compared to the literature value of -1.37 V. The reduction potential of NMN was measured as -1.65 V.

Fluorescence Quenching of NMN. General Conditions. Fluorescence quenching experiments were carried out on 1×10^{-4} M solutions of NMN in spectral grade acetonitrile. Typically, five samples containing from 10^{-3} to 10^{-2} M quencher were prepared. The excitation wavelength was 300 nm unless competitive absorption from the quencher was significant, in which case a longer excitation wavelength was chosen. Fluorescence intensities were monitored at 371 nm. The data was interpreted by using the standard Stern-Volmer relationship.

Fluorescence Quenching of NMN by 2,3-Butanedione. Estimation of the Singlet-State Lifetime of NMN. Efficient fluorescence quenching of NMN was observed in the presence of butanedione [(9.12×10^{-4})-(4.56×10^{-3}) M]. A Stern-Volmer plot of the data was linear with a slope of 101 ± 1. Since the singlet-state energy of butanedione is 65.3 kcal/mol and that of NMN is estimated to be 79 kcal/mol (vide supra) energy transfer should proceed at the diffusion-controlled rate, 2×10^{10} M/s in acetonitrile. The average $k_q\tau$ value for butanedione (and for 2,5-dimethyl-2,4-hexadiene) is 104 ± 3. The lifetime (τ) of the singlet state of NMN is calculated as 5.2 ns.

Solvent Isotope Studies. Identical samples containing 50 mg of NMP and 0.50 mL of **24** in 2 mL of the appropriate solvent (MeOH, MeOD, CH_3CN, CD_3CN) were irradiated through Pyrex in a merry-go-round apparatus. A minimum of three samples of each solvent was examined by HPLC vs. an internal standard. The **28**/**29** ratio was unchanged in MeOH/MeOD. The **28**/**29** ratio decreased by 16% in going from CH_3CN to CD_3CN.

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Polar Effects in Free-Radical Reactions. Rate Constants in Phenylation and New Methods of Selective Alkylation of Heteroaromatic Bases

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The rate constants for the addition of the phenyl radical to protonated and unprotonated 4-substituted pyridines have been determined by competition with chlorine abstraction from CCl_4. The constants range from 2×10^5 to 6×10^6 M^{-1} s^{-1} depending on the substituent and on the degree of protonation. The phenyl radical shows a clear-cut nucleophilic character. On the basis of these rate constants, the use of phenyl radical from diazonium salt or benzoyl peroxide to generate alkyl radicals by iodine or hydrogen abstraction has been developed as a general procedure for the alkylation of heteroaromatic bases. This reaction is characterized by high yields and selectivities.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is a general reaction of large synthetic interest. It reproduces most of the numerous aspects of the Friedel-Crafts aromatic alkylation and acylation, but with opposite reactivity and selectivity.[1,2] Actually the high reactivity and selectivity and the consequent synthetic interest are not limited to the protonated heteroaromatic bases. They are quite general towards electron-deficient unsaturated compounds, particularly, if a positive charge is placed on the unsaturated system (pyrilium,[3] diazonium,[4] iminium salts[5]). This suggests a large contribution of charge separation to the transition states of these systems (eq 1). The homolytic

$$R^{\bullet} X{=}Y^{+} \leftrightarrow R^{+} X{=}Y^{\bullet} \qquad (1)$$

phenylation of heteroaromatic bases has been extensively investigated,[6] and the large change of selectivity by passing from unprotonated to protonated derivatives has been ascribed to the polar effect[7] rather than to the free valence numbers or the atom localization energies.[6] It was of interest to know the rate constants of the phenyl radical addition to protonated and unprotonated heteroaromatic bases mainly for two reasons: (i) a better understanding of the change of selectivity with the protonation and of the polar effect and (ii) the evaluation of the limits in utilizing the phenyl radical as source of more nucleophilic carbon-

Scheme I

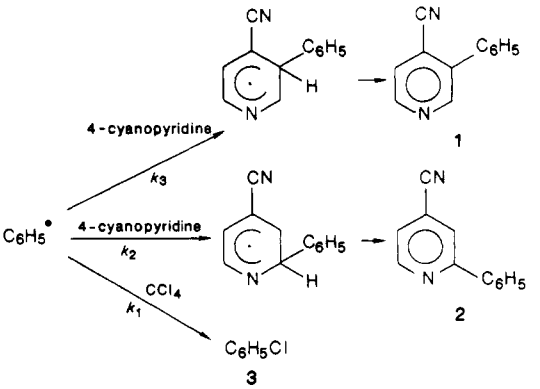

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Table I. Absolute Rate Constants (M^{-1} s^{-1}) in the Phenylation of 4-Cyanopyridine ($k_1 = 3.7 \times 10^6$ M^{-1} s^{-1})

radical source	k_2/k_1	k_2	k_3/k_1	k_3	k_2/k_3
		$Ph-N_2^+ + Cu^+$			
protonated	1.43	5.3×10^6	0.83	3.1×10^6	1.71
unprotonated	0.19	7.0×10^5	0.82	3.0×10^6	0.23
		$Ph-N_2^+ + Fe^{2+}$			
protonated	1.52	5.6×10^6	0.86	3.2×10^6	1.75
unprotonated	0.22	9.2×10^5	0.88	3.3×10^6	0.28
		$(PhCOO)_2 + Cu^{2+}$			
protonated	1.62	6.0×10^6	0.97	3.6×10^6	1.70
unprotonated	0.33	1.2×10^6	0.92	3.4×10^6	0.35

centered radicals useful in heteroaromatic substitution (i.e., by hydrogen or iodine abstraction).

In this paper we report the rate constants of the addition of the phenyl radical to protonated and unprotonated pyridine derivatives, determined by the competitive methods and the utilization of the aryl radicals as source of more nucleophilic radicals suitable for the selective heteroaromatic substitution.

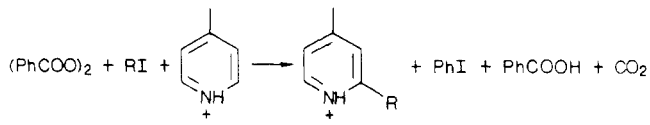
Results

Rate Constants for the Addition of the Phenyl Radical to Pyridine Derivatives. 4-Cyanopyridine has been utilized as a substrate for several reasons: it is significantly more reactive than unsubstituted pyridine, the reaction is quite clean at the low conversions required by the competitive method, only two isomers are formed (2-phenyl- and 3-phenyl-4-cyanopyridine), and the GLC analysis is particularly simple. The chlorine atom abstraction from CCl_4 by the phenyl radical has been chosen as the reference reaction for which the absolute rate constant is known (Scheme I).

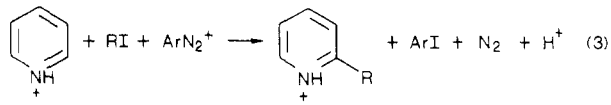
The ratios of the concentrations of the reaction products, [1]:[3] and [2]:[3], at low conversion allow us to evaluate the rate constants k_2/k_1 and k_3/k_1. The value of k_1 has been reported by two research groups, and the agreement is satisfactory: Lorand[8] reports the values 2.7, 3.3, 3.7, and 5.8×10^6 M^{-1} s^{-1} with different competitive methods at 45 °C and Scaiano[9] a value of 7.8×10^6 M^{-1} s^{-1} at 25 °C by using a laser flash photolysis technique. Two radical sources have been utilized: benzenediazonium tetrafluoborate and Cu^+ or Fe^{2+} in Me_2SO at 25 °C and benzoyl peroxide and $Cu(OAc)_2$ in acetonitrile at 50 °C. The agreement between the two radical sources is good considering the difference of temperature. The results are reported in Table I by assuming for k_1 a value of 3.7×10^6 M^{-1} s^{-1}. In order to obtain the rate constants of other substituted pyridines it was analytically more convenient to study the competition between pairs of pyridines with the phenyl radical generated from benzoyl peroxide or silver-catalyzed oxidative decarboxylation of benzoic acid with peroxydisulfate.[7] The results are summarized in Table II.

Alkylation of Heteroaromatic Bases Using Aryl Radicals as the Source of Alkyl Radicals. The systems, benzoyl peroxides–alkyl iodides and arenediazonium salt–alkyl iodides, are selective sources of alkyl radicals suitable for the alkylation of protonated heteroaromtic bases. Benzoyl peroxide has been utilized both in the presence and the absence of iron salt redox catalysis in several solvents (eq 2).

Diazonium salts gave results only in Me_2SO by using iron or copper salt redox catalysis (eq 3); the *p*-chloro-



(2)



(3)

benzenediazonium tetrafluoborate was chosen for reasons of stability.

Some results are reported in Table III.

The alkylation of heteroaromatic bases by hydrogen abstraction from a variety of solvents by the phenyl radical has been also achieved as the results of Table IV show. It is important in these cases to employ a large excess of solvent in order to have a good substrate selectivity.

Discussion

Rate Constants in the Addition of the Phenyl Radical to Pyridines. In order for the competitive method of determining the relative rate to be valid, it is necessary that the competitive reaction be irreversible. The chlorine atom abstraction from CCl_4 by the phenyl radical is certainly irreversible because it is an exothermic process; the reversibility of the addition of the phenyl radical to the aromatic ring has been extensively discussed, and most of the evidences support the irreversible character of the process.[10] Thus the results of Tables I and II seem to be sufficiently reliable.

The phenyl radical has been the most investigated radical in homolytic aromatic substitution. It is considered[11] a highly reactive, unselective radical in agreement with the reactivity–selectivity principle (RSP). Moreover the polar effect of the phenyl radical reactions is generally considered negligible (a ρ value close to 0 has been reported[12] for the substitution of benzene derivatives).

We[13] have previously reported evidence that, while the RSP is a valid criterion for free-radical reactions when the reaction enthalpy mainly governs the reactivity, the RSP can be reversed when the polar effect plays a dominant role. Moreover we[14] have also expressed the concept that the polar effect, being kinetic in nature, is not an intrinsic property of a free radical, but may change with the varying polar nature of a particular reaction. Thus, in principle, it is not correct to fix a polar character for a given radical without taking into account the particular type of reaction involved; the same radical can behave as an electrophilic, a nucleophilic, or a nonpolar species depending on the particular reaction involved.

The results of Table II illustrate these concepts: the phenyl radical substantially behaves as a nonpolar species in the addition to benzene derivatives, but it shows a clear-cut nucleophilic character in the addition to pyridines. This occurs because the polar effect depends on several factors, but the polarity and polarizability of both the partners, the radical and the substrate, are among the most important.[1] The polarity of the substrate is no less important than that of the radical in determining the

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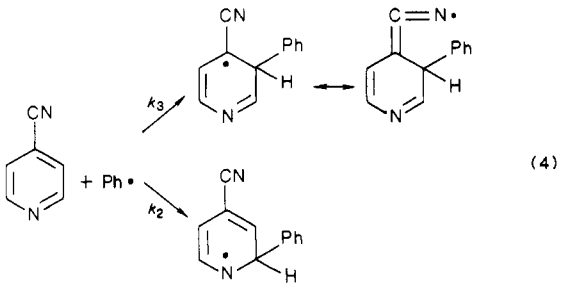
Table II. Absolute Rate Constants (M^{-1} s^{-1} × 10^6) for the Homolytic Phenylation of 4-Substituted Pyridines

	acidic				acidic				nonacidic			
	k_{CN}/k_x		k_x(PhCOOH)		k_{CN}/k_x		$k_x/(PhCOO)_2$		k_{CN}/k_x		$k_x/(PhCOO)_2$	
substituent x	2	3	2	3	2	3	2	3	2	3	2	3
CN	1.00	1.00	6.02	3.61	1.00	1.00	6.02	3.61	1.00	1.00	1.22	3.41
Cl	1.13	2.57	5.30	1.41	1.15	2.41	5.23	1.50	1.35	2.43	0.90	1.43
H[a]	1.88	15.65	3.18	0.23	1.64	14.81	3.67	0.24	2.73	13.6	0.44	0.25
Me	3.31	10.06	1.81	0.36	3.08	9.27	1.95	0.40	3.75	9.14	0.32	0.36
MeO	6.37	15.12	0.94	0.24	5.04	14.38	1.19	0.25	5.21	8.95	0.23	0.38

[a] The position 4 is also attacked: 3.15 × 10^6 M^{-1} s^{-1} (PhCOOH and protonated pyridine), 3.12 × 10^6 M^{-1} s^{-1} ($(PhCOO)_2$ and protonated pyridine), 0.28 × 10^6 M^{-1} s^{-1} ($(PhCOO)_2$ and unprotonated pyridine).

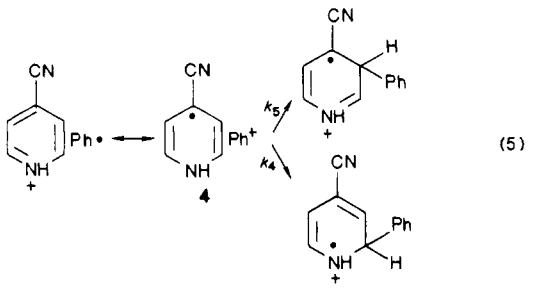
sensitivity to the polar effect.[1] Thus with unprotonated pyridines the reactivity and the regioselectivity of the homolytic phenylation appears to be mainly governed by the stability of the intermediate radical adduct (eq 4), and



(4)

the polar effect is a minor factor so that $k_2 < k_3$. The phenomenon is general with all the substitutents, also with electron-releasing groups.

With protonated pyridines in which the polarity is strongly increased, the polar effect, due to the charge separation in the transition state (eq 5), plays a significant



(5)

role in determining reactivity and regioselectivity. The position of lower electron density is attacked faster, $k_4 > k_5$, and the phenyl radical shows a clear-cut nucleophilic character.

The charge separation is in this case also favored by the fact that **4** is a captodative radical[15] but the phenomenon is general with all the substituents. This interpretation is supported by the fact that the rates of the β-position remain substantially unchanged ($k_3 \simeq k_5$), whereas the rates of the α- and γ-positions are significantly increased by protonation ($k_4 > k_2$). The polar character of this phenomenon is further supported by the fact that the addition rates to the α-positions are increased by electron-withdrawing groups in the γ-position, where there is no radical-stabilizing effect.

The protonation of the pyridine derivatives increases both reactivity and selectivity in homolytic phenylation, reversing the RSP. This has previously been observed with other more nucleophilic alkyl and acyl radicals.[16] However, when polar effects are important in free-radical reactions, the same general concept of reactivity acquires a particular meaning. Thus the phenyl in many reactions is actually much more reactive (>10^3) and much less selective than the alkyl and acyl radicals; that also occurs in the addition to benzene (Table V). However, with protonated 4-cyanopyridine the alkyl and acyl radicals are much more selective (regio- and chemoselectivity), but even more reactive than the phenyl radical (Table V). In these cases it has less sense to consider the reactivity of the free radicals in general without specifying the particular kind of reaction and the particular selectivity involved.

Alkylation of Heteroaromatic Bases by Iodine (R–I) and Hydrogen (R–H) Abstraction by the Phenyl Radical. The rapid rate of iodine abstraction from alkyl iodides by the phenyl radical makes this reaction (eq 6)

$$i\text{-PrI} + \text{Ph}^\bullet \xrightarrow{k} i\text{-Pr}^\bullet + \text{PhI} \qquad (6)$$

a particularly selective general source of alkyl radicals. The reaction occurs on nearly every collision, and the rate constant ($k = 1.27 \times 10^9$ M^{-1} s^{-1}) is about three orders of magnitude higher than those for the addition of the phenyl radical to aromatic or heteroaromatic derivatives and for hydrogen abstraction from C–H bonds (10^6 M^{-1} s^{-1}).[8] Thus when 1:1 molar ratios of alkyl iodide and heteroaromatic base are used, no significant attack of the phenyl radical to the heterocyclic ring takes place, but only the alkyl radical from the alkyl iodide is formed. Moreover a variety of solvents can be utilized without the occurrence of significant competitive reactions between the phenyl radical and the solvent. Solvents such as acetonitrile, acetic acid, and Me_2SO are, in any case, preferable because, even if the hydrogen abstraction from the solvent occurs to a certain extent (depending on the concentration of alkyl iodide), the resulting alkyl radicals are electrophilic and do not react with the protonated base. Good results have been also obtained using benzene as the solvent with only traces of biphenyl being formed. When an excess of alkyl iodide is used, the side reactions of the phenyl radical are further minimized. The mechanism of the reaction utilizing a diazonium salt as the source of phenyl radical is shown in Scheme II. A competitive process[4] is the addition of the alkyl radical to the diazonium group (eq 7).

$$\text{ArN}^+\equiv\text{N} + \text{R}^\bullet \xrightarrow{k} \text{ArN}^{+\bullet}=\text{NR}, \quad k \sim 10^5\text{–}10^8\ M^{-1}\ s^{-1} \qquad (7)$$

$$\text{ArN}^{+\bullet}=\text{NR} + \text{M}^+ \rightarrow \text{ArN}=\text{NR} + \text{M}^{2+} \qquad (8)$$

This is a fast reaction because of polar factors. It can lead to formation of alkylarylazo derivatives (eq 8). This

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Table III. Alkylation of Heteroaromatic Bases by *p*-Chlorobenzenediazonium Tetrafluoroborate (ArN_2^+), Benzoyl Peroxide, and Alkyl Iodides

heteroaromatic base	radical,[a] source	alkyl iodide	position of attack	conversion, %	yield,[b] %
quinoline	$A_2N_2^+/Cu^+$	*i*-PrI	4	50	96
		c-C_6H_{11}I	4	26	91
leipdine		c-C_6H_{11}I	2	37	82
		c-C_6H_{11}OH			
	ArN_2^+/Fe^{2+}	*n*-BuI	2	38	98
		c-C_6H_{11}I	2	43	95
		t-BuI[c]	2	23	76
quinoline		c-C_6H_{11}I	2 (44%)	50	86
			4 (56%)		
	ArN_2^+/Cu^+		2 (43%)	37	93
			4 (57%)		
isoquinoline	ArN_2^+/Fe^{2+}		1	15	90
4-cyanopyridine	$(PhCOO)_2$	*i*-PrI	2 (66%)	72	100
			2,6 (34%)		
		n-BuI	2 (75%)	58	96
			2,6 (25%)		
		i-BuI	2 (58%)	85	98
			2,6 (42%)		
isoquinoline		c-C_6H_{11}I	1	98	85
		EtI	1	78	92
quinaldine	$(PhCOO)_2$	c-C_6H_{11}I	4	92	88
		n-BuI	4	96	93
		i-BuI	4	76	98
leipdine		c-C_6H_{11}I	2	76	95
e		*n*-BuI	2	76	88
		i-PrI	2	75	98
d			2	100	77
		2-iodopentane	2	68	97
d			2	98	85
d			2	92	85
		$I(CH_2)_2COOEt$	2	60	93
e			2	64	88
acridine		c-C_6H_{11}I	9	82	94
benzothiazole[d]		*i*-PrI	2	66	90

[a] Ratio of the radical source: heteroaromatic base 1:1. [b] Yields of isolated products based on the converted heteroaromatic base. [c] ArN_2^+ and *t*-BuI are simultaneously dropped to the reaction mixture. [d] Ratio of the radical source: heteroaromatic bae 2:1. [e] Benzene has been utilized as solvent without iron salt.

"free-radical diazocoupling"[4] is a reaction of general synthetic interest. The stoichiometry of the reaction is shown by eq 9.

$$2ArN_2^+ + RI + 2M^+ \rightarrow ArI + ArN{=}NR + N_2 + 2M^{2+} \quad (9)$$

To overcome the competition of the fast diazocoupling reaction in the alkylation of the heteroaromatic base, it is necessary to keep the steady-state concentration of the diazonium salt in the reaction medium very low in order to minimize reaction 7. That has been achieved by the slow addition of the diazonium salt to a solution of the protonated heteroaromatic base, the alkyl iodide, and the reducing metal salt (Cu^+ or Fe^{2+}) in Me_2SO. Fast reduction of the diazonium salt by the reducing metal salt produces a low, stationary concentration of the desired species. The thermal decomposition of benzoyl peroxide in the presence of alkyl iodides also gives good results. The mechanism for this reaction is shown by the Scheme III, where an induced decomposition via electron transfer propagates the chain.

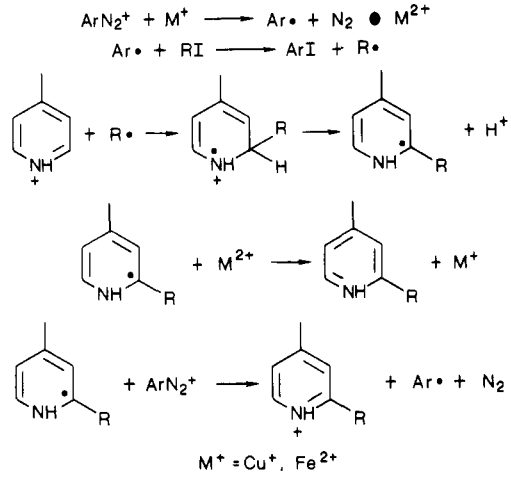
The reaction becomes faster in the presence of small amounts of iron salt because a redox chain is superimposed on the free-radical chain of Scheme III. The reaction is quite general with alkyliodides with exception of *tert*-alkyl iodides, which react with benzoyl peroxide before the formation of the phenyl radical. In a benzene solution of ethyl iodoacetate, no attack on lepidine occurs. Only iodobenzene and ethyl phenylacetate are formed (eq 10).

$$PhH + ICH_2COOEt + (PhCOO)_2 \rightarrow PhCOOH + PhI + PhCH_2COOEt + CO_2 \quad (10)$$

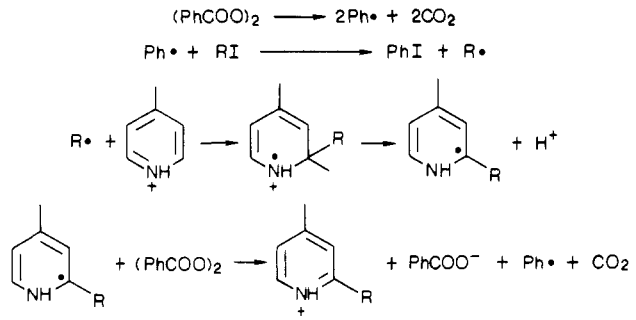
When ethyl 3-iodopropionate is used, however, only the position 2 of lepidine is attacked by the radical $^{\bullet}CH_2CH_2COOEt$ and no attack to benzene takes place. This again shows the great importance of the polar effect: the electron-withdrawing group (COOEt) directly bound to the radical center inhibits the reaction with heteroaromatic bases because of the decreased nucleophilic character. It is, however, sufficient that the electron-withdrawing group is in the β position and the alkyl radical has enough nucleophilic character for the selective alkylation of the heterocyclic ring.

The rates of hydrogen abstraction by the phenyl radical from aliphatic C–H bonds are of the same order of magnitude (i.e., 1.6×10^6 M^{-1} s^{-1} for the *t*-C–H bond and 4.8×10^6 for the C–H bond in THF)[8,9] of the rates of addition to the heterocyclic ring (Table II). Thus, in order to have a good substrate selectivity in the heteroaromatic alkylation, it is necessary to use a large excess of that substrate from which the hydrogen abstraction occurs. Another consideration is the regioselectivity of the hydrogen abstraction. Good synthetic results are obtained when only one kind of C–H bond is present (i.e., with methanol or symmetrical molecules such as cycloalkanes, dioxane, trioxane, etc.) or a particular C–H bond is substantially

Scheme II



Scheme III



more reactive than the other C–H bonds, such as the α C–H bonds in ethanol and THF or benzylic C–H bonds in methyl benzenes. The selectivity of the reaction is still good when the hydrogen abstraction leads to only one kind of nucleophilic radical; thus in a mixture of solvents such as cyclohexane, $CHCl_3$, and acetonitrile, only the cyclohexylation of the heteroaromatic base takes place, even if the $^{\bullet}CCl_3$ and $^{\bullet}CH_2CN$ radicals are extensively formed; the electrophilic character of these last radicals completely inhibits the reaction towards protonated heteroaromatic bases. Similarly, ethyl acetate gives electrophilic ($^{\bullet}CH_2COOEt$) and nucleophilic radicals ($CH_3COO\dot{C}H$–CH_3), but ony this last reacts with the heterocyclic ring.

Conclusions

The protonation of pyridine derivatives increases the reactivity and the selectivity towards the phenyl radical. The phenomenon, due to polar effects, is much less marked than with alkyl and acyl radicals. The knowledge of the rate constants has allowed the development of new general procedures of alkylation of heteroaromatic bases, characterized by high yields and selectivities, by utilizing diazonium salt and benzoyl peroxide to generate alkyl radicals.

Experimental Section

GLC were performed by a Carlo Erba 4200 or Dani 3600 instruments equipped with flame ionization detectors.

Competitive Reactions of the Phenyl Radical with CCl_4 and 4-Cyanopyridine. Benzoyl Peroxide. All the reactions were run in sealed glass ampules flushed with nitrogen. 4-Cyanopyridine (6.2 mmol), 37.2 mmol of CCl_4, 1.2 mmol of benzoyl peroxide, and 0.3 mmol of $Cu(OAc)_2$ in 20 mL of MeCN were warmed for 6 h at 50 °C in a thermostatically controlled water bath. The solution was diluted with 30 mL of water, made basic with 10% NaOH solution, extracted with CH_2Cl_2, and analyzed by GLC: chlorobenzene was analyzed by a column packed with Carbowax 20M with *p*-chlorotoluene as the internal standard; the phenylcyanopyridines were analyzed by a column packed with OV 17 3% with quinaldine as internal standard.

The procedure was identical with protonated 4-cyanopyridine with the difference that 37 mmol of CF_3COOH were added to the reaction mixture.

Duplicate runs were performed and the averaged results, expressed as relative and absolute rates, are reported in Table I. Standard deviations were ±4%.

Benzenediazonium Salt. 4-Cyanopyridine (5.3 mmol), 53 mmol of CCl_4, 1.6 mmol of benzenediazonium tetrafluoroborate, and 6 mmol of AcONa in 18 mL of Me_2SO were flushed with nitrogen, then 0.6 mmol of Cu powder and 0.1 mmol of $Cu(OAc)_2$ were added, and the solution was kept at 25 °C for 12 h in a thermostatically controlled water bath. The solution was diluted with 50 mL of water, made basic with 10% NaOH solution, extracted with CH_2Cl_2, and analyzed by GLC as described with benzoyl peroxide.

The same procedure was utilized by using 2.2 mmol of $FeSO_4$ instead of Cu + $Cu(OAc)_2$.

The procedures were identical with protonated 4-cyanopyridine with the difference that 15 mmol of $MeSO_3H$ and no AcONa was added to the reaction mixture.

Duplicate runs were performed and the results, averaged and expressed as relative and absolute rates, are reported in Table I. Standard deviations were ±3%.

Table IV. Alkylation of Heteroaromatic Bases by Hydrogen Abstraction from RH by $(PhCOO)_2$

heteroaromatic[a] base	RH	position of attack	conversion, %	yield, %
lepidine[c]	c-C_6H_{12}	2	74	96
		2	100	86
quinaldine	c-C_6H_{12}	4	68	94
	c-C_8H_{16}	4	65	98
isoquinoline	c-C_6H_{12}	1	72	87
4-cyanopyridine		2 (67%)	58	93
		2.6 (33%)		
	c-C_8H_{16}	2 (65%)	60	96
		2.6 (35%)		
	dioxane	2 (72%)	61	88
		2.6 (28%)		
		2 (76%)	54	85
		2.6 (24%)		
lepidine		2	68	86
	dioxane	2	71	91
quinaldine		4	65	87
		4	58	82
lepidine	MeOH	2	74	98
	$MeCH_2OH$	2	38	87
	$CHON(CH_3)CH_2H$[e]	2	57	83
	$MeCOOCH_2Me$	2	35	78

[a] Ratio $(PhCOO)_2$:heteroaromatic base 1:1. [b] Yields of isolated products based on converted base. [c] Ratio $(PhCOO)_2$:base 2:1. [d] Small amounts of products arising from the tetrahydrofuranyl radical are formed. [e] Small amounts of product arising from the radical $\bullet CON(CH_3)_2$ are formed.

Table V. Absolute Rate Constants for the Addition of Carbon-Centered Radicals to Benzene and Protonated 4-Cyanopyridine (Position 2)

radical	benzene	ref	4-cianopyridine	ref
$Ph^{\bullet}$	1.03×10^6	7	6.02×10^6	this work
$n\text{-}Bu^{\bullet}$	3.8×10^2	15	8.9×10^5	16
$t\text{-}Bu^{\bullet}$	no reaction		6.3×10^7	17
$t\text{-}Bu\dot{C}O$	no reaction		$\sim 10^6$	18
$^{\bullet}CH_2OH$	no reaction		$\sim 10^7$	19

Competitive Reactions of the Phenyl Radical with 4-Substituted Pyridines. A solution of 10 mmol of 4-cyanopyridine, 30 mmol of pyridine derivative (pyridine, 4-chloro-, 4-methyl-, 4-methoxypyridine), 40 mmol of H_2SO_4, 4 mmol of $(NH_4)_2S_2O_8$, and 0.8 mmol of $AgNO_3$ in 35 mL of water was warmed for 3 h at 80 °C in a thermostatically controlled bath. The solution was made basic by 10% NaOH solution, extracted with CH_2Cl_2, and analyzed by GLC by using a column packed with OV 17 3% (quinaldine as the internal standard). The results are reported in Table II.

Benzoyl Peroxide. A solution of 5 mmol of 4-cyanopyridine, 15 mmol of 4-substituted pyridine, 1.4 mmol of benzoyl peroxide, and 0.3 mmol of $Cu(OAc)_2$ in 60 mL of MeCN was warmed for 6 h at 50 °C in a thermostatically controlled bath. The solution was diluted with 30 mL of water, made basic with 10% NaOH solution, extracted with CH_2Cl_2, and analyzed by GLC as in the preceding case.

The procedure was identical with protonated bases with the difference that 80 mmol of CF_3COOH were added to the reaction mixture.

All the phenyl derivatives were identified by comparison with authentic samples (GLC, NMR, MS).[7]

In all cases duplicate runs were performed, and the results, expressed as relative and absolute rates, are reported in Table II. Standard deviations are ±5%.

Alkylation of Heteroaromatic Bases by Benzoyl Peroxide and Alkyl Iodides. General Procedures. A solution of 1.5 mmol of the heteroaromatic base, 2 mmol of CF_3COOH, 4 mmol of the alkyl iodide, 0.1 mmol of $FeOH(OAc)_2$, and benzoyl peroxide (in the amount reported in Table III) in 20 mL of acetonitrile was refluxed untill complete decomposition of the peroxide (4 h). The solution was diluted with 50 mL of water, made basic with 10% NaOH solution, extracted with ethyl acetate, and analyzed by GLC by using a column packed with 10% OV 101 on Chromosorb W HP DMCS (lepidine or quinaldine as the internal standards). All the reaction products have been previously prepared by us by different methods[1,20] and identified by GLC, NMR, and MS comparison, with the exception of the product obtained from lepidine and ethyl 3-iodopropionate. This product has been identified by NMR and MS as arising from the substitution of position 2 of lepidine by the radical $^{\bullet}CH_2CH_2COOEt$. NMR: δ 1.2 (3 H, t, CH_3 of Et), 2.6 (3 H, s, CH_3 in position 4), 2.8 (2 H, t, CH_2), 3.2 (2 H, t, CH_2), 4.2 (2 H, q, OCH_2), 7.1 (1 H, s, aromatic in position 3), 7.4–8.1 (4 H aromatic, m). MS: m/e 243 ($M^{\bullet+}$), 214, 198, 170, 142.

Benzene has been in a few cases utilized as solvent instead of acetonitriile with substantially similar results. With ethyl iodoacetate and lepidine in benzene no attack of the base occurs, but ethyl phenylacetate was obtained in 30% conversion. The results are reported in Table III.

Alkylation of Heteroaromatic Bases by *p*-Chlorobenzenediazonium Fluoroborate and Alkyl Iodides. General Procedure. A solution of 3.5 mmol of *p*-chlorobenzenediazonium tetrafluoroborate in 5 mL of Me_2SO was added dropwise with stirring over a period of 30 min to a mixture of 3.5 mmol of the heteroaromatic base, 16 mmol of CF_3COOH, 6 mmol of alkyl iodide, 0.6 mmol of Cu powder, and 0.06 mmol of $Cu(OAc)_2$ in 10 mL of Me_2SO at 40 °C. The solution is then diluted with 30 mL of water, made basic with 10% NaOH solution, extracted with ethyl acetate, and analyzed by GLC as with benzoyl peroxide.

The same procedure was utilized by using 3.5 mmol of $FeSO_4$ instead of Cu + $Cu(OAc)_2$, *t*-BuI, which is not stable in Me_2SO, was dropped simultaneously with the diazonium salt in the reaction mixture. The results are reported in Table III.

Alkylation of Heteroaromatic Bases by Benzoyl Peroxide and Several Solvents. General Procedure. A solution of 4 mmol of the heteroaromatic base, benzoyl peroxide (in the amount reported in Table IV), 10 mmol of CF_3COOH in 50 mL of the solvent reported in Table IV was refluxed untill complete decomposition of the peroxide (with DMF the temperature was kept at 85 °C). Cycloalkanes, which are poor solvents of the reagents, are used with equal volumes of $CHCl_3$ and MeCN. The solution was then diluted with water, made basic with 10% NaOH solution, extracted with ethyl acetate, and analyzed by GLC. All the reaction products have been previously prepared by us by different methods[1,19-21] and identified by comparison with authentic samples, with the exception of the product from lepidine and ethyl acetate. This product has been identified by NMR and MS as arising from the substitution of the position 2 of lepidine by the radical $MeCOO\dot{C}HMe$. MS: m/e 229 (M^+), 186 (M^+ – MeCO), 170 (M^+ – MeCOO), 143. NMR: δ 1.6 (3 H, d, MeCH), 2.1 (3 H, s, MeCO); 2.7 (3 H, s, Me in position 4), 6.0 (1 H, q, CHMe), 7.2 (1 H, s, aromatic in position 3), 7.5–8.2 (m, 4 H aromatic).

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Registry No. Cl_2, 7782-50-5; Hz, 1333-74-0; I_2, 7553-56-2; $Ph^{\bullet}$, 2396-01-2; CCl_4, 56-23-5; $PhCO_2COPh$, 94-36-0; $PhN_2^+BF_4^-$, 369-57-3; ICH_2CO_2Et, 623-48-3; $PhCH_2CO_2Et$, 101-97-3; *p*-$ClC_6H_4N_2^+BF_4^-$, 673-41-6; Cu^+, 17493-86-6; Fe^{2+}, 15438-31-0; Cu^{2+}, 15158-11-9; *i*-PrI, 75-30-9; *c*-$C_6H_{11}I$, 626-62-0; BuI, 542-69-8; *t*-BuI, 558-17-8; *i*-BuI, 513-38-2; EtI, 75-03-6; $MeCHI(CH_2)_2Me$, 637-97-8; $I(CH_2)_2CO_2Et$, 6414-69-3; *c*-C_6H_{12}, 110-82-7; *c*-C_8H_{16}, 292-64-8; MeOH, 67-56-1; EtOH, 67-63-0; $OHCNMe_2$, 68-12-2; $MeCO_2Et$, 141-78-6; $Me_2NCO^{\bullet}$, 23686-93-3; 4-cyanopyridine, 100-48-1; 4-cyanopyridine conjugate acid, 37449-63-1; 4-chloropyridine, 626-61-9; 4-chloropyridine conjugate acid, 37449-65-3; pyridine, 110-86-1; pyridine conjugate acid, 16969-45-2; 4-methylpyridine, 108-89-4; 4-methylpyridine conjugate acid, 16950-21-3; 4-methoxypyridine, 620-08-6; 4-methoxypyridine conjugate acid, 33613-95-5; quinoline, 91-22-5; lepidine, 491-35-0; isoquinoline, 119-65-3; quinaldine, 91-63-4; acridine, 260-94-6; benzothiazole, 95-16-9; 2-iodocyclohexanol, 28141-32-4; dioxane, 123-91-1; tetrahydrofuran, 109-99-9; 4-(1-methylethyl)quinoline, 17507-25-4; 4-cyclohexylquinoline, 33357-38-9; 2-cyclohexyllepidine, 56947-80-9; 2-butyllepidine, 30980-47-3; 2-(1,1-dimethylethyl)lepidine, 97691-25-3; 2-cyclohexylquinoline, 1613-43-0; 1-cyclohexylisoquinoline, 33538-11-3; 2-(1-methylethyl)-4-cyanopyridine, 33538-10-2; 2,6-bis(1-methylethyl)-4-cyanopyridine, 33538-08-8; 2-butyl-4-cyanopyridine, 72679-69-7; 2,6-dibutyl-4-cyanopyridine, 72679-70-0; 2-(2-methylpropyl)-4-cyanopyridine, 99067-83-1; 2,6-bis(2-methylpropyl)-4-cyanopyridine, 104293-29-0; 1-ethylisoquinoline, 7661-60-1; 4-cyclohexylquinaldine, 37597-46-9; 4-butylquinaldine, 37520-55-1; 4-(2-methylpropyl)quinaldine, 104293-30-3; 2-(1-methylethyl)lepidine, 91879-71-9; 2-(1-methylbutyl)lepidine, 93845-95-5; 2-(2-hydroxycyclohex-1-yl)-lepidine, 93845-93-3; 3-(2-lepidinyl)propanoic acid ethyl ester, 93845-94-4; 9-cyclohexylacridine, 35242-12-7; 2-(1-methylethyl)-benzothiazole, 17626-86-7; 4-cyclooctylquinaldine, 104293-31-4; 2-cyclohexyl-4-cyanopyridine, 40114-95-2; 2,6-dicyclohexyl-4-cyanopyridine, 83001-42-7; 2-cyclooctyl-4-cyanopyridine, 40114-96-3; 2,6-dicyclooctyl-4-cyanopyridine, 104293-32-5; 2-dioxanyl-4-cyanopyridine, 33787-71-2; 2,6-didioxanyl-4-cyanopyridine, 33787-72-3; 2-(tetrahydrofuran-2-yl)-4-cyanopyridine, 104293-33-6; 2,6-bis(tetrahydrofuran-2-yl)-4-cyanopyridine, 104293-34-7; 2-(tetrahydrofuran-2-yl)lepidine, 87991-96-6; 2-dioxanyllepidine, 33787-74-5; 2-dioxanylquinaldine, 33787-73-4; 2-(tetrahydrofuran-2-yl)quinaldine, 104293-35-8; 2-(hydroxymethyl)lepidine, 33787-85-8; 2-(1-hydroxyethyl)lepidine, 41412-35-5; *N*-methyl-*N*-(2-lepidinylmethyl)formamide, 30721-99-4; 2-(1-(acetyloxy)-ethyl)lepidine, 104293-36-9; 2-tetrahydrofuran free radical, 19426-60-9.

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