curves similar to those expected for consecutive reactions shown in eq 6 when $k_1 \approx k_2$. From these data, and from

$$\mathrm{ATP} \xrightarrow{+H_2O\ (k_1)} \mathrm{ADP} \xrightarrow{+H_2O\ (k_2)} \mathrm{AMP} \qquad (6)$$

the observations that a maximum of 10% of AMP is formed within the first half-life of the hydrolysis in 1 N HCl, it seems unlikely that P_α attack (and one of the P_β attack pathways) could contribute much more than 10% to the hydrolysis of ATP under these conditions of very high acidity.

In conclusion, the mechanisms of the nonenzymatic hydrolysis of unionized $ATPH_4$ and of three of its ionized species, $ATPH_3^-$, $ATPH^{3-}$, and ATP^{4-}, and the effects of magnesium and calcium ions on the rates of these reactions are reasonably well-known. However, it is still uncertain to what extent the addition–elimination and the elimination–addition mechanisms contribute to nucleophilic displacements on the dianion $ATPH_2^{2-}$. Working in water and in acetonitrile–water mixtures, we have been unable to obtain information bearing on this point.

These conclusions refer to nonenzymatic reactions of ATP in solutions and are not regarded as necessarily applicable to nucleophilic displacements on MgATP and CaATP at the enzymatic active site.

Registry No. $ATPH_2^{2-}[(CH_3)_4N^+]_2$, 75010-81-0; $MgATPH_2$, 1476-84-2; $CaATPH_2$, 71937-66-1; $ATPH_4$, 56-65-5.

Supplementary Material Available: Table III, rates of hydrolysis of ATP in acetonitrile–water; Figure 2, hydrolysis of ATP in 0.01 M acetonitrile–water at 70 °C (2 pages). Ordering information is given on any current masthead page.

Nucleophilic Character of the Alkyl Radicals. 19.[1a] Absolute Rate Constants in the Homolytic Alkylation of Protonated Heteroaromatic Bases by *n*-Butyl and *tert*-Butyl Radicals

Attilio Citterio,* Francesco Minisci,* and Valeria Franchi

Istituto di Chimica del Politecnico, Milano, Italy

Received January 16, 1980

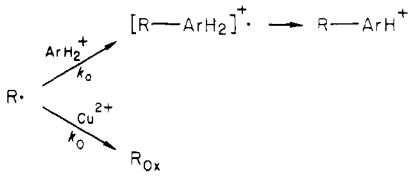
The rate constants for the homolytic alkylation of protonated heteroaromatic bases (quinoline, pyridine, and 4-cyano-, 4-acetyl-, 4-methyl-, and 4-methoxypyridine) by *n*-butyl and *tert*-butyl radicals were measured at 57 °C by competition of the aromatic addition with the alkyl radical oxidation by Cu^{2+} salts (for which the rates are known). With the more activated substrates (quinoline and 4-cyano- and 4-acetylpyridine) the *tert*-butyl radical is significantly more reactive than the *n*-butyl radical, clearly showing that polar effects are more important than steric and enthalpic effects in determining the reaction rates. The reversibility of the alkylation by the *tert*-butyl radical is discussed.

The homolytic substitutions of protonated heteroaromatic bases by nucleophilic carbon-centered radicals are among the most important aromatic substitutions from a synthetic point of view.[1b,c]

Thus, homolytic alkylation can be considered in the heterocyclic series as being as the Friedel–Crafts alkylation is in the homocyclic aromatic series, but without the complications of rearrangement and isomerization of the electrophillic process. The interest is due to the large variety of cheap sources of alkyl radicals which can be used, the good yields, the simple experimental conditions, and the high positional and substrate selectivities. These last characteristics have been ascribed to polar effects; the substrate selectivity increases in the series methyl < primary < secondary < tertiary alkyl radical, in agreement with the expected increasing nucleophilic characer,[2] and a very large ρ value of 5.5 has been determined for *tert*-butylation of 3-substituted pyridines.[3]

However, the much higher selectivity of the *tert*-butyl radical compared with the *n*-butyl radical could not reflect a polar effect. It could be determined either by a lower reactivity of the tertiary alkyl radical, due to unfavorable energetics and steric requirements, in agreement with the reactivity–selectivity relationship, or by the reversibility of the alkyl radical additions to the aromatic rings.

Scheme I



For a better understanding of the polar effect, it was therefore necessary to know the absolute rate constants in the addition of alkyl radicals to aromatic substrates. That is particularly important in view of the fact that the positive ρ values reported for hydrogen abstraction from substituted toluenes by alkyl radicals have been cast into doubt by a recent report,[4] which would exclude a significant polar effect in these reactions.

We report in this paper the absolute rate constants for the addition of *n*-butyl and *tert*-butyl radicals to some protonated heteroaromatic bases.

For primary alkyl radicals the use of the 5-hexenyl radical[5] gave good results; a similar model shows consid-

(1) (a) Part 18. A. Citterio, A. Arnoldi, and F. Minisci, *J. Org. Chem.*, **44**, 2674 (1979). (b) F. Minisci, *Top. Curr. Chem.*, **62**, 1 (1976). (c) F. Minisci and A. Citterio, "Advances in Free-Radical Chemistry", Vol. VI, G. H. Williams, Ed., 1980, p 65.

(2) F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *Tetrahedron*, **28**, 2403 (1972).

(3) A. Clerici, F. Minisci, and O. Porta, *Tetrahedron*, **30**, 4201 (1974).

(4) D. D. Tanner, P. W. Samal, T. C. S. Ruo, and R. Henriquez, *J. Am. Chem. Soc.*, **101**, 1168 (1979).

(5) A. Citterio, F. Minisci, O. Porta, and G. Sesana, *J. Am. Chem. Soc.*, **99**, 7960 (1977).

0022-3263/80/1945-4752$01.00/0

erable experimental difficulties for a tertiary alkyl radical.

Thus in order to compare the absolute rates in the addition of *n*-butyl and *tert*-butyl to protonated heteroaromatic bases, we investigated a different kinetic model, based on the competition between the oxidation of the alkyl radical by cupric salt and the addition to the arom. compound (Scheme I).

The alkyl radicals were generated by the silver-catalyzed oxidation of the corresponding carboxylic acids by peroxydisulfate.

Since the oxidation of the alkyl radical with the cupric salt competes with the addition to the aromatic compound, the final yields of the alkyl aromatic and the alkene should be related to the concentrations of the aromatic compound and the cupric salt according to eq 1, if both reactions are irreversible.

$$\frac{k_a[ArH_2^+]}{k_0[Cu_2^+]} = \frac{[RArH^+]}{[R_{Ox}]} \quad (1)$$

The irreversibility of the oxidation of the alkyl radicals by cupric salt is well documented,[6] and recently it has been assumed that the addition of *tert*-butyl radical to substituted toluenes can be reasonably considered irreversible.[4] However, we have already reported[5] that in the absence of cupric salt the addition of primary alkyl radicals to 4-methylpyridine has characteristics of reversibility, and we should expect a more accentuated reversiblility for a tertiary alkyl radical.

It was therefore important to verify this point, and thus a close investigation has been carried out for *tert*-butylation of 4-cyanopyridine. The choice of this last substrate was suggested by two reasons: it is the most reactive among the investigated substrates, and the positional selectivity is somewhat affected by the reaction conditions.

Structures of the Reaction Products from 4-Cyanopyridine and *n*-Butyl and *tert*-Butyl Radicals. All the products arising from the alkylation of 4-cyanopyridine were isolated and identified by spectroscopic analysis or comparison with authentic samples. The identification of the different isomers was quite simple and unambiguous, due to the chemical shifts of the protons in the pyridine ring in the NMR spectra (δ 7.2–7.7 for H_3 and H_5 and δ 8.5–8.9 for H_2 and H_6).

Thus 2-*tert*-butyl-4-cyanopyridine (**1**) shows in the mass spectrum a m/e 160 molecular ion, indicating that monoalkylation of 4-cyanopyridine occurred. An IR band at 2230 cm^{-1} indicates the presence of the CN group. The singlet at δ 1.4 in the NMR spectrum, corresponding to nine aliphatic protons for three aromatic protons (δ 7.36–8.76), is ascribed to the three methyls of the *tert*-butyl group and further supports monoalkylation. The aromatic pattern of the NMR spectrum clearly indicates the position of the ring substituents; the chemical shifts of the three aromatic protons (a singlet at δ 7.60 and two doublets at δ 7.36 and 8.76) indicate that positions 3, 5, and 6 of the ring are free.

For 3-*tert*-butyl-4-cyanopyridine (**2**) the spectral data are similar to those of **1**, with the exception of the aromatic pattern in the NMR spectrum: a singlet at δ 8.90 and two doublets at δ 7.57 and 8.67 indicate that positions 2, 5, and 6 of the ring are free.

For 2,6-di-*tert*-butyl-4-cyanopyridine (**3**) the mass spectrum (molecular ion m/e 216), IR spectrum (2240 cm^{-1}, CN group), and NMR spectrum (a singlet at δ 1.38, corresponding to 18 aliphatic protons for two aromatic protons, singlet at δ 7.37) show the di-*tert*-butylation of 4-cyanopyridine and that positions 3 and 5 are free.

For 2,5-di-*tert*-butyl-4-cyanopyridine (**4**) the spectral data are similar to those of **3**, with the difference that the two *tert*-butyl groups are not equivalent (two singlets at δ 1.36 and 1.52) and also that the two aromatic protons are not equivalent (two singlets at δ 7.55 and 8.78), indicating that positions 3 and 6 of the ring are free.

The corresponding *n*-butyl isomers were identified on the grounds of analogous spectroscopic characteristics. With the *n*-butyl radical, 2,3-di-*n*-butyl-4-cyanopyridine is also formed. Its identification was based on its mass spectrum (molecular ion m/e 216), IR spectrum (2236 cm^{-1}, CN group), and NMR spectrum (18 aliphatic protons and two aromatic protons). The pattern of the aromatic protons (two doublets at δ 7.30 and 8.53) indicates that positions 5 and 6 of the ring are free. The corresponding isomer is not formed with the *tert*-butyl radical for steric reasons.[3]

2,*N*-Di-*tert*-butylpyridine-4-carboxamide was characterized by its IR spectrum (1645 and 3390 cm^{-1}, CONH group), mass spectrum (molecular ion m/e 234), and NMR spectrum (18 aliphatic protons, three aromatic protons, and one NH proton). The presence of three aromatic protons indicates that the ring is monoalkylated; the aromatic pattern (two doublets at δ 7.70 and 8.36 and a doublet of doublets at δ 7.28 indicates that positions 3, 5, and 6 of the ring are free; the two *tert*-butyl groups show two singlets at δ 1.37 and 1.47).

Table I. Reaction Products for *tert*-Butylation[a] of 4-Cyanopyridine at 57 °C

	% products				ratio	ratio
$[Cu^{2+}]$, M	1	2	3	4	1/2	3/4
0	92.50	0.99	4.30	2.44	93	1.76
0.0025	79.12	10.20	3.80	6.70	7.7	0.56

[a] 4-Cyanopyridine (0.05 M), H_2SO_4 (0.75 M), and $K_2S_2O_8$ (0.01 M) in 50 mL of water. The compounds as follows: **1**, 2-*tert*-butyl-4-cyanopyridine; **2**, 3-*tert*-butyl-4-cyanopyridine; **3**, 2,6-di-*tert*-butyl-4-cyanopyridine; **4**, 2,5-di-*tert*-butyl-4-cyanopyridine.

Reversibility of the *tert*-Butylation of 4-Cyanopyridine. In order to have indications concerning the reversibility of the *tert*-butylation of 4-cyanopyridine, we investigated the influence of three factors (Cu^{2+} salt, temperature, and acidity) on the positional selectivity.

(i) Effect of the Cu^{2+} Salt. The reaction has been carried out in acidic (water/CH_3CN, 19:1) solution by silver-catalyzed decarboxylation of pivalic acid in the absence and presence of cupric acetate. Five reaction products were obtained and are given as follows: 2-*tert*-butyl-4-cyanopyridine (**1**), 3-*tert*-butyl-4-cyanopyridine (**2**), 2,6-di-*tert*-butyl-4-cyanopyridine (**3**), 2,5-di-*tert*-butyl-4-cyanopyridine (**4**) and *N*-*tert*-butylpyridine-4-carboxamide (**5**). Compound **5** is always present in a small amount (<1%), and it arises from the addition of the *tert*-butyl radical or cation to the cyano group. The amounts of **3** and **4** obviously increase with the increasing of the conversions of 4-cyanopyridine. The presence of cupric acetate has the effect of decreasing the ratios of **1** to **2** and **3** to **4**. The results at 57 and 25 °C are, respectively, summarized in Tables I and II. The results of Table I are quite unexpected because the α position of 4-cyanopyridine is more reactive than the β position, and **3** should greatly prevail over **4** for disubstitution; that is not the case in the presence of the cupric salt in which case **4** is the prevailing dialkylated isomer (Table I). In order to understand this apparent anomaly, we investigated the *tert*-butylation of

(6) J. K. Kochi, "Free Radicals", Vol. I, J. K. Kochi, Ed., Wiley, New York, 1973, p 598.

Table II. Reaction Products for *tert*-Butylation[a] of 4-Cyanopyridine at 25 °C at Different Acidities

$[Cu^{2+}]$, M	$[H_2SO_4]$, M	% products 1	2	3	4	ratio 1/2
0	1.50	94.70	1.98	1.99	1.28	47.8
0	0.025	87.4	3.7	6.0	2.9	23.6
0.0025	1.50	88.7	7.40	2.47	1.30	12.0

[a] 4-Cyanopyridine (0.05 M) and $K_2S_2O_8$ (0.01 M) in 50 mL of H_2O and CH_3CN in a 19:1 ratio.

Table III. Reaction Products for *tert*-Butylation[a] of 2-*tert*-Butyl-4-cyanopyridine at 57 °C

$[Cu^{2+}]$, M	3	4	ratio 3/4
0	93.3	6.7	13.94
0.0025	52.1	35.9	1.45

[a] 2-*tert*-Butyl-4-cyanopyridine (0.05 M), H_2SO_4 (0.75 M), and $K_2S_2O_8$ (0.01 M) in 20 mL of water.

Table IV. Temperature Effect on the Isomer Distribution in *tert*-Butylation[a] of 4-Cyanopyridine

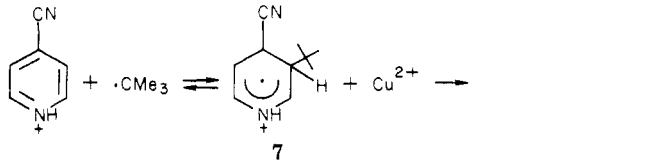
temp, °C	% 2-*t*-Bu	% 3-*t*-Bu	% 2,5-di-*t*-Bu
18	94.35	4.39	1.26
90	96.30	1.56	2.14

[a] 4-Cyanopyridine (0.05 M), H_2SO_4 (0.75 M), and $K_2S_2O_8$ (0.005 M) in 50 mL of water.

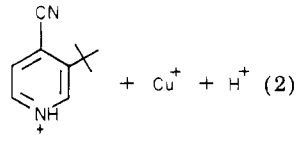
2-*tert*-butyl-4-cyanopyridine under the same conditions as those used for 4-cyanopyridine. The results are summarized in Table III. The effect of the cupric salt at the same medium acidity shows the same trend with both substrates (Tables I and III): the ratio of **4** to **3** increases in the presence of the cupric salt. However, in *tert*-butylation of 2-*tert*-butyl-4-cyanopyridine, **3** always prevails over **4**, in agreement with the higher reactivity of the α position.

The results can be rationalized on the basis of two mechanisms of formation of **4** from 4-cyanopyridine. The first one is the normal reaction of the *tert*-butyl radical with monoalkylated 4-cyanopyridine which leads to a mixture of **3** and **4**, and it occurs when the conversions of 4-cyanopyridine are high enough. The other mechanism would involve cross-dimerization of the *tert*-butyl radical with the radical adduct **6** (Scheme II), and it would lead only to **4**.

This mechanism would explain the prevailing formation of the isomer **4** at low conversion of 4-cyanopyridine, but it occurs only to a minor extent as the results of Tables I and II show. A further support is provided by the fact that at still lower conversion only the disubstituted isomer **4** is formed (Table IV). The effect of the cupric salt on the positional selecivity would show that the addition of *tert*-butyl radical to 4-cyanopyridine can be reversible; the fast oxidation of the radical adduct **7** by the cupric salt (eq 2) would reduce or minimize the effect of the reversibility on the positional selectivity, increasing the products arising from the attack of the β position.

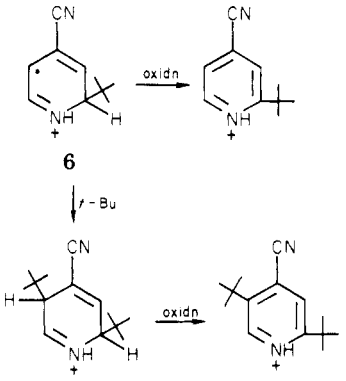


7



(2)

Scheme II



6

(ii) Effect of the Acidity. A comparison of the results of Tables I and III clearly shows that the relative reactivities of the positions α and β are considerably different in 4-cyanopyridine and 2-*tert*-butyl-4-cyanopyridine. In 4-cyanopyridine position α is in any case much more reactive than position β, whereas in the 2-*tert*-butyl-4-cyanopyridine in the presence of the cupric salt the reactivities of positions α and β are of the same order of magnitude. It is unlikely that the effect of the *tert*-butyl group on the positional selectivity is electronic in nature, because the same effect was not observed with the *n*-butyl group; the origin must therefore be steric. A steric inhibition of protonation (solvation of the protonated base) of the 2-*tert*-butyl-4-cyanopyridine would well explain the behavior. We should in fact expect an increased relative reactivity of the β position in unprotonated pyridine in agreement with the results obtained in homolytic phenylation of 4-cyanopyridine:[7] with the protonated base the α position is more reactive than the β position, and the opposite occurs with the unprotonated base. For verification of this effect, the *tert*-butylation of 4-cyanopyridine has been carried out at different acidities. Actually the **1/2** ratio increases with the acidity of the medium: when the molar ratio of sulfuric acid to 4-cyanopyridine changes from 0.5 to 30, all the other conditions being equal, the **1/2** ratio correspondingly increases from 23 to 48 (Table II).

(iii) Effect of the Temperature. The reversibility of the addition of the *tert*-butyl radical to 4-cyanopyridine should be affected by the temperature; the effect of the reversibility on the positional selectivity should increase with the temperature. That seems to be the case. An increase of the temperature from 18 to 90 °C, all the other conditions being equal, results in an increase of the **1/2** ratio from 18 to 62 (Table V). All these results provide circumstantial evidence that the addition of *tert*-butyl radical to 4-cyanopyridine is a reversible process and that the presence of cupric salt reduces or minimizes the effect of the reversibility.

The behavior of the *n*-butyl radical is not affected by the same factors. At low conversion the reaction products of 4-cyanopyridine butylation are shown in Table V. The results are not substantially affected by the temperature, the medium acidity, or the presence of cupric salt (Table V), supporting our previous report[5] that the addition of primary alkyl radicals to 4-cyanopyridine is practically irreversible also in the absence of cupric salt. It is noteworthy that also with *n*-butyl radical the disubstitution in positions 2 and 5 prevails over that in positions 2 and

(7) A. Clerici, F. Minisci, and O. Porta, *Gazz. Chim. Ital.*, **103**, 171 (1973).

Table V. Reaction Products for *n*-Butylation[a] of 4-Cyanopyridine

[Cu⁺], M	temp, °C	[H_2SO_4], M	% products				
			2-*n*-Bu	3-*n*-Bu	2,6-di-*n*-Bu	2,5-di-*n*-Bu	2,3-di-*n*-Bu
0	57	0.75	96.0	0.9	0.7	2.0	0.4
0	90	0.75	95.7	1.0	0.8	2.1	0.4
0.0025	57	0.75	96.1	0.9	0.7	2.0	0.5
0	57	0.25	95.8	0.8	0.7	2.2	0.5
0	57	1.50	96.2	1.0	0.6	1.9	0.3

[a] 4-Cyanopyridine (0.05 M) and $K_2S_2O_8$ (0.01 M) in 20 mL of water.

Table VI. Products from Silver-Catalyzed Oxidative Decarboxylation[a] by Peroxydisulfate in the Presence of $Cu(OAc)_2$ and Heteroaromatic Compounds at 57 °C

heterocyclic compd	reacted carboxylic acid (mmol)	alkyl aromatics (mmol)	oxidn products of butyl radicals (mmol)
quinoline	valeric (2.99)	2-*n*-Bu (0.77), 4-*n*-Bu (0.79)	1-butene (1.42)
	pivalic (4.92)	2-*t*-Bu (1.4)	isobutylene (2.25), *tert*-butyl alcohol (1.27)
4-cyanopyridine	valeric (3.02)	2-*n*-Bu (1.15)	1-butene (1.85)
	pivalic (4.96)	2-*t*-Bu (4.24)	isobutylene (0.44), *tert*-butyl alcohol (0.25)
4-acetylpyridine	valeric (2.88)	2-*n*-Bu (1.52)	1-butene (1.34)
	pivalic (4.86)	2-*t*-Bu (1.44)	isobutylene (2.16), *tert*-butyl alcohol (1.22)

[a] Heterocyclic compound (20 mmol), $Cu(OAc)_2$ (0.4 mmol), $K_2S_2O_8$ (5 mmol), and $AgNO_3$ (2 mmol) in 30 mL of H_2SO_4 (0.8 M).

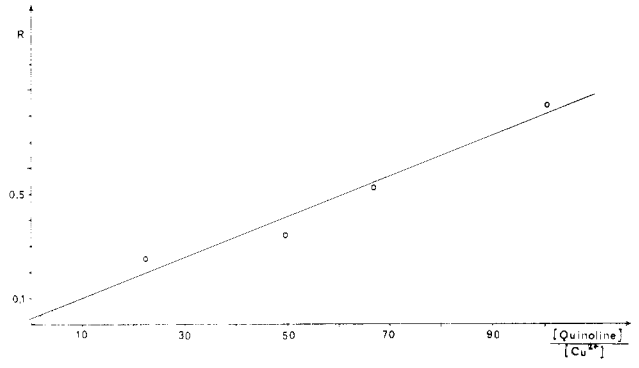


Figure 1. Plot of R (ratio of $[RArH^+]/[R_{Ox}]$, where Ar = quinoline) against $[quinoline]/[Cu^{2+}]$ for the *n*-butylation of quinoline.

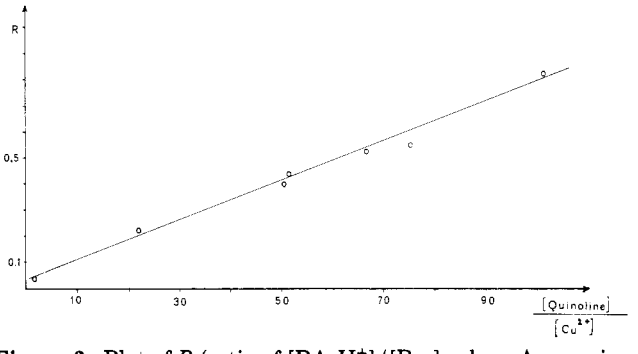


Figure 2. Plot of R (ratio of $[RArH^+]/[R_{Ox}]$, where Ar = quinoline) against $[quinoline]/[Cu^{2+}]$ for the *tert*-butylation of quinoline.

6 at low conversion, indicating that the mechanism of Scheme II is working to a minor extent in this case also.

Kinetic Results and Discussion

The synthetic interest of the homolytic alkylation of protonated heteroaromatic bases is further confirmed by the quantitative yields of alkylation of quinoline and 4-cyanopyridine, based on peroxydisulfate used in the absence of cupric salt; that means that the oxidation–decarboxylation is very effective, and all the alkyl radicals generated are trapped by the protonated bases with rates much higher than other possible reactions of the alkyl radicals (oxidation, hydrogen abstraction, etc.).

In the presence of cupric salt the oxidation of the alkyl radical competes with the aromatic addition for quinoline and 4-cyano- and 4-acetylpyridine; the reactions in all cases are quite clean. The stoichiometry was determined in all these cases (Table VI). Only the oxidation of the alkyl radicals and the aromatic substitution take place. The sum of the alkyl aromatic compounds and the oxidation products of alkyl radicals (1-butene from *n*-Bu· and isobutylene and *tert*-butyl alcohol from *t*-Bu·) exactly corresponds to the reacted carboxylic acid (Table VI), so that the kinetics can be simply followed by the analysis of the alkyl aromatics and the disappearance of the carboxylic acid.

Since k_0 at 57 °C is very high (5.5×10^8 M^{-1} s^{-1}) for *t*-Bu·, the kinetic equation (eq 1) is practically suitable only for aromatic compounds, whose reactivities are higher than 10^5 M^{-1} s^{-1}. Plots of $[RArH^+]/[R_{Ox}]$ against $[Cu^{2+}]$ concentration offered straight lines, passing through the origin (Figures 1 and 2 are reported for quinoline with *n*-Bu· and *t*-Bu·). The values of k_a/k_0 evaluated from the slopes enable us to calculate k_a. The kinetic model seems to be reliable because the results obtained with *n*-Bu· are in good agreement with those previously[5] obtained with the 5-hexenyl radical (8.5×10^5 M^{-1} s^{-1} with *n*-Bu· and 8.4×10^5 M^{-1} s^{-1} with 5-hexenyl radical[5] in the case of quinoline).

Table VII. Relative Rates for Homolytic Butylation of Protonated Heterocyclic Compounds[a] in the Absence of Cu^{2+} at 57 °C

heterocyclic compd	rate	
	n-Bu·	*t*-Bu·
4-methoxypyridine	1	1
4-methylpyridine	3	28
pyridine	10	194
quinoline	193	2411

[a] The following couples of aromatics were used in competition: quinoline–pyridine (molar ratio 1:10 with both radicals); pyridine–4-methylpyridine (molar ratios of 1:10 with *t*-Bu· and 1:1 with *n*-Bu·); 4-methylpyridine–4-methylpyridine (molar ratios of 1:10 with *t*-Bu· and 1:1 with *n*-Bu·).

For the less reactive bases (pyridine and 4-methyl- and 4-methoxypyridine) the kinetic method related to the expression 1 is not suitable because the oxidation of the alkyl radicals by Cu^{2+} is too fast compared with the aromatic addition. In order to have indications concerning the rate

Table VIII. Relatives Rates for Homolytic Butylation of Quinoline and 4-Cyano- and 4-Acetylpyridine by *n*-Bu· and *t*-Bu· Radicals

		rate	
	method[a]	*n*-Bu·	*t*-Bu·
quinoline	a	1	1
	b	1	1
	c	1	1
4-acetylpyridine	a	0.68	0.82
	b	0.81	0.92
	c	0.76	0.89
4-cyanopyridine	a	1.16	17.2
	b	1.12	16.5
	c	1.05	15.3

[a] a, from competition of couples of substrates in the absence of Cu^{2+}; b, as in a in the presence of Cu^{2+}; c, from the kinetic expression 1. The results of a and b were obtained from the competition of the following couples quinoline–4-cyanopyridine and quinoline–4-acetylpyridine both in a 1:1 molar ratio.

Table IX. Absolute Rate Constants for the Homolytic Alkylation of Protonated Heteroaromatic Bases by *n*-Butyl and *tert*-Butyl Radicals at 57 °C

heteroaromatic compd	rate, M^{-1} s^{-1}	
	n-Bu·	*t*-Bu·
4-cyanopyridine	8.9×10^5	6.3×10^7
quinoline	8.5×10^5	4.1×10^6
4-acetylpyridine	6.8×10^5	4.6×10^6
pyridine	4.4×10^4	3.3×10^4
4-methylpyridine	1.3×10^4	4.8×10^3
4-methoxypyridine	4.4×10^3	1.7×10^2

constants for these substrates also, we used a different competitive kinetic approach: the determination of relative rates by competitions of couples of aromatics in the absence of Cu^{2+} salt. The results are summarized in Table VII. The reliability of this last kinetic procedure in the absence of Cu^{2+} salt is certainly lower than that involving the expression 1, owing to the possible effects of the reversibility on the substrate selectivity. To verify, however, the reliability of this competitive method, we also used it with quinoline and 4-cyano- and 4-acetylpyridine in the presence and in the absence of the Cu^{2+} salt. The results are compared in Table VIII with those obtained from the kinetic expression 1; the agreement is satisfactory. That suggests that the results of Table 7 can be reasonably used to evaluate the absolute rate constants from the value of quinoline obtained from the expression 1. These rate constants are summarized in Table IX. It may be that the effects of reversibility on the substrate selectivity are more marked with the less reactive substrates; however, we believe that probably these effects are reduced by the fact that couples of aromatics closer in reactivity are compared (Tables VII and VIII) and that the order of magnitude of the rate constants is in all cases reliable.

The results of Table IX have four main conceptual involvements which are given as follows.

(i) The fact that the *tert*-butyl radical is more reactive than the *n*-butyl radical with quinoline, 4-cyanopyridine, and 4-acetylpyridine *can be explained only by polar effects* (the higher nucleophilic character of the *tert*-butyl radical compared with that of the *n*-butyl radical) because steric and enthalpic effects favor the reaction of the *n*-butyl radical.

The effect of the reversibility can only strengthen this conclusion because, in any case, the reversibility of the addition of the *tert*-butyl radical is higher than that of the *n*-butyl radical, whereas the oxidation of the alkyl radicals by the cupric salt is certainly irreversible, and k_0 for the *tert*-butyl radical is higher than k_0 for the *n*-butyl radical.

Thus, even if the effect of the reversibility is not minimized by the presence of cupric salt, the rate constants of Table IX must be considered minimum values (the real values can only be higher), and also, above all, the reactivity differences between the *tert*-butyl and *n*-butyl radicals must be considered minimum values (the real values can only be higher).

This behavior is noteworthy because the reaction is very sensitive to steric effects. The *tert*-butyl radical, in fact, attacks only position 2 of quinoline, and position 4 is not attacked for steric reasons, whereas the *n*-butyl radical attacks both positions 2 and 4 in comparable amounts. With pyridine both radicals have a higher reactivity toward position 4.

(ii) The results of Table V respresent a further confirmation of our previous assumption [1b,5] that the reactivity–selectivity relationship does not hold when polar effects play a prominent role in determining the reaction rates. The *tert*-butyl radical is always more selective than the *n*-butyl radical in the additions to aromatics, but it can be more or less reactive, depending on the electron availability of the aromatic ring; it is more reactive when polar effects prevail over steric and thermodynamic effects, but it is less reactive when these last aspects are prevailing. The reactivity differences in the same series of reactions can be so high that the same concept of general reactivity acquires an ambiguous meaning and must be referred to a well-defined situation. Thus the *tert*-butyl radical is very reactive toward 4-cyanopyridine but not toward 4-methoxypyridine or benzene.

(iii) The rate constants of Table V well explain the great synthetic interest of the homolytic alkylation of protonated heteroaromatic bases, which overcome other possible side reactions of the alkyl radicals and at the same time determine a high positional and substrate selectivity.

(iv) The high rate constants for the addition of alkyl radicals to protonated 4-cyanopyridine (other protonated heteroaromatic bases such as diazines are still more reactive[1a]) make this reaction a particularly useful diagnostic criterion for revealing the presence of alkyl radicals, especially tertiary alkyl radicals. The criterion is very effective because the rate constants are higher or of the same order of magnitude as those observed in the "spin trapping" technique.[8] Moreover, it has the advantage, compared with the "spin trapping" technique, of allowing the simple isolation, identification, and quantitative evaluation of the products of attack.

Experimental Section

Reagents and Products. Quinoline, pyridine, and 4-cyano-, 4-acetyl-, 4-methyl-, and 4-methoxypyridine were Fluka products (>99% pure by GLC). Quantitative GLC analyses were performed on a DANI Model 3600 instrument equipped with a flame detector on a 2 m × $^1/_2$ in., 3% OV-17 on Chromosorb W, a 1.5 m × $^1/_8$ in. 10% Versamid A 900 on Chromosorb P, or a 1 m × $^1/_8$ in. 10% UCC on Chromosorb P column. Product yields were calculated from the GLC data after calibration of the authentic samples against a standard (4-methylquinoline or 2-*tert*-butylpyridine). All the reaction products were isolated by column chhromatography on silica gel eluted with hexane–ethyl acetate (95:5 and 80:20) and were identified by comparison with authentic samples or by IR, NMR, and mass spectroscopic analysis.

2-*tert*-Butyl-4-cyanopyridine (1): mp 53–54 °C; NMR ($CDCl_3$) δ (s, 9 H), 7.36 (d, 1 H, H_5, J = 5.1 Hz), 7.60 (s, 1 H, H_3), 8.76 (d, 1 H, H_6); mass spectrum, m/e (relative intensity) 160 (M^+, 11), 159 (12), 146 (13), 145 (100), 118 (15), 117 (14), 104 (9), 77

(8) K. U. Ingold, *J. Am. Chem. Soc.*, **102**, 6063 (1980). We thank Professor Ingold for sending a preprint of the work.

(11), 42 (21), 39 (21); IR ν_{max} 2230 cm^{-1} (CN).

3-*tert*-Butyl-4-cyanopyridine (2): bp 85–87 °C (2 mm); NMR ($CDCl_3$) δ 1.58 (s, 9 H), 7.57 (d, 1 H, H_5, J = 5.6 Hz), 8.67 (d, 1 H, H_6), 8.90 (s, 1H, H_6); mass spectrum, m/e (relative intensity) 160 (M^+, 32), 159 (16), 145 (100), 118 (19), 117 (55), 105 (21); IR ν_{max} 2230 cm^{-1} (CN).

2,5-Di-*tert*-butyl-4-cyanopyridine (4): mp 115–116 °C; NMR ($CDCl_3$) δ 1.36 (s, 9 H), 1.52 (s, 9 H), 7.55 (s, 1 H, H_3), 8.78 (s, 1 H, H_6); mass spectrum, m/e (relative intensity) 216 (M^+, 27), 215 (21), 202 (16), 201 (100), 185 (12), 184 (9), 174 (32), 171 (19), 159 (12), 41 (31), 39 (17); IR ν_{max} 2222 cm^{-1} (CN).

2,6-Di-*tert*-butyl-4-cyanopyridine (3): bp 120–122 °C (2 mm); NMR ($CDCl_3$) δ 1.38 (s, 18 H), 7.37 (s, 2 H); mass spectrum, m/e (relative intensity) 216 (M^+, 19), 215 (23), 201 (100), 186 (14), 185 (23), 174 (35), 171 (14), 145 (39), 97 (30), 41 (28), 39 (20); IR ν_{max} 2240 cm^{-1} (CN).

2,*N*-Di-*tert*-butylpyridine-4-carboxamide: mp 154–155 °C; NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.47 (s, 9 H), 6.2 (1 H, NH), 7.28 (dd, 1 H, H_5, $J_{5,6}$ = 5.6 Hz, $J_{5,3}$ = 0.5 Hz), 7.70 (d, 1 H, H_3), 8.63 (d, 1 H, H_6); mass spectrum, m/e 234 (M^+), 219, 192, 163, 145, 117, 91, 77; IR 1645, 3390 cm^{-1} (CONH).

2-*n*-Butyl-4-cyanopyridine: bp 92–93 °C (3 mm); NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.2–1.9 (m, 4 H), 2.85 (t, 2 H), 7.38 (d, 1 H, H_5, $J_{5,6}$ = 5.6 Hz), 7.43 (s, 1 H, H_3), 8.73 (d, 1 H, H_6); mass spectrum, m/e (relative intensity) 160 (M^+, 2), 159 (4), 145 (16), 131 (48), 118 (100), 104 (5); IR 2240 cm^{-1} (CN).

3-*n*-Butyl-4-cyanopyridine: bp 90–91 °C (2 mm); NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.1–1.9 (m, 4 H), 2.84 (t, 2 H), 7.49 (d, 1 H, H_5, J = 4.8 Hz), 8.65 (d, 1 H, H_6), 8.7 (s, 1 H, H_2); mass spectrum, m/e (relative intensity) 160 (M^+, 15), 159 (7), 145 (100), 118 (60), 107 (30); IR 2235 cm^{-1} (CN).

2,3-Di-*n*-butyl-4-cyanopyridine: bp 112–114 °C (2 mm); NMR ($CDCl_3$) δ 1.1–2.0 (m, 14 H), 2.87 (t, 4 H), 7.3 (d, 1 H, H_5, J = 5.0 Hz), 8.53 (d, 1 H, H_6); mass spectrum, m/e (relative intensity) 216 (M^+, 10), 215 (9), 201 (29), 187 (100), 174 (79), 159 (87), 146 (82), 145 (59), 143 (40), 132 (94), 133 (45); IR 2236 cm^{-1} (CN).

2,6-Di-*n*-butyl-4-cyanopyridine: bp 110–111 °C (3 mm); NMR ($CDCl_3$) δ 1.96 (t, 6 H), 1.1–1.9 (m, 8 H), 2.84 (t, 4 H), 7.25 (s, 2H); mass spectrum, m/e (relative intensity) 216 (M^+), 215 (11), 201 (33), 187 (61), 174 (84), 132 (100); IR 2240 cm^{-1} (CN).

2,5-Di-*n*-butyl-4-cyanopyridine: bp 108–109 C (3 mm); NMR δ 1.1–2.0 (m, 14 H), 2.84 (t, 4 H), 7.34 (s, 1 H, H_3), 8.68 (s, 1 H, H_6); mass spectrum, m/e (relative intensity) 216 (M^+ 10), 215 (15), 201 (20), 187 (20), 174 (100); IR 2240 cm^{-1} (CN).

The other 2-*n*-butyl- and 2-*tert*-butylquinolines and -pyridines substituted at position 4 were already prepared by the same reaction in previous works.[2,9]

Preparative-Scale Reactions. A mixture of the heterocyclic compound (0.1 mol), H_2SO_4 (0.3 mol), $AgNO_3$ (0.008 mol), and *n*-pentanoic acid (or 2,2-dimethylpropanoic acid) (0.2 mol) in 400 mL of water was heated at 80 °C. A solution of $K_2S_2O_8$ (0.08 mol) in 40 mL of water was added in 2 h. The reaction was made basic with NH_3 and extracted with ether. The residue was analyzed by GLC and the reaction products were isolated by silica gel chromatography.

Kinetics. The 50-mL stock solutions of the heterocyclic compound (0.4 M), H_2SO_4 (0.8 M), and $AgNO_3$ (0.04 M) were thermostated at 57 °C under nitrogen for 0.5 h. $(NH_4)_2S_2O_8$ (0.003 M) and the weighed amounts of $Cu(OAc)_2 \cdot H_2O$ and *n*-pentanoic or 2,2-dimethylpropanoic acid were added, and the reaction was run for 3 h. (It has been verified that under these conditions no appreciable hydrolysis of 4-cyanopyridine occurs.) 4-Methylquinoline and *n*-butanoic acid were added as internal standards, respectively, for the heterocyclic compounds and the carboxylic acids. The exhaustive extraction by ethyl ether of the acidified and basified solutions allows the separation of the heterocyclic compounds and the carboxylic acids, which were analyzed by GLC using a 10% FTAP on Chromosorb W column at 100 °C for the carboxylic acids and a Versamid or UCC column at 130 °C for the heterocyclic compounds.

The reacted carboxylic acid amounts to 70–98% of the theoretical quantity based on the peroxydisulfate used. It has been verified according to the Kochi[10] procedure that all the alkyl radicals, which do not attack the heterocyclic compound, are oxidized by the Cu^{2+} salt (exclusive formation of 1-butene from *n*-Bu· and of isobutylene and *tert*-butyl alcohol from *t*-Bu·). The results are summarized in Table VI.

Relative Rates by the Competitive Method. General Procedure. A 100-mL sample of a water solution of 0.04 M aromatic compounds, 0.06 M H_2SO_4, 0.002 M $AgNO_3$, 0.0004 M $Cu(OAc)_2$, 0.04 M *n*-pentanoic acid (or 2,2-dimethylpropanoic acid), and 0.005 M $(NH_4)_2S_2O_8$ was kept at 57 °C for 4 h. The exhaustive extraction by ethyl ether of the basified solution provides the alkylated heterocycles, which are analyzed by GLC after calibration of the authentic samples against a standard (methylquinoline). The results are summarized in Table VIII for quinoline and 4-cyano- and 4-acetylpyridine.

The same procedure was used for all the investigated aromatic compounds, with the difference that no $Cu(OAc)_2$ was used. The results are reported in Tables VII and VIII.

Registry No. 1, 33538-09-9; 2, 74808-75-6; 3, 37581-48-9; 4, 74808-76-7; 4-cyanopyridine, 100-48-1; 2-butyl-4-cyanopyridine, 72679-69-7; 3-butyl-4-cyanopyridine, 7136-18-7; 2,6-dibutyl-4-cyanopyridine, 72679-70-0; 2,5-dibutyl-4-cyanopyridine, 74808-77-8; 2,3-dibutyl-4-cyanopyridine, 74825-01-7; quinoline, 91-22-5; 4-acetylpyridine, 1122-54-9; valeric acid, 109-52-4; pivalic acid, 75-98-9; 2-butylquinoline, 7661-39-4; 4-butylquinoline, 74808-78-9; 2-*tert*-butylquinoline, 22493-94-3; 2-butyl-4-acetylpyridine, 74808-79-0; 2-*tert*-butyl-4-acetylpyridine, 60159-35-5; 1-butene, 106-98-9; isobutylene, 115-11-7; *tert*-butyl alcohol, 75-65-0; 4-methoxypyridine, 620-08-6; 4-methylpyridine, 108-89-4; pyridine, 110-86-1; 2,*N*-di-*tert*-butylpyridine-4-carboxamide, 74808-80-3; butyl radical, 2492-36-6; *tert*-butyl radical, 1605-73-8; $Cu(OAc)_2$, 142-71-2.

(9) F. Minisci, R. Bernardi, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron*, **27**, 3575 (1971).

(10) J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.*, **92**, 1651 (1970).