical **7** is the precursor of the pyridone **2** and R'$^\bullet$. An alternative path B involves an electron-transfer step from imide **3** to oxygen to generate first the corresponding anion radical, but seems less likely because of the endothermicity of the step.[13]



Scheme 2. Suggested pathways for the radical fragmentation of **3** in D_2O.

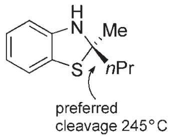
Once formed, the alkyl radical $R'^{\bullet}$ can engage in a chain reaction by further D abstraction, in competition with being trapped by dissolved oxygen.[14] In one of the early papers on ethyl radical generation in water, a switch from radical recombination to radical–oxygen chemistry was observed in the presence of O_2.[14a] Reaction of an alkyl radical with O_2 in water is diffusion-controlled, at $k = 2\times10^{9}\,\mathrm{L\,mol^{-1}\,s^{-1}}$ for ethyl. This is consistent with the radical lifetime of several microseconds observed herein, at air under ambient conditions ($[O_2] = 2.5\times10^{-4}\,\mathrm{M}$[14b]).

The feasibility of the proposed pathway was further tested through DFT calculations at the B3LYP/6-31G(d,p) level. The results are summarized in Scheme 3, and presented more fully in the Supporting Information. They indicate that the key step of a H/D abstraction from C3 of anion **3g** by $^{\bullet}i\mathrm{Pr}$ in the radical chain is enthalpically favored by nearly 20 kcal $\mathrm{mol^{-1}}$, and by 1.7 $\mathrm{kcal\,mol^{-1}}$ with $^{\bullet}\mathrm{OO}i\mathrm{Pr}$ (Scheme 3 a). The corresponding abstraction from CH_3CN by $^{\bullet}i\mathrm{Pr}$ is shown for comparison in Scheme 3 b. The resulting radical **7** bears a resemblance to the stabilized long-lived radicals characterized by Scaiano's group. These react slowly with O_2 once formed, and in our case would give the alternative fragmentation of radical **7** time to occur.[15] This subsequent fragmentation (Scheme 3 c) is also facilitated by the aromaticity of the pyridindionyl anion **2**, which provides a thermodynamic driving force for the ensuing C–C cleavage step, also entropically favored. For the alternative direct formation of the radical at C4 by homolytic C–C cleavage, ΔH_0 is 51 kcal $\mathrm{mol^{-1}}$. Finally, the competing pathway of oxygen trapping of the alkyl radical is shown in Scheme 3 d.



Scheme 3. Enthalpy changes in key steps of the proposed fragmentation mechanism, computed at the B3LYP/6-31G(d,p) level. All the data on individual species were corrected to include zero-point energies, without taking thermal contributions into account.

There are several scattered examples in which a heterocyclic aromatic compound is formed by elimination of an alkyl group, generally under forcing conditions.[16,17] Coherent interpretation of these processes has previously been lacking; for example, Elderfield and co-workers opted for carbanion pathways in the thermal fragmentation of **8**, but favored radical pathways in the fragmentation of the related compound **9**.[16] Guareschi's chemistry is important for its uniqueness: ambient conditions, near-neutral aqueous solution, dependency on an unusual intervention of molecular oxygen. There is both chemical and biochemical significance in the ability to generate alkyl radicals under such mild conditions.[18]



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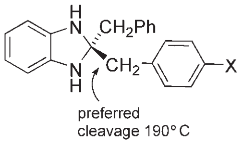

9 (X = Cl, OMe)

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[1] The work described was initially published in *Atti. R. Accad. Torino 32–35*, 1897–1899; a useful, and more accessible précis of Guareschi's work appeared in *Chem. Zentralblatt II* **1901**, 577–582; this journal is not available in electronic format but the parallel *J. Chem. Soc. Abstracts* (free Web access) is; see particularly the successive summaries of work by E. Grande, E. Quenda, A. Pasquali, L. Sabbatini, I. Guareschi, *J. Chem. Soc. Abstr.* **1898**, *74*, 272–274.

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[3] For example: a) U. Schoen, J. Antel, R. Brückner, J. Messinger, R. Franke, A. Gruska, *J. Med. Chem.* **1998**, *41*, 318–331; b) G. J. Handley, E. R. Nelson, T. C. Somers, *Aust. J. Chem.* **1960**, *13*, 127–144; c) S. M. McElvain, D. H. Clemens, *J. Am. Chem. Soc.* **1958**, *80*, 3915–3923; d) A. J. Birch, R. Robinson, *J. Chem. Soc.* **1942**, 488–497; G. A. R. Kon, J. Thorpe, *J. Chem. Soc.* **1919**, *115*, 686–704.

[4] Example: "Martindale, the complete drug reference, 2006" (http://www.medicinescomplete.com).

[5] The ^{13}C NMR spectrum of imide **1a** in [D_6]DMSO shows two symmetrical diastereomers in a 1:1 ratio. For the ammonium salt **3a** in D_2O, two unsymmetrical diastereomers (diastereotopic CH_2 groups) with traces of a third symmetrical isomer were observed. For full details see the Supporting Information.

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[8] See: a) Z. Majerski, S. Borcic, D. E. Sunko, *Tetrahedron* **1969**, *25*, 301–313; b) M. Nikoletic, S. Borcic, D. E. Sunko, *Tetrahedron* **1967**, *23*, 649–660.

[9] D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1980**, *13*, 317.

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[11] C. Walling, S. A. Buckler, *J. Am. Chem. Soc.* **1955**, *77*, 6032–6038.

[12] S. Gronert, *J. Org. Chem.* **2006**, *71*, 1209–1219, and references therein.

[13] Electron transfer from the radical anion to O_2 is endothermic, given the standard potentials derived from CV study (see above) and for the half-reaction $O_2 + e \rightarrow O_2^{\bullet -}$ (−0.13 V: J. Petlicki, T. G. M. van de Ven, *J. Chem. Soc. Faraday Trans.* **1998**, *94*, 2763–2767).

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[15] See for example: a) E. Font-Sanchis, C. Aliaga, R. Cornejo, J. C. Scaiano, *Org. Lett.* **2003**, *5*, 1515–1518; b) E. Font-Sanchis, C. Aliaga, E. V. Bejan, R. Cornejo J. C. Scaiano, *J. Org. Chem.* **2003**, *68*, 3199–3204; c) E. Font-Sanchis, C. Aliaga, K. S. Focsaneanu, J. C. Scaiano, *Chem. Commun.* **2002**, 1576–1577; d) J. C. Scaiano, A. Martin, G. P. A. Yap, K. U. Ingold, *Org. Lett.* **2000**, *2*, 899–901.

[16] R. C. Elderfield, E. C. McClenachan, *J. Am. Chem. Soc.* **1960**, *82*, 1982–1988, and earlier papers.

[17] Selected examples: a) K. N. Zelenin, I. V. Ukraintsev, V. V. Alekseev, *Chem. Heterocycl. Compd.* **1998**, *34*, 329–333; b) S. D. Larsen, E. Martinborough, *Tetrahedron Lett.* **1989**, *30*, 4625–4628; c) A. P. Reddy, V. Veeranagaiah, *Indian J. Chem. Sect. B* **1989**, *28*, 272–273; d) K. Schulze, C. Richter, R. Ludwig, *Tetrahedron Lett.* **1989**, *30*, 2369–2370; e) P. K. Dubey, C. V. Ratnam, *Indian J. Chem. Sect. B* **1980**, *19*, 863–865; f) R. Huisgen, R. Grashey, H. Gotthardt, R. Schmidt, *Angew. Chem.* **1962**, *74*, 29; *Angew. Chem. Int. Ed.* **1962**, *1*, 48–49.

[18] For full experimental details see the Supporting Information. CCDC 653648–653653 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.