Tetrahedron Vol. 37, No 16, pp 2917 to 2919, 1981
Printed in Great Britain

0040-4020/81/162917-03$02.00/0

SOLVENT EFFECT IN FREE RADICAL REACTIONS ON PROTONATED HETEROAROMATIC BASES

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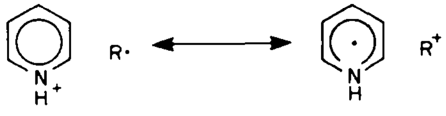
(*Received in the UK* 5 *February* 1981)

Abstract—The influence of reaction medium on the relative reactivity of various carbon radicals towards 4-CH_3- and 4-CN- quinolines has been investigated. A relevant solvent effect for α-amidoalkyl and α-oxyalkyl radicals has been demonstrated and a solvent-radical interaction is proposed to explain the phenomenon.

Solvent effects on radical reactions have generally been considered of low importance in determining reactivity and selectivity. The transition state in these reactions seem to have low charge separation and polar factors cannot affect it and modify the reaction rate.[1,2] In recent years some important polar factors have been implicated particularly to explain the dramatic selectivity of the carbon radicals towards protonated heteroaromatic bases.[3,4] Selectivities were explained considering the contribution of polar forms of the kind **I** and **II** in the transition state:



I II

The importance given to polar factors and some selectivity variations occasionally observed in these reactions with different media,[5] prompted us to consider the role that solvents play in determining the relative reactivity and selectivity of carbon radicals on heteroaromatic bases.

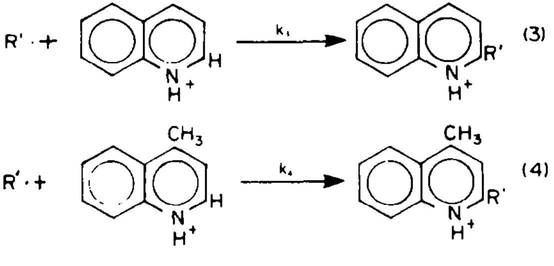
To investigate reaction medium effects we chose as aromatic substrates 4-cyano- and 4-methyl-quinoline, where only the 2-positions is attacked in high yield by carbon radicals in acidic medium. The relative reactivity is high enough to allow a clear appreciation of variation; finally the work-up of the reaction mixture as well as the product analysis is straightforward and reproducible. We assume that the same mechanism is operative for both substrates.

RESULTS AND DISCUSSION

As a radical source we used hydrogen abstraction from suitable compounds (dioxane, benzaldehyde, DMF: R'H in eqn 2) by Fenton's like redox systems (eqns 1 and 2):

$$ROX + M^{n+} \xrightarrow{k_1} MX^{n+} + RO\cdot \quad (1)$$

$$RO\cdot + R'H \xrightarrow{k_2} ROH + R'\cdot \quad (2)$$



where R = H, t-but, SO_3^-, and X = OH, Cl, SO_4^-.

The thermal decomposition of azoisobutyrronitrile (AIBN), $S_2O_8^{2-}$ and other peroxides were used as a source of hydrogen abstracting species.

The carbon radical studied first was the dioxanyl which is easily obtainable in high yield from dioxane by several radical generator systems. This radical, found to be one of the most affected by the reaction medium, permitted us to test if parameters such as the redox or thermal generation systems could in any way influence the relative reactivity defined as k_3/k_4 ratio (eqns 3 and 4). As we can see from Table 1, the reactivity ratio varies very little.

The other radicals tested did not show greater differences.

Similar figures for k_3/k_4 were obtained for dioxanyl radical with the following redox systems: $Fe(CN)_6^{4-}/H_2O_2$, Ce^{3+}/H_2O_2 and Co^{2+}/H_2O_2. To avoid the effect of possible coordinating metal ions, we also generated dioxanyl radicals by thermal decompositions of AIBN (62°, $k_3/k_4 = 44$), $S_2O_8^{2-}$ (90°, $k_3/k_4 = 52$) and directly from the dioxanoyl peroxide (100°, $k_3/k_4 = 52$), thereby demonstrating the negligible effect of the temperature between 20° and 100°. We also checked the effect of the medium by varying the ratio between water, dioxane and the mineral acid: increasing amounts of sulphuric acid (0.2–2.0 mol/l) did not affect the k_3/k_4 values of the dioxanyl radical while the ratio water/dioxane had an actual effect, decreasing from 45 (water/dioxane = 10) to about 20 (water/dioxane = 0.3) the relative reactivity of the radical. (Fig. 1a)

The decrease of k_3/k_4 was always followed by an increase of the global reaction yield. Even more dramatic selectivities were revealed by gradually substituting water with acetic acid and formic acid (Fig. 1 b, c). Also in this case increases of k_3/k_4 occurred together with decreases of the yields. This phenomenon was found with different intensities by all the radicals used; indicative data of the k_3/k_4 variations against reaction medium compositions for dioxanyl, benzoyl, α-amidoalkyl, carbamoyl, and undecanyl radicals were plotted in the Fig. 1.

These results demonstrate that the solvent has a real effect in determining the relative reactivities for such a kind of homolitic substitution and this effect is similar to the one generally recognized for the nucleophilic bimolecular substitutions where non protic solvents (dioxane, DMF) favour the reaction, while protic solvents (water, acetic acid, formic acid) reduce the yields and increase the selectivity by solvating the reagents through hydrogen bridges.[6] We recognise an effect of substrate stabilization by solvation of the quinolinium salts and an interaction on the nucleophilic sites of the radical reagents. The former effect does not

Table 1. Relative reactivities of the dioxanyl radical generated with different redox systems

ROX / M^{n+}	H_2O_2	$S_2O_8^{--}$	t-but-OOH	t-but-OCl
Fe^{2+}	44	44	48	51
Ti^{3+}	46	51	52	48
Cu^{1+}	52	48	52	51

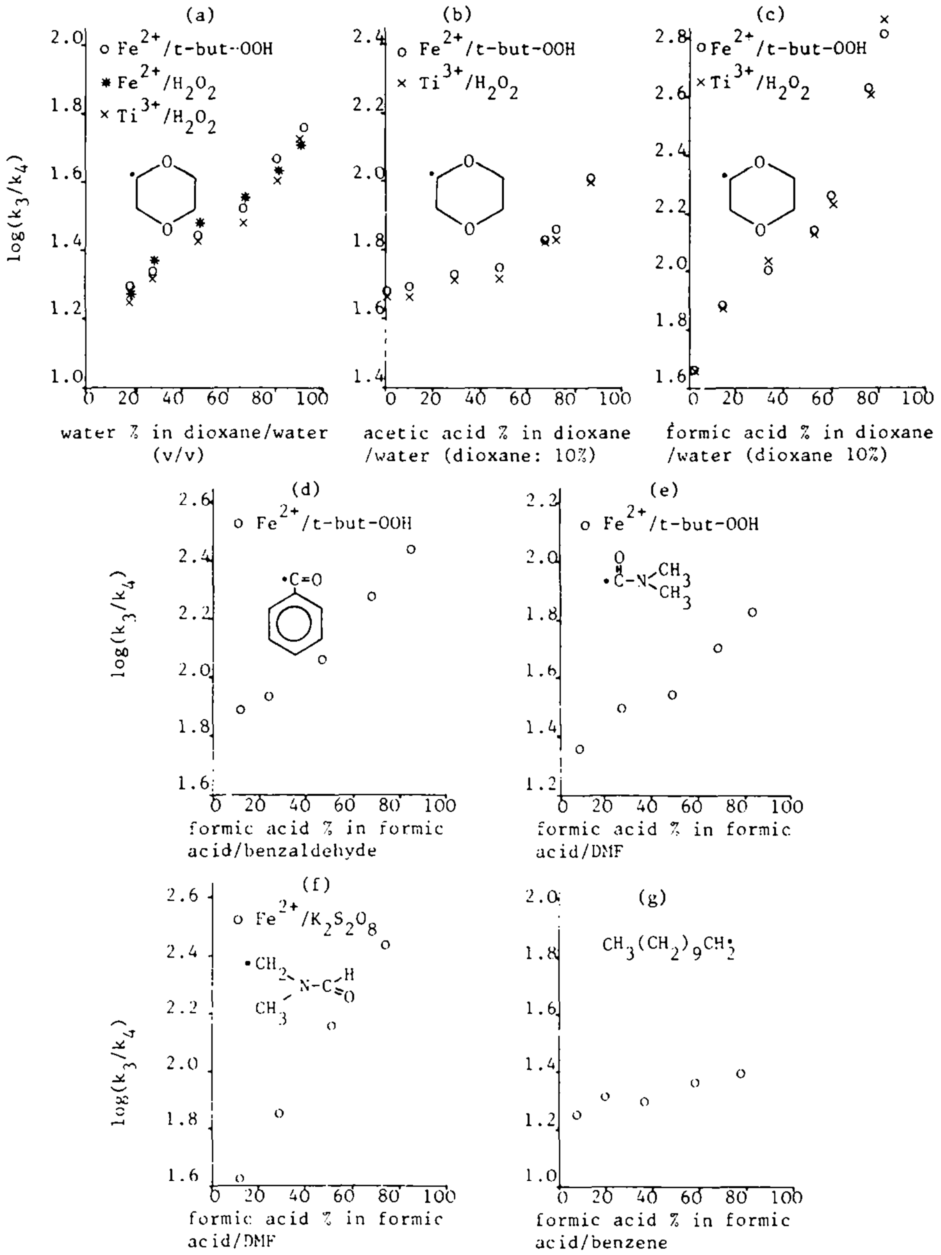
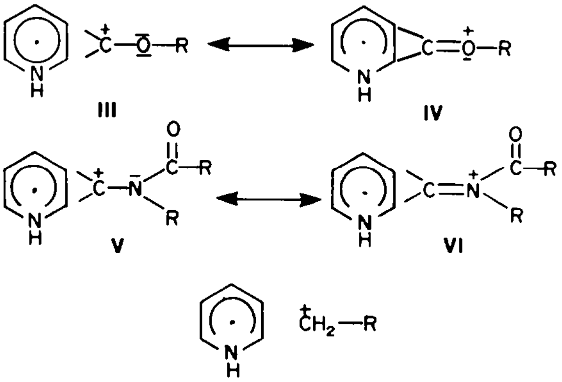


Fig. 1. Correlation of relative rate by medium composition for dioxanyl (a,b,c), benzoyl (d), carbamoyl (e), α-amidomethyl (f) and undecanyl (g) radicals.

influence appreciably the reaction rate, as solvation occurs similarly in the transition state. The latter interaction, instead, could explain the different variations of k_3/k_4 detected. α-Amidoalkyl and α-oxyalkyl radicals are the most influenced by the solvent. Dioxanyl radical reacts well in dioxane/water; in 90% formic acid the reaction yield approaches zero and the relative reactivity reaches about 1000 (Fig. 1c). Alkyl radicals are the least affected by the solvent; acyl radicals behave in an intermediate way. This behaviour could be explained by considering that solvent interactions on lone pair electrons of the radical reagent reduce the contribution of the form **II** in the transition state, unfavouring the reaction. On this account where larger such a contribution is, greater the solvent effect. In fact, the solvent chiefly influences the reactivities of α-oxyalkyl and α-amidoalkyl radicals, where the polar forms (**III–IV** and **V–VI**) stabilize the transition state. Carbamoyl and acyl radicals (σ-radicals, lower polarizability) are less influenced by the solvent and even weaker is the action on primary alkyl radicals, owing to the poor delocalization of the positive charge (polar form **VII**).


III **IV** **V** **VI** **VII**

Nevertheless alkyl radicals are the most energetic (C-H about 100 kcal/M) and very reactive even if polar effects are weak. Alkyl radicals react also on free heteroaromatic bases but with a different pattern of selectivity, attacking several nuclear positions.[7] The other radicals considered do not appreciably attack the free bases; however we found that dioxanyl and α-amidoalkyl radicals react selectively in low yields on 4-CN-quinoline giving the 3-derivative; in this case the CN group seems to activate the homolytic substitution more than the nuclear nitrogen.

EXPERIMENTAL

B.ps are uncorrected. Glc analyses were performed on a Varian aerograph 2000 chromatograph, using 6 ft × 0.2 in column packed with 5% XE 60 on Chromosorb W AW-DMCS. 4-Methylquinoline was commercial product, dried over KOH and distilled before use; 4-cyano-quinoline was prepared by known methods. The dioxanoyl peroxide was prepared by the usual Kochi's procedure[8] by oxidation at low temperature with pyridine/H_2O_2 (in ether) the corresponding acyl chloride, obtained from the carboxylic acid[9] with excess $SOCl_2$ (liquid, b.p. 82–83°/15 mm Hg). The peroxide was particularly stable (oily product, 99% by iodometric titration, half life 96 hr at 83° in toluene). Other reagents used were commercial products.

General procedure for competitive reactions

Dioxanyl radical. In a three necked flask, fitted with magnetic stirrer, reflux condenser and glass stopcocks, samples of 4-CN-quinoline (50 mg, 0.32 mmol) and 4-CH_3-quinoline (0.5 ml, 3.8 mmol) were dissolved in 50 ml of solvent (water, dioxane, acetic acid, formic acid in the desired %) and protonated by adding 50 mmol of conc H_2SO_4 (benzensulphonic acid when quinolinium sulphates precipitated.). For redox reactions (M^{n+}/ROX) the temperature was set to 20°; the reduced metal salt (0.05 mmol) dissolved in water (0.2–1 ml) and the ROX (0.05 mmol) were added simultaneously and separately under stirring. After 10 min the reaction mixture was treated with 10% aqueous NaOH, extracted four times with ether or chloroform and the organic fraction concentrated under vacuum to about 5 ml; analyses by glc were performed using the pure products as external standards. Reactions with AIBN (0.1 mmol) were performed at 62° for 24 hr. Reactions by thermal decomposition of dioxanoyl peroxide (0.1 mmol) were carried out at 100° for 2 hr. Reactions on free bases were effected in the presence of 1 ml of 10% aqueous NaOH. Yields, when reported, are calculated as moles of products/mole of radical generator.

Acyl radicals. Reactions were carried out with radical generators as described for dioxanyl; the media were obtained by mixing the aldehyde with different amounts of formic acid.

Carbamoyl and α-amidoalkyl radicals. Reaction were carried out with Fe^{2+}/t-But-OOH and $Fe^{2+}/K_2S_2O_8$ as radical generators in DMF, DMF and formic acid, under the conditions indicated for dioxanyl radical.

Undecanyl radical. Undecanyl radical was generated by thermal way from lauroyl peroxide. The peroxide (0.1 mmol) was dissolved in the reaction medium (benzene, formic acid) and decomposed at 80°. Benzenesulphonic acid (50 mmol) was used to protonate the quinolines.

Acknowledgement—The author wishes to thank the Italian National Research Council (C.N.R.) for financial support.

REFERENCES

[1] W. A. Pryor, *Free Radicals* pp. 13, 157. McGraw-Hill, New York (1966).

[2] E. S. Huyser, *Advances in Free Radical Chemistry*, Vol. 1, pp. 77–135. Logos Press Academic Press, New York (1965).

[3] F. Minisci, *Top. Cur. Chem.* **62**, 1 (1976) and Refs. cited therein.

[4] F. Minisci, R. Galli, V. Malatesta and T. Caronna, *Tetrahedron* **26**, 4083 (1970); G. P. Gardini, F. Minisci, G. Palla, A. Arnone and R. Galli, *Tetrahedron Letters* 59 (1971); W. Buratti, G. P. Gardini, F. Minisci, F. Bertini, R. Galli and M. Perchinunno, *Tetrahedron* **27**, 3655 (1971); G. P. Gardini, *Tetrahedron Letters* 4113 (1972).

[5] M. Ferrari, *Thesis Dissertation*, Parma University (1975).

[6] A. J. Parker, *Chem. Rev.* **69**, 1 (1969).

[7] K. C. Bass and P. J. Nababsing, *J. Chem. Soc.* (*C*) 2169 (1970); F. Minisci, A. Selva, O. Porta, P. Barilli and G. P. Gardini, *Tetrahedron* **28**, 2415 (1972).

[8] J K. Kochi and A. Bemis, *J. Amer. Chem. Soc.* **90**, 4083 (1968).

[9] B. A. Nelson, R. C. Minsek, J. I. Simon and D. L. Underwood, *Ibid.* **77**, 1695 (1955).