# Nucleophilic Character of Acyl Radicals. Absolute Rate Constant for the Acylation of Protonated Benzothiazole by Pivaloyl Radical

By **Marta Bellatti, Tullio Caronna,* Attilio Citterio,** and **Francesco Minisci,** Istituto di Chimica del Politecnico, Piazza Leonardo de Vinci 32, 20133 Milano, Italy

The absolute rate constant for the addition of pivaloyl radical to protonated benzothiazole is determined by evaluating the ratio of decarbonylation and aromatic attack. The high rate constant ($7.1 \times 10^5$ l mol$^{-1}$ s$^{-1}$ at 5 °C) is discussed in terms of polar effects and a divergence from the classical reactivity : selectivity relationship is suggeste

HOMOLYTIC aromatic substitution by nucleophilic free radicals becomes particularly interesting only for electron-deficient aromatic substrates,[1] as is also the case for ionic nucleophilic substitution. Thus homolytic aromatic acylation is of little importance in homocyclic aromatic compounds because several reactions of the acyl radicals (oxidation, dimerization, decarbonylation, *etc.*) successfully compete with the simple substitution. The only intermolecular attack so far reported concerns the reaction of benzoyl radical and anthracene,[2] in which C-9 is highly reactive towards free radicals.

On the other hand, the reaction is of great importance in heteroaromatic compounds.[3] Heteroaromatic bases are electron-deficient substrates, which readily react with nucleophilic species. Protonation strongly increases their electron-deficient nature and therefore their reactivity towards nucleophilic reagents. Thus, treating the nitrogen atom of pyridine as a substituent in a benzene ring, the high value of 4 was estimated for the $\sigma_p$ Hammett constant of protonated pyridine,[4] the corresponding value of unprotonated pyridine[5] being 0.93.

The increased nucleophilic reactivity of protonated heteroaromatic bases can rarely be exploited by ionic nucleophilic species, which cause, as the primary effect, deprotonation of the bases. This incompatibility does not occur with nucleophilic radicals, such as the acyl radicals, which attack the protonated heteroaromatic bases with high selectivity giving products in good yield.

## RESULTS AND DISCUSSION

The high reactivity and selectivity of acyl radicals towards protonated benzothiazole shows the possibility

[1] F. Minisci, *Synthesis*, 1973, 1; F. Minisci and O. Porta, *Adv. Heterocyclic Chem.*, 1974, **16**, 123.

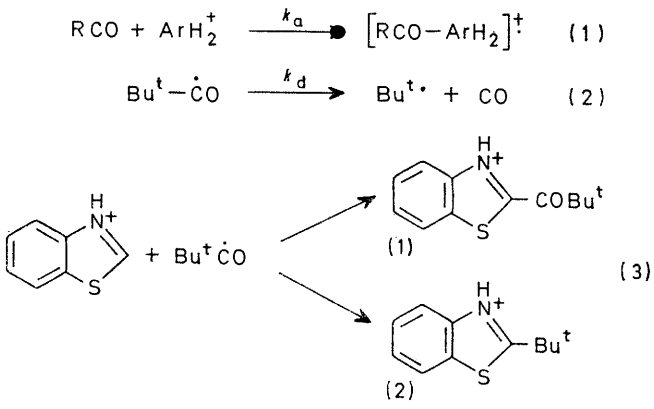
[2] A. L. J. Beckwith and R. J. Leydon, *Austral. J. Chem.*, 1968, **21**, 817.

[3] T. Caronna, G. P. Gardini, and F. Minisci, *Chem. Comm.*, 1969, 201; T. Caronna, G. Fronza, F. Minisci, and O. Porta, *J.C.S. Perkin II*, 1972, 2035; G. P. Gardini and F. Minisci, *J. Chem. Soc.* (*C*), 1970, 929.

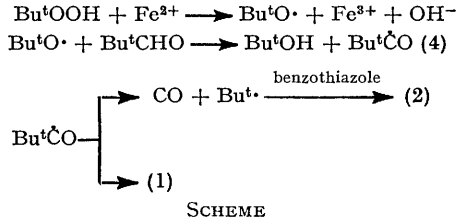
[4] H. H. Jaffé, *J. Amer. Chem. Soc.*, 1955, **77**, 4445.

[5] H. H. Jaffé, *J. Chem. Phys.*, 1952, **20**, 1554.

of the use of homolytic acylation of this substrate as a diagnostic criterion for the presence of acyl radicals as intermediates in oxidation processes.[6] These results made particularly interesting a knowledge of the absolute rate constant $k_a$ for the reaction between acyl radicals RĊO and protonated heteroaromatic bases ($ArH_2^+$) [equation (1)]. For determining $k_a$ in (1) when RCO is pivaloyl and $ArH_2^+$ is protonated benzothiazole, we took advantage of the recent determination of the rate constant for the unimolecular decomposition of the pivaloyl radical [7] [equation (2)] and of the fact that the pivaloyl radical gives rise to 2-pivaloyl- (1) and 2-t-butyl-benzothiazole (2) [equation (3)].



Reaction (3) is very clean; only compounds (1) and (2) are formed in high yield in the presence of an excess of benzothiazole. The kinetic treatment was based on the mechanism illustrated in the Scheme.



SCHEME

The reaction was investigated for three different experimental conditions. (i) The solution of iron(II) salt was dropped into a mixture of all the other reagents. (ii) The solution of iron(II) salt and $Bu^tOOH$ were simultaneously dropped into a mixture of the other reagents. (iii) $Bu^tOOH$ was dropped into a mixture of the other reagents containing an excess of iron(II) salt. We chose the process (iii) which gave the highest reproducibility of the results.

Since the addition of pivaloyl radical to protonated benzothiazole competes with the unimolecular decarbonylation, the final yields of (1) and (2) should be related to the mean benzothiazole concentration according to expression (5). The results are given in Table 2.

$$[(1)]/[(2)] = k_a[\text{benzothiazole}]/k_d \quad (5)$$

The influence of protonation of benzothiazole on the reaction rate of acylation is shown by the results obtained under the same experimental conditions, in which the acidity of the medium is determined only by acetic acid and iron(II) sulphate in water; a plot of [(1)]/[(2)] against [benzothiazole] affords a straight line (Figure), which enables $k_a/k_d$ to be evaluated. The small intercept can very probably be explained by a small contribution to the Scheme by the hydrogen abstraction reaction (6).

$$Bu^{t}\cdot + Bu^t\text{–CHO} \xrightarrow{k_c} Bu^tH + Bu^t\text{–}\dot{C}O \quad (6)$$

The kinetic treatment in this case is given by equation (7) in which $k_b$ is the rate constant for the addition of $Bu^t$ radical to benzothiazole. Even with this more complex treatment, however, our values of $k_a$ remain essentially unaffected.

$$[(1)]/[(2)] = k_a[B]/k_d + k_ak_c[\text{aldehyde}]/k_dk_b \quad (7)$$

The value of $k_d$ at 5 °C was taken from the results obtained by Fischer and his co-workers [7] by e.s.r. spectroscopy [$\log (k_d/s^{-1}) = 11.9 - 9.3/2.303RT$]. The solvent used in the two reactions are different (methylcyclo-

TABLE 1

Spectral, physical, and analytical data for compounds (1) and (2)

| Compound | | *m/e* | Chemical shift (δ) | Calc. (%) | Found (%) |
|---|---|---|---|---|---|
| (1) | M.p. 49 °C | 90, 108, 135, 149, 162, 176, 191, 204, 219 | 1.6 (9 H, s), 7.3—8.2 (4 H, m) | C, 65.7<br>H, 6.0<br>N, 6.4<br>O, 7.3<br>S, 14.6 | C, 65.75<br>H, 6.0<br>N, 6.4<br>O, 7.2<br>S, 14.65 |
| (2) | B.p. 138 °C at 16 mmHg | 109, 135, 149, 160, 176, 191 | 1.45 (9 H, s), 7.10—8.12 (4 H, m) | C, 69.1<br>H, 6.85<br>N, 7.35<br>S, 16.75 | C, 69.05<br>H, 6.85<br>N, 7.3<br>S, 16.75 |

TABLE 2

Kinetic data [a]

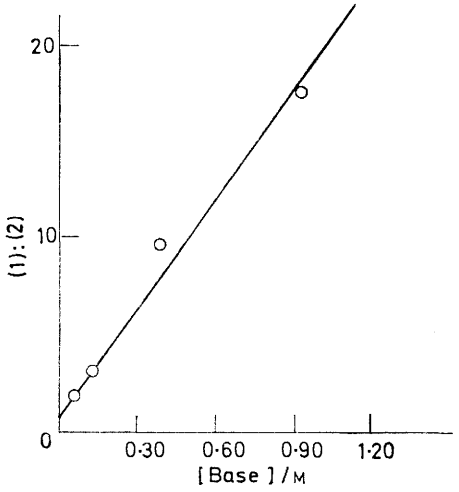
| Base molarity | (1) (%) | (2) (%) | (1) : (2) [b] |
|---|---|---|---|
| 0.068 | 63.90 | 36.10 | 1.77 |
| 0.13 | 75.37 | 24.63 | 3.06 |
| 0.38 | 90.71 | 9.29 | 9.76 |
| 0.91 | 94.63 | 5.37 | 17.61 |
| 0.38 [c] | 35.13 | 64.87 | 0.54 |

[a] Mean value of at least two independent experiments. [b] Molar ratio. [c] In acetic acid alone.

[6] T. Caronna, R. Galli, V. Malatesta, and F. Minisci, *J. Chem. Soc. (C)*, 1971, 1747.

[7] H. Schuh, E. J. Hamilton, H. Paul, and H. Fischer, *Helv. Chim. Acta*, 1974, **57**, 2011.

pentane and benzene for decarbonylation and aqueous acidic solution for aromatic acylation); however we can assume that the solvent effect is negligible in decarbonylation of RĊO, whose rate is affected by the stability of the radical R· but scarcely by polar effects,[8] indicating little charge separation in the transition state. In any




Variation of product ratio (1) : (2) with concentration of base

case, the validity of our results depends on this assumption. A value of $k_a = 7.1 \times 10^5$ l mol$^{-1}$ s$^{-1}$ at 5 °C was obtained by assuming that the addition of pivaloyl radical is irreversible.

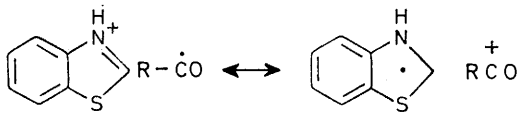
This is, as far as we know, the first absolute rate constant obtained for the addition of an acyl radical to an aromatic substrate. Since no trace of attack of the benzene ring in benzothiazole was observed under analytical conditions which clearly reveal the presence of 0.1% of isomers, we conclude that the rate constant of attack of the pivaloyl radical on the benzene ring of benzothiazole is certainly $<7 \times 10^2$ l mol$^{-1}$ s$^{-1}$. This explains the great difference in behaviour between homocyclic aromatic compounds and protonated heteroaromatic bases and the considerable synthetic interest in the latter case.

It was recently suggested [9] that the nonselectivity of phenyl radical attack on aromatic substrates is also reflected in the high rate constant which has been estimated [10] for the interaction of phenyl radical with benzene. At 80 °C this is $2 \times 10^3$ l mol$^{-1}$. This value is, however, considerably lower than our value of $k_a$ (benzothiazole is only three times more reactive than benzene towards phenyl radical; all the positions are attacked at about the same rate), which, on the contrary, characterizes a very selective reaction, so that high reactivity is not necessarily related to low selectivity.

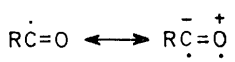
We think that the reactivity : selectivity relationship holds for free radical reactions only when polar effects do not play an important role in determining the reaction rates.

It appears surprising that the addition of phenyl radical to an aromatic ring is slower than that of an acyl radical upon considering the different strengths of the bonds formed by the two radicals (*e.g.* Ph–H and RCO–H bond energies [11] are, respectively, 468 and 364 kJ mol$^{-1}$). Perhaps the value of $2 \times 10^3$ l mol$^{-1}$ s$^{-1}$ for the rate constant for addition of phenyl radical to benzene is somewhat lower than the real one, this value having been estimated from a very complex kinetic scheme. A more recent value of $7.4 \times 10^4$ l mol$^{-1}$ s$^{-1}$, has been reported [12] for the homolytic phenylation of benzene on the basis of spin-trapping experiments; this value, however, is also lower than the rate of acylation.

We explain the high rate constant for homolytic acylation of protonated heteroaromatic bases by a large contribution of polar forms to the transition state, which decreases the activation energy of the reaction. The transition state is, in our opinion, similar to a charge-transfer complex (3). The degree of charge development in the transition state depends on the donor character of the aromatic substrate, a complete electron




(3)




(4)

transfer being the limiting case (this has been shown [13,14] for example, in the reaction of the strongly nucleophilic diphenylketyl radical, $Ph_2\dot{C}$–OH with protonated 4-cyanopyridine).

The nucleophilicity of acyl radicals can be related in the ground state to the resonance structure (4) and in the transition state to the stability of the corresponding acyl cation $R\overset{+}{C}O$.[13]

The absolute rate constant determined in this work is, in our opinion, of wider significance than just for the specific case of the pivaloyl radical. This is because our previous studies [15] concerning the relative rates of homolytic aromatic acylation indicated that a change of structure of the acyl radicals has little effect on their selectivity, in contrast to the behaviour of the alkyl radicals. Thus a variety of aliphatic and aromatic acyl radicals all show a selectivity between that of a primary and a secondary alkyl radical, so that acetyl is more

[8] D. E. Applequist and L. Kaplan, *J. Amer. Chem. Soc.*, 1965, **87**, 2194; T. Caronna and F. Minisci, ' Reviews on Reactive Species in Chemical Reactions,' in the press.
[9] M. J. Perkins, ' Free Radicals,' ed. J. K. Kochi, Wiley, New York, 1973, p. 248.
[10] D. F. DeTar, *J. Amer. Chem. Soc.*, 1967, **89**, 4058.
[11] S. W. Benson, *J. Chem. Educ.*, 1965, **42**, 502.
[12] E. J. Janzen and C. A. Evans, *J. Amer. Chem. Soc.*, 1975, **97**, 205.
[13] F. Minisci, *Topics Current Chem.*, 1976, **62**, 21.
[14] B. M. Vittimberga, F. Minisci, and S. Morrocchi, *J. Amer. Chem. Soc.*, 1975, **97**, 4397.
[15] T. Caronna, G. Fronza, F. Minisci, O. Porta, and G. P. Gardini, *J.C.S. Perkin II*, 1972, 1477.

selective than ethyl, but benzoyl is much less selective than benzyl. This was explained by the fact that acyl radicals are of σ-type and alkyl radicals of π-type. This behaviour however means that the order of magnitude of the rate constants for homolytic acylation of protonated heteroaromatic bases is the same for all acyl radicals.

## EXPERIMENTAL

*Materials.*—Benzothiazole and pivalaldehyde were pure commercial samples.

*Procedures.—Preparation of 2-t-Butylbenzothiazole and 2-Pivaloylbenzothiazole.*—A four-necked, round-bottomed flask was equipped with a mechanical stirrer, a thermometer, and two dropping funnels with a pressure equalizer side arm. t-Butyl hydroperoxide (4.3 ml, 0.033 mol) and a solution of $FeSO_4,7H_2O$ (10 g, 0.033 mol) in $H_2O$ (25 ml) were added to a stirred solution (10 ml) of $H_2SO_4$ (2.45 g, 0.025 mol) and pivalaldehyde (4.3 g, 0.05 mol) at 5 °C. The mixture was basified with 3N-NaOH to pH 10—12 with stirring and cooling, extracted with $CHCl_3$, and dried ($Na_2SO_4$). Chloroform was evaporated and the products were isolated by column chromatography with hexane–ethyl acetate (9 : 1) as eluant [pivaloylbenzothiazole (2.1 g), t-butylbenzothiazole (1.15 g), total yield 96%]. Spectral, physical, and analytical data are in Table 1.

*General Procedure for Kinetic Experiments.*—A three-necked round bottomed flask was equipped with a mechanical stirrer, a thermometer, and a dropping funnel. t-Butyl hydroperoxide was added to a solution of benzothiazole, acetic acid (37 ml), $H_2SO_4$ (19 ml), $H_2O$ (15 ml), $FeSO_4,7H_2O$ (10 g) dissolved in $H_2O$ (37 ml), and pivalaldehyde (4.3 g) at 5 °C.

The benzothiazole–hydroperoxide ratio was normally kept at 2 : 1; some results were obtained using a benzothiazole–hydroperoxide ratio of 5 : 1. The benzothiazole molarities were 0.068, 0.13, 0.38, and 0.91. In one case $H_2SO_4$ was substituted by the equivalent amount of acetic acid. The mixture was basified 30 min after addition of hydroperoxide with cooling and stirring, exhaustively extracted with $CHCl_3$, and dried ($Na_2SO_4$). Solvent was evaporated and the residue analysed by g.l.c. on a HP-57504 instrument using a 6 ft × 1/8 in steel column, packed with 10% VCC-W-082 on Chromosorb W, 80—100 mesh (column temperature 180 °C). A correction was made in the calculation of the peak area ratios for experimental detector responses, determined for pure samples. Data are in Table 2.

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