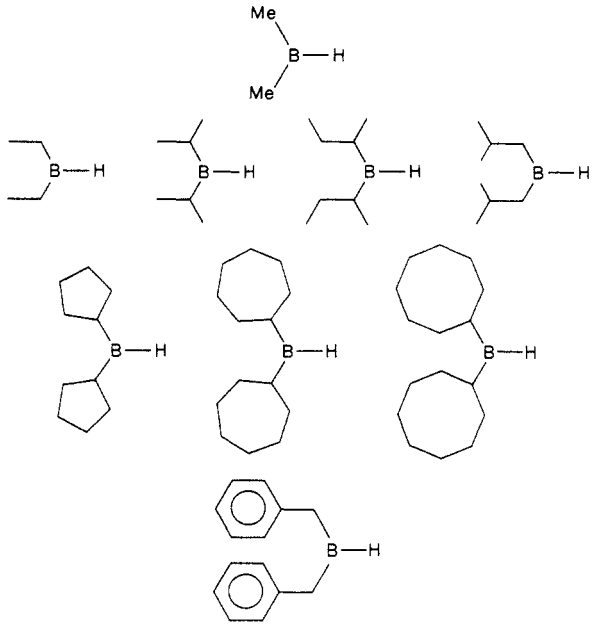
Chart I



mediates for dialkylboranes, the present procedure provides, for the first time, a general and convenient access to a wide variety of highly desirable dialkylboranes (such as shown in Chart I).

Experimental Section

General. All of the manipulations involving air-sensitive substances were carried out under nitrogen according to standard procedures.[4] The ^{11}B NMR spectra of all compounds were recorded on a Varian FT-80A spectrometer. All hydride analyses were performed on the gasimeter.[4]

Materials. Tri-*sec*-butylborane and tricyclopentylborane were prepared by the hydroboration of *cis*-2-butene and cyclopentene with BH_3·SMe_2 in THF.[4] All other triorganylboranes used in the above procedure were made via our modified organometallic route.[13] Anhydrous ethyl ether from Mallinckrodt (+99.9%) was directly used in all of the experiments. $LiAlH_4$ was purchased from Alfa. A glycerol-water-THF (1:1:1) mixture was used as the hydrolysis solution for the hydride estimation of the lithium dialkylborohydrides.

General Procedure for the Preparation of LiR_2BH_2. The following procedure for the preparation of lithium diisopropylborohydride is representative.

To a well-stirred solution of triisopropylborane[13] (14.0 g, 100 mmol) in anhydrous ether (100 mL) was added $LiAlH_4$ in EE (100 mL, 1.0 M, 100 mmol) dropwise at 25 °C over a period of 0.5 h. The resulting homogeneous mixture was stirred for an additional 15 min and cooled to 0 °C, and then a solution of triethylenediamine in EE (100 mL, 0.5 M, 50 mmol) was slowly added to it. A white precipitate of bis(monoisopropylalane)-triethylenediamine was instantly thrown out of solution. The reaction mixture was stirred vigorously at 25 °C for 15 min and then allowed to settle overnight. The clear supernatant ether layer was then transferred into another flask and the precipitate was washed with anhydrous ether (2 × 50 mL). The washings were once again transferred into the other flask. The ^{11}B NMR analysis of the ethereal solution confirmed the formation of $Li(i\text{-}Pr)_2BH_2$ (δ −7.6, t, J = 62 Hz), while hydride analysis established its yield to be 99%.

Preparation of $LiMe_2BH_2$. Me_3B was first prepared directly from a mixture of methyl iodide, Mg turnings, and BF_3·OEt_2 according to our modified organometallic method[13] and collected as a gas into anhydrous ether at 0 °C. Subsequently, $LiAlH_4$ in EE (100 mL, 1.0 M, 100 mmol) which was initially cooled to 0 °C was added dropwise while stirring the solution. The reaction mixture was thus stirred for 15 min at 0 °C and then a cooled solution of triethylenediamine in EE (100 mL, 0.5 M, 100 mmol) was slowly added to it. A voluminous white precipitate of bis(monomethylalane)-triethylenediamine was instantly thrown out of solution. The reaction mixture was vigorously stirred for 15 min at 0 °C and then allowed to settle overnight at room temperature. The supernatant ether layer was transferred into another flask and the precipitate was thoroughly washed with ether (2 × 50 mL). The washings were next combined with the ethereal solution already separated into another flask. Once again, the ^{11}B NMR analysis of the ethereal solution confirmed the formation of $LiMe_2BH_2$ (δ −21.8, t, J = 64 Hz) while its yield was established to be 85% by the hydride analysis.

Acknowledgment. We thank the National Science Foundation (Grant CHE 8414171) for the financial support of this research.

Polar Effects in Free-Radical Reactions. Solvent and Isotope Effects and Effects of Base Catalysis on the Regio- and Chemoselectivity of the Substitution of Protonated Heteroaromatic Bases by Nucleophilic Carbon-Centered Radicals

Francesco Minisci,* Elena Vismara,* Francesca Fontana, Giampiero Morini, and Marco Serravalle

Dipartimento di Chimica del Politecnico, 20133 Milano, Italy

Claudio Giordano

Zambon Chimica S.p.A., Cormano (MI), Italy

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The substitutions of protonated pyridine, quinaldine, lepidine, and 3-cyano- and 4-cyanopyridine by Ph, Me, *n*-Pr, *n*-Bu, *i*-Pr, *t*-Bu, α-tetrahydrofuranyl (α-THF), dioxanyl, and benzyl radicals are affected by the nature of the solvent as concerns the regioselectivity and the relative rates. The isotope effect is negligible with the phenyl radical, but it is significant and solvent-dependent with isopropyl and α-THF radicals. The effect of the solvent increases by increasing the nucleophilic character of the carbon-centered radicals. The results support a strong influence of the reversibility and of the polar effect on the substitutions of protonated heteroaromatic bases by nucleophilic carbon-centered radicals.

Few cases are known[1] where solvents do have a significant effect on the rates and selectivity of free-radical reactions.

The best known and striking example of solvent effect

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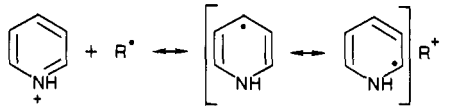
in free-radical reactions is in the chlorine atom reactions, where selectivity is markedly increased by aromatic solvents, CS_2, and SO_2. Perhaps it is not strictly correct to consider these as examples of true solvent effects, at least in the classical sense given to the solvent effect in ionic reactions. Thus, according to the original suggestion of Russell,[2] the subsequent confirmation of Walling and Mayahi,[3] and the recent kinetic support of Bunce et al.,[4] chlorine atom reacts very fast with benzene at room temperature (6×10^9 M^{-1} s^{-1}) to form a defined new radical species, identified as the $C_6H_6Cl^{\bullet}$ π-complex, which has rate and selectivity different from those of the "free" chlorine atom. Within a large range of concentrations, two well-distinct radical species in equilibrium, the "free" chlorine and the π-complex, are simultaneously present and account for the selectivity of hydrogen abstraction.[4] Thus, the π-complex can be considered more an intermediate radical than a solvated species. In this sense a true significant solvent effect has been observed in the competition between β-scission and H abstraction of *tert*-butoxy radical, which has been shown to be quite solvent-dependent, with β-scission favored by π-electron systems and hydrogen-bonding solvents.[5]

From a general point of view, the solvent effects could be significant when polar effects and charged species are involved in free-radical reactions, because polar transition states are involved. The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is a general reaction of high synthetic value in that it reproduces most of the numerous aspects of the aromatic Friedel–Crafts substitution, but with opposite reactivity and selectivity.[6] The great synthetic interest is related to the high regio- and chemoselectivity, which are due mainly to very large polar effects, with transition states similar to charge-transfer complexes (eq 1). Thus, the



(1)

substitution occurs exclusively in the α and γ positions of the protonated heterocyclic ring,[6] and, for example, protonated 4-cyanopyridine reacts very fast with *tert*-butyl radical (a rate constant $>10^7$ M^{-1} s^{-1}),[7] whereas the reaction of benzene with the same radical is much slower (a rate constant $\sim$ 1–10 M^{-1} s^{-1}).[8]

These high regio- and chemoselectivities were ascribed to polar effects.[6] It was therefore of interest to investigate the effect of the solvents on the reactivity and selectivity of these reactions.

In this paper we report a new significant solvent effect in the substitution of protonated pyridine derivatives with several nucleophilic carbon-centered radicals, which remarkably affects the regio- and chemoselectivity. Moreover, the phenomenon appears to be general for the substitution of protonated heteroaromatic bases with nucleophilic radicals.

Table I. Solvent Effect on the Regioselectivity of the α- and γ-Positions in the Substitution of Protonated Pyridine

radical	solvent	procedure	% α	% γ
Ph[a]	water	a	63.8	31.9
Ph[a]	benzene	b	70.2	23.8
Me	water	a	62.3	37.7
Me	water	c	62.5	37.5
Me	benzene	c	73.2	26.7
n-Pr	water	a	57.6	42.4
n-Bu	water	a	56.3	43.7
n-Bu	MeCN	d	64.5	35.5
n-Bu	benzene	d	74.6	25.4
n-Bu	benzene	e	73.8	26.2
i-Pr	water	a	31.7	68.3
i-Pr	Me_2SO	i	46.1	53.9
i-Pr	MeCN	d	56.3	43.7
i-Pr	MeCN–H_2O (4:1)	a	32.0	68.0
i-Pr	$HCONH_2$	a	43.8	56.2
i-Pr	MeCONHMe	a	59.3	40.7
i-Pr	$MCONMe_2$	a	61.3	38.7
i-Pr	benzene	d	72.1	27.9
i-Pr	benzene	e	72.8	27.2
t-Bu	water	a	23.0	77.0
t-Bu	benzene	e	71.4	28.6
α-THF	THF–H_2O (1:1)	f	20.0	80.0
α-THF	THF	g	85.8	14.2
dioxanyl	dioxane–H_2O (1:1)	f	25.5	74.5
dioxanyl	dioxane	g	76.3	23.4
benzyl[b]			no reaction	

[a] Small amounts (4–6%) of the β-isomer were formed. [b] Procedures a, d, e, h, and i in water, benzene, toluene, MeCN, and Me_2SO; bibenzyl is the main reaction product.

Table II. Substitution of Pyridine by α-THF Radical. Solvent and Acidity Effect

solvent	acid (pH)	procedure	*T*, °C	% 2	% 4
THF–H_2O (1:1)	H_2SO_4 (1.2)	f	20	25.0	75.0
THF–H_2O (1:1)	H_2SO_4 (2.8)	f	20	24.7	75.3
THF–H_2O (1:1)	H_2SO_4 (4.6)	f	20	40.8	59.2
THF–H_2O (1:1)	H_2SO_4 (1.2)	f	65	20.2	79.8
THF–H_2O (1:1)	CF_3COOH[a]	f	20	26.7	73.3
THF–H_2O (1:1)	CH_3COOH[a]	f	20	33.9	66.1
THF–H_2O (1:1)	no acid			no reaction	
THF	CF_3COOH[a]	g	65	85.8	14.2
THF–MeCN (1:1)	CF_3COOH[a]	g	72	87.0	13.0
THF–MeCN (1:1)	$MeSO_3H$[a]	g	72	52.6	47.4
THF–MeCN (1:1)	no acid			no reaction	

[a] Ratio, acid: pyridine, 2:1.

Results

Several sources of carbon-centered radicals, previously utilized by us[6] for the heteroaromatic substitution, have been used: (a) silver-catalyzed oxidative decarboxylation of carboxylic acids by peroxydisulfate for Ph•, Me•, *n*-Pr•, *n*-Bu•, *i*-Pr•, *t*-Bu•, and $PhCH_2$• in water; (b) thermal decomposition of benzoyl peroxide for Ph• in benzene; (c) Fe(II)-catalyzed decomposition of *t*-BuOOH for Me• in benzene or water; (d) thermal decomposition of benzoyl peroxide and alkyl iodides for *n*-Pr•, *n*-Bu•, and *i*-Pr• in benzene and in acetonitrile; (e) silver-catalyzed decarboxylation of carboxylic acids by peroxydicarbonate for *i*-Pr•, *n*-Bu•, and *t*-Bu• in benzene; (f) hydrogen abstraction from THF and dioxane by the redox system *t*-BuOOH/Fe(II) for α-tetrahydrofuranyl (α-THF•) and dioxanyl radicals in water; (g) hydrogen abstraction by benzoyl peroxide from THF and dioxane for α-THF• in THF and dioxanyl radical in dioxane; (h) hydrogen abstraction from toluene by peroxydicarbonate for $PhCH_2$•; (i) redox decomposition of *p*-chlorobenzenediazonium tetrafluoroborate and isopropyl iodide for *i*-Pr radical in Me_2SO.

Table I summarizes the results of the regioselectivity for the substitution of the α- and γ-positions of the protonated pyridine, whereas the β-position is not attacked with the

(1) Walling, C. *Tetrahedron* **1985**, *41*, 3887.
(2) Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 2977.
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(7) Minisci, F.; Citterio, A.; Franchi, V. *J. Org. Chem.* **1980**, *45*, 4752.
(8) Fisher, H., private communication.

Table III. Effect of the Temperature on the Regioselectivity for the Substitution of Protonated Pyridine

radical	solvent	procedure	T, °C	% 2	% 4
t-Bu	water	a	20	33.5	66.5
t-Bu	water	a	60	28.6	71.4
t-Bu	water	a	100	23.0	77.0
t-Bu	benzene	e	60	71.4	28.6
dioxanyl	dioxane–H_2O (1:1)	f	25	46.0	54.0
dioxanyl	dioxane–H_2O (1:1)	f	100	36.0	63.9
dioxanyl	dioxane	g	100	76.3	23.7
α-THF	THF–H_2O (1:1)	f	20	25.0	75.0
α-THF	THF–H_2O (1:1)	f	65	20.2	79.9
α-THF	THF	g	65	85.8	14.2

Table IV. Relative Rates in the Alkylation of 4-Cyanopyridine and Lepidine

radical	solvent	procedure	T, °C	acid (molar ratio, acid:bases)	rel rates[a] (4-cyanopyridine: lepidine)
t-Bu	water	a	80	H_2SO_4 (1:1)	>100
t-Bu	water	a	80	CF_3COOH (2:1)	>100
t-Bu	benzene	e	80	CF_3COOH (2:1)	0.28
t-Bu	benzene	e	80	CF_3COOH (4:1)	1.53
$PhCH_2$	water	a	80	CF_3COOH (2:1)	>100
$PhCH_2$	toluene	h	80	CF_3COOH (2:1)	0.68
α-THF	THF–H_2O (1:1)	f	65	CF_3COOH (2:1)	1.82
α-THF	THF	g	65	CF_3COOH (2:1)	<0.01

[a] Corrections for two reactive positions (2 and 6) of 4-cyanopyridine and one position (2) of lepidine have been introduced.

Table V. Isomer Distribution in the Alkylation of Protonated 3-Cyanopyridine

radical	solvent	procedure	isomer distribution % 2	% 4	% 6
t-Bu	water	a	tr[a]	tr	95
t-Bu	benzene	e	tr	tr	95
$PhCH_2$	water	a	13	36	51
$PhCH_2$	toluene	h	43	tr	57
α-THF	THF–H_2O (1:1)	f	15	tr	85
α-THF	THF	g	40	tr	60

[a] tr = traces.

exception of the phenyl radical. The conversions have been kept lower than 30% in order to minimize the formation of disubstituted derivatives. The effects of the acidity and of the solvent on the regioselectivity for α-THF• are reported in Table II.

In Table III, the effect of the temperature on the regioselectivity for t-Bu, dioxanyl, and α-THF radicals is shown. The relative rates of lepidine and 4-cyanopyridine with t-Bu•, $PhCH_2$•, and α-THF• in various solvents are summarized in Table IV. The regioselectivity and the relative rates of 3- and 4-cyanopyridine are reported in Table V and VI. The relative rates between lepidine and quinaldine are summarized in Table VII. The deuterium isotope effect with phenyl, isopropyl, and α-THF radicals in water, benzene, and THF has been evaluated in competitive experiments between pyridine and deuteriated pyridine. The analysis by capillary GLC associated with mass spectrometry did not give reliable results because the separation of deuteriated from nondeuteriated isomers was incomplete. It has been more convenient to isolate the α- and γ-isomers (as mixtures of deuteriated and non-deuteriated) by silica gel chromatography and to analyze the mixtures by mass spectrometry. The results are summarized in Table VIII.

Table VI. Relative Rates in the Alkylation of Position 6 of 3-Cyanopyridine and Position 2 of 4-Cyanopyridine

radical	solvent	procedure	rel rates (3-cyano:4-cyano)
t-Bu	water	a	2.3
t-Bu	benzene	e	1.5
$PhCH_2$	water	a	1.8
$PhCH_2$	toluene	h	1.7
α-THF	THF–H_2O (1:1)	f	2.8
α-THF	THF	g	1.7

Table VII. Relative Rates in the Alkylation of Quinaldine and Lepidine

radical	solvent	procedure	rel rates (quinaldine: lepidine)
i-Pr	water	a	1.5
i-Pr	benzene	d	0.9
t-Bu	water	a	<0.01
t-Bu	benzene	e	<0.01
$PhCH_2$	water	a	6.7
$PhCH_2$	toluene	h	1.7
α-THF	THF–H_2O (1:1)	f	5.8
α-THF	THF	g	1.2

Discussion

The results of Tables I–VII show a new example of large solvent effects in free-radical reactions, which affect the regio- and chemoselectivity of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals.

Regioselectivity in the Substitution of Protonated Pyridine. The following facts emerge from the results of Tables I–III.

i. Only the α- and γ-positions of protonated pyridine are attacked, with the exception of the phenyl radical, which attacks also the β-position in small amounts (4–6%).

ii. The regioselectivity is substantially independent of the radical source, but it depends mainly on the solvent and the acidity.

iii. The solvent dependence of the regioselectivity is small with the phenyl, the least nucleophilic, radical, and it progressively increases from methyl to primary, secondary, and tertiary alkyl and α-THF radicals. The dioxanyl radical is less nucleophilic than the α-THF radical because the electron-releasing effect of the α-oxygen atom is in part counterbalanced by the inductive electron-withdrawing effect of the β-oxygen atom, and that is reflected in the solvent effect.

iv. With the most nucleophilic radicals (t-Bu•, α-THF•), no substitution was observed with unprotonated pyridine in all the solvents investigated (water, benzene, acetonitrile, Me_2SO, THF), clearly showing that the protonated base is involved in the substitution. On the other hand, we have previously established that the addition rate of primary alkyl radicals to the protonated pyridine is 10^3 higher than the addition to the unprotonated base.[9] Thus, also with primary alkyl radicals in the presence of an equilibrium between protonated and unprotonated pyridines, the protonated form is substantially involved if the equilibrium of protonation is not too unfavorable.

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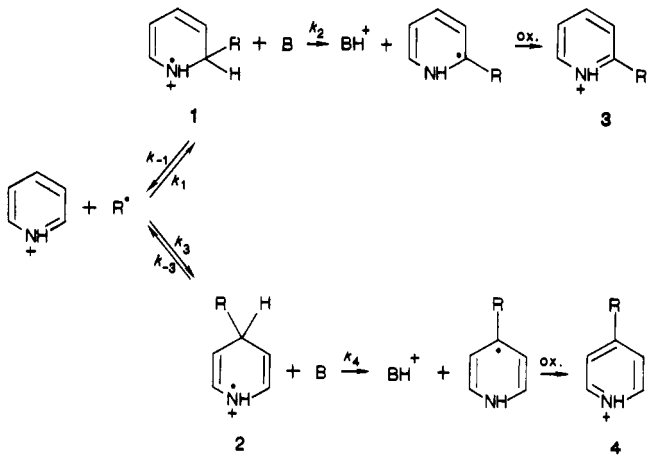
Table VIII. Deuterium Isotope Effect in the Substitution of Protonated Pyridine

radical	solvent	procedure	acid[a]	isomer distribution Py(H) % α	Py(H) % γ	Py(D) % α	Py(D) % γ	k_H/k_D α	k_H/k_D γ
Ph[b]	water	a	H_2SO_4	63.8	31.9	63.8	31.9	1.0	1.0
Ph[b]	water	a	CF_3COOH	63.6	31.8	63.4	31.7	1.0	1.0
Ph[b]	benzene	b	CF_3COOH	70.2	23.8	70.3	23.7	1.0	1.0
i-Pr	water	a	H_2SO_4	31.8	68.2	29.4	70.6	3.8	4.1
i-Pr	water	a	CF_3COOH	31.4	68.6	29.6	70.4	3.9	4.2
i-Pr	benzene	d	CF_3COOH	72.0	28.0	76.6	23.4	1.7	1.9
α-THF	THF–H_2O (1:1)	f	H_2SO_4	23.2	76.8	21.3	78.7	7.7	6.6
α-THF	THF	g	CF_3COOH	75.5	25.0	76.5	23.5	2.5	2.3
α-THF	THF–MeCN (1:1)	g	CF_3COOH	85.9	14.1	83.4	16.6	3.7	2.8
α-THF	THF–MeCN (1:1)	g	$MeSO_3H$	52.6	47.4	50.1	49.9	4.5	3.5

[a] Two equivalents of acid per mole of pyridine. [b] Small amounts (4–6%) of the β-isomer were formed.

Scheme I



v. With the benzyl radical, no substitution was observed in all the solvents with both protonated and unprotonated pyridine, but bibenzyl was the only reaction product.

Now the increased nucleophilic character of the radicals of Table I is associated with an increased stability and with a consequent increased possibility of reversibility of the radical addition.

The reversibility is related to the enthalpy of the radical addition: it increases as the addition becomes less exothermic by increasing the stability of the radicals according to the sequence Ph < Me < primary alkyl < secondary alkyl < tertiary alkyl ~ dioxanyl ~ α-THF < benzyl. On the other hand, we have already reported evidence that, with secondary and tertiary alkyl,[7,9] benzyl,[6] and acyl radicals,[10] the addition to a protonated heteroaromatic ring is reversible. Thus, considering the general mechanism we[6] have suggested for the substitution reaction (Scheme I), eq 2 and 3 account for the rates of the α- and γ-positions.

$$k_{\alpha obsd} = \frac{k_1 k_2[B]}{k_{-1} + k_2[B]} \quad (2)$$

$$k_{\gamma obsd} = \frac{k_3 k_4[B]}{k_{-3} + k_4[B]} \quad (3)$$

The dilemma is therefore the following: can the solvent effect be mainly related to the nucleophilicity of the radical (different values of k_1 and k_3 in different solvents as a consequence of the positively charged species involved and of the solvation of polar transition states (eq 1)) or to the reversibility of the addition, reflected by the values of $k_{-1}/k_2[B]$ and $k_{-3}/k_4[B]$ in different solvents?

The substitutions, which are subject to base catalysis, also exhibit a H/D kinetic isotope effect when the hydrogen atom at the point of attack is isotopically replaced; this is to be expected for reactions in which hydrogen transfer is kinetically important. In particular, k_2 and k_4 are sensitive to the isotopic composition of the substrate, whereas k_1 (k_{-1}) and k_3 (k_{-3}) are effectively independent of it. Consequently, an increase in the partition factors, $k_{-1}/k_2[B]$ and $k_{-3}/k_4[B]$, moving the kinetic control toward the second step, increases both the sensitivity of the reaction to base catalysis and the magnitude of the kinetic isotope effect.

Thus, in an attempt to recognize the step in which the solvent effect is working, the deuterium kinetic isotope effect has been determined with phenyl, isopropyl, and α-THF radicals in various reaction media (Table VIII). With phenyl radical, no isotope effect has been observed, indicating that the first step of the mechanism of Scheme I is rate-determining: $k_{-1} << k_2[B]$ and $k_{-3} << k_4[B]$, the terms in [B] fall out; $k_{obsd} = k_1$ or k_3, and the addition to the pyridine ring is substantially irreversible.[11]

The behavior of the benzyl radical must be probably ascribed at the other extreme, when $k_{-1} >> k_2[B]$ and $k_{-3} >> k_4[B]$; the lower addition enthalpy determines in this case higher values of k_{-1} and k_{-3}, allowing achievement of a steady-state concentration of the benzyl radical suitable for irreversible dimerization, which is characterized by a diffusion-controlled rate, and no substitution product is observed.

With isopropyl and α-THF radicals, a significant isotope effect has been observed for the α- and γ-positions, indicating that the C–H bond is broken in a rate-determining step. Since also isopropyl and α-THF radicals dimerize with diffusion-controlled rates, the results suggest that the terms k_{-1} and k_{-3} are in these cases comparable, respectively, to $k_2[B]$ and $k_4[B]$ and the rate depends on [B] in a nonlinear way. Under nonlinear catalysis, small changes in the reacting system can have large effects on the kinetics. That appears to be the case: both the isotope effect and the regioselectivity are considerably affected by the reaction medium. The solvent and the acidity have in fact a large influence on the regioselectivity and on the isotope effect because they affect the base catalysis and the terms $k_2[B]$ and $k_4[B]$ of the kinetic equations 2 and 3. Thus, a possible explanation is that the solvent and the base catalysis mainly influence the reversibility of the radical addition, which is higher in water than in benzene or THF, contrary to what we have previously hypothesized for the benzylation of quinoline.[6] It appears that the poorly solvated radical ion pair in benzene (eq 4) irreversibly loses

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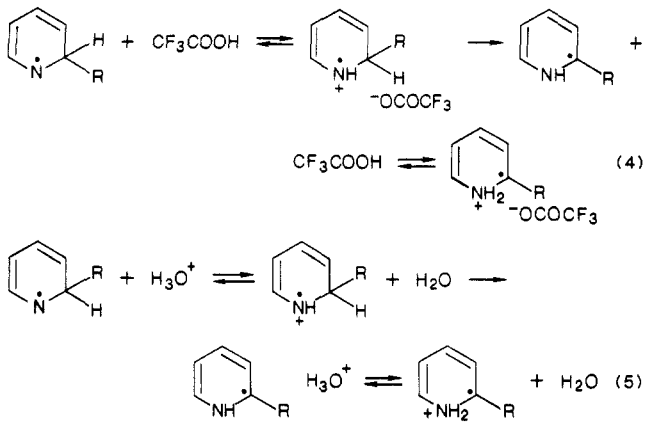
the proton from the C–H bond faster than the solvated radical ion in water (eq 5). If we assume that an increased



(4)

(5)

isotope effect reflects an increased reversibility of the radical addition and that the reversibility is higher for the adduct 1 than for the adduct 2, the increasing amount of the isomer 4 with the increasing stability of the nucleophilic radical would be justified in water, where the isotope effect is higher. The effect of the temperature actually supports a marked influence of the reversibility on the regioselectivity in water (Table III): an increase of the temperature increases the amount of the γ-isomer. Similarly, the increase of the acidity, decreasing the base catalysis, increases the amount of the γ-isomer (Table II).

However, the influence of the solvent and of the acidity on the terms k_2[B] and k_4[B] would not appear to be the only factor affecting the regioselectivity of the substitution. A smaller, but significant, solvent effect occurs also with the phenyl radical, for which no isotope effect was observed, and the addition has all the features of irreversibility: in aqueous solution, a statistical isomer distribution occurs in the α- and γ-positions of pyridine whereas, in benzene solution, the α-position is somewhat more reactive than the γ-position; the β-position is attacked only a small amount (4–6%) in both cases.

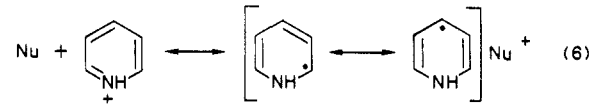
Moreover, in benzene solution, the regioselectivity is not substantially affected by the nature of the radical, even when the isotope effect is still significant, indicating some degree of reversibility, and when the differences of the reaction enthalpies are considerable (the addition enthalpies increase in the series tertiary alkyl < secondary alkyl < primary alkyl < Me < Ph radicals). The regioselectivity is similar also with dioxanyl radical in dioxane and α-THF radical in THF, although the isotope effect is still significant. In water solution, all the other conditions being equal (in particular, with the same base catalysis), the regioselectivity is strongly affected by the nature of the radical, the attack of the γ-position increasing by increasing the nucleophilic character and the stability of the radical. In acetonitrile and Me_2SO, a behavior intermediate between those for water and benzene was observed.

It would appear that, in addition to the influence of the base catalysis and the reversibility, also the solvation of polar transition states (eq 1) plays a role in determining the regioselectivity in the most polar solvents. The contribution of the polar forms of eq 1 to the transition states must increase as the ionization potentials of the carbon-centered radicals and the enthalpies of the addition reactions decrease. Both these factors increase the contribution of polar forms to the transition states according to the following sequence: Ph < Me < primary alkyl < secondary alkyl < tertary alkyl < THF radicals. It is the same sequence observed for the γ/α isomer ratio in the substitution of pyridine in water.

An explanation could be related to the hypothesis, recently put forward by us,[6] that the HSAB (hard and soft acids and bases) principle can be extended to free-radical reactions when the polar effect is the dominant factor, in the sense that the softness of a nucleophilic radical generally increases by decreasing the ionization potential (similarly, the softness of the ionic nucleophiles increases by decreasing the ionization potentials, which are roughly the energies of the HOMOs).

Now it is known[6] that with ionic soft nucleophiles (i.e., CN^-) the pyridinium salt undergoes 4-substitution and 2-substitution with hard nucleophiles (i.e., OH^-) because position 2 is harder than position 4. Similarly, the increased softness of the carbon-centered radicals would determine the increased attack of position 4 in polar solvents.

The similarity of behavior between nucleophilic free-radicals and ionic nucleophilic species could be related to a contribution of charge-transfer character to the transition states in both reactions (eq 1 for nucleophilic free radicals and eq 6 for ionic nucleophiles).



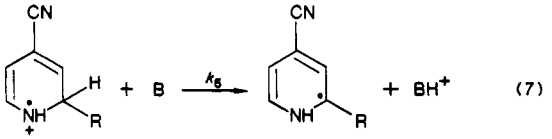
(6)

From a synthetic point of view, the results are interesting with the most nucleophilic radicals because it is possible to obtain in large prevalence the α- or γ-isomer, depending on the solvent utilized.

Chemo- and Regioselectivity with Protonated Lepidine, Quinaldine, and 3- and 4-Cyanopyridine. The solvent effect appears to be a general phenomenon in the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals. It has been qualitatively observed in the regioselectivity of other substrates with two nonequivalent positions of high nucleophilic reactivitiy (quinoline, pyrimidine, pyridazine) and also in the chemoselectivity between different substrates. A quantitative investigation has been carried out with lepidine, quinaldine, and 3- and 4-cyanopyridine and the most nucleophilic radicals of the series (t-Bu$^\bullet$, α-THF$^\bullet$, and $PhCH_2^\bullet$). With all these bases, the substitution occurs also with the benzyl radical because the corresponding rate constants of eq 2 and 3 are favorably influenced: k_1 and k_3 increase for polar and enthalpic reasons, k_{-1} and k_{-3} decrease mainly for the higher exothermicity of the addition, and k_2 and k_4 increase for the higher acidity of the C–H bonds involved compared with those in pyridine. Thus, in all cases, bibenzyl and the products a heterocyclic benzylation are obtained. With t-Bu$^\bullet$, α-THF$^\bullet$, and $PhCH_2^\bullet$, no substitution occurs in the absence of acids. Lepidine, quinaldine, and 4-cyanopyridine give a single monosubstituted product, and no problem of regioselectivity is involved. 3-Cyanopyridine has three nonequivalent positions of high nucleophilic reactivity (2, 4, and 6), and the regioselectivity is also in this case strongly influenced by the solvent with $PhCH_2^\bullet$ and α-THF$^\bullet$ (Table V), whereas with t-Bu radical only position 6 is substantially attacked, for steric reasons. The substitution is exceptionally sensitive to steric effects, so that protonated quinaldine does not react with t-Bu$^\bullet$ under conditions in which lepidine is highly reactive. Thus, the hydrogen atom in position 5 of quinaldine sterically prevents the addition of t-Bu to position 4. The steric nature of this effect is clearly shown by the fact that, with protonated pyridine under the same conditions, position 4 is more reactive than position 2 toward t-Bu$^\bullet$ (Table I). The relative rates, determined by the competitive method, between lepidine

and 4-cyanopyridine are dramatically influenced by the solvent (Table IV).

Only 4-cyanopyridine reacts in aqueous solution, whereas the substitution of lepidine is negligible with *t*-Bu and $PhCH_2$ radicals. In benzene or toluene solution, the substitution of lepidine prevails over the substitution of 4-cyanopyridine, unless a large excess of CF_3COOH, which obviously also changes the nature of the solvent, is utilized. Certainly the different equilibria of protonation (4-cyanopyridine is less basic than lepidine) are an unfavorable factor for the alkylation of 4-cyanopyridine in benzene and toluene. The fact, however, that also with a large excess of acid in benzene the relative rates are quite different from those obtained in aqueous solution suggests that other factors must by significant. These factors can be the same discussed for the regioselectivity of pyridine: the reversibility and the solvation of polar transition states, both influencing in water more the alkylation of 4-cyanopyridine, which has higher electron deficiency, than the alkylation of lepidine. The higher acidity of the α-C–H bond makes less reversible the radical addition to 4-cyanopyridine in water (eq 7) (higher value of k_5 compared with the corresponding rate constant for lepidine).



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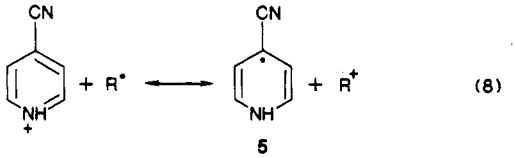
Moreover, the solvation of a more polar transition state (eq 8) could contribute to determining a higher reactivity of 4-cyanopyridine in water. In the particular case of eq



(8)

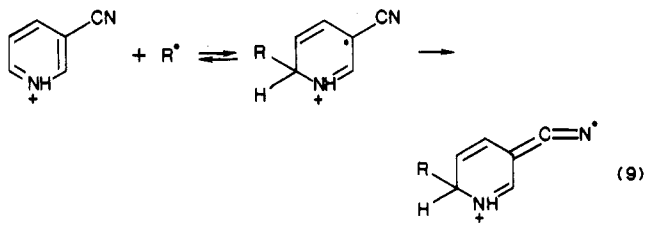
5

8, the polar effect should be favored by the captodative character of structure **5**. The relative rates in the addition of the THF radical to 4-cyanopyridine and lepidine have a similar trend. In THF, the attack on lepidine strongly prevails, and in water–THF (1:1), the attack on 4-cyanopyridine is somewhat prevailing. The results of Table VII show that the effect of the solvent on the relative rates is remarkable also with substrates of quite similar basicity (lepidine and quinaldine), where the protonation equilibria cannot be a discriminating factor. The effect is significant with *i*-Pr radical and becomes much more considerable with the more nucleophilic α-THF and benzyl radicals; with *t*-Bu radical, quinaldine does not react for steric reasons.

The effect of the solvent on the relative rates is small with 3- and 4-cyanopyridine. In all cases, position 6 of the 3-cyano compound is slightly more reactive than position 2 of the 4-cyano compound. These two positions are sterically equivalent, but the cyano group is, respectively, in meta and para position to the radical attack. The contribution of a captodative effect (eq 8) in the transition state for the 4-cyano compound could be counterbalanced by the lower reversibility of the adduct of the 3-cyano compound, stabilized by conjugation (eq 9).

Conclusions

The regio- and chemoselectivity of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is strongly affected by the nature of the solvent and the base catalysis. The isotope effect em-



(9)

phasizes the importance of the reversibility of the radical addition, but the solvation of polar transition states could contribute to determining the changes of rates and selectivity. Thus, selectivity and relative rates must be considered very carefully when different reaction media are utilized in these reactions, and the rate constants determined by the competitive methods[7,9,10] in which the "radical clock" is an irreversible process must often be considered minimum values.

Experimental Section

GLC analyses were performed with a Carlo Erba 4200 or a Dani 3600 instrument equipped with a flame ionization detector. Use was made of 2-m columns packed with 10% OV-101 on Chromosorb W HP DMCS (80–100 mesh) and 10% Carbowax 20 M on Chromosorb W DMCS.

General Procedures of Substitution of Heteroaromatic Bases. a. Alkylation and Phenylation by Silver-Catalyzed Decarboxylation of Carboxylic Acid by $S_2O_8^{2-}$. A solution (20 mL) of carboxylic acid (0.6 M), heteroaromatic base (0.2 M), H_2SO_4 (0.2 M) (or CF_3COOH, 0.4 M), $(NH_4)_2S_2O_8$ (0.05 M), and $AgNO_3$ (0.01 M) was heated for 4 h at 80 °C. With pivalic acid, the reaction was carried out at the temperatures reported in Table III. The reaction mixture was made basic by 10% NaOH solution and extracted with ether. The extract was analyzed by GLC, and the results are reported in Tables I and III–VIII.

b. Phenylation of Pyridine by Benzoyl Peroxide in Benzene. A benzene solution (20 mL) of pyridine (0.2 M), CF_3COOH (0.4 M), and $(PhCOO)_2$ (0.05 M) was refluxed for 5 h. The benzene solution was washed with 10% NaOH and analyzed by GLC. The results are reported in Tables I and VIII.

c. Methylation of Pyridine by *t*-BuOOH in Benzene or Water. A solution (20 mL) of pyridine (0.2 M), CF_3COOH (0.4 M), *t*-BuOOH (0.1 M), and $Fe(OAc)_3$ (0.04 M) was heated for 6 h at 80 °C. The benzene solution was washed with water and then with 10% NaOH and analyzed by GLC. When the reaction solvent was water, the mixture was made basic by 10% NaOH, extracted with ether, and analyzed by GLC. The results are reported in Table I.

d. Alkylation by Alkyl Iodides and Benzoyl Peroxide in Organic Solvents. A solution (20 mL) of the heteroaromatic base (0.2 M), alkyl iodide (0.2 M), CF_3COOH (0.4 M), and $(PhCOO)_2$ (0.05 M) was heated for 6 h at 80 °C. The reaction solution was made basic with 10% NaOH, extracted with ether, and analyzed by GLC. The results are reported in Tables I, VII, and VIII.

e. Alkylation by Silver-Catalyzed Decarboxylation of Carboxylic Acids by Peroxydicarbonate. A benzene solution (20 mL) of the heteroaromatic base (0.2 M), perkadox (bis(4-*tert*-butylcyclohexylperoxydicarbonate); 0.1 M), carboxylic acid (0.4 M), CF_3COOH (0.4 M), and $AgNO_3$ (0.02 M) was refluxed for 4 h. The benzene solution was washed with 10% NaOH and analyzed by GLC. The results are reported in Tables I and III–VII.

f. Substitution by Dioxanyl and α-THF Radicals in Water. An aqueous solution (4 mL) of $FeSO_4$ (0.25 M) was dropped with stirring to 20 mL of a solution (dioxane–H_2O, 1:1) of the heteroaromatic base (0.2 M), *t*-BuOOH (0.05 M), and CF_3COOH (0.4 M) (or H_2SO_4, 0.2 M). The reaction mixture was then made basic by a 10% NaOH solution, extracted with ether, and analyzed by GLC. For α-THF•, THF was utilized instead of dioxane. The results are reported in Tables I–VIII.

g. Substitution by Dioxanyl Radical in Dioxane and α-THF Radical in THF. A dioxane or THF solution (20 mL) of heteroaromatic base (0.2 M), benzoyl peroxide (0.05 M), and

CF_3COOH (0.4 M) was warmed for 8 h at 65 °C. The solution was made basic with 10% NaOH, extracted with ether, and analyzed by GLC. The results are reported in Tables I–VIII.

h. Benzylation by Toluene and Perkadox. A toluene solution (20 mL) of heteroaromatic base (0.2 M), perkadox (0.05 M), and CF_3COOH (0.4 M) was heated for 3 h at 70 °C. The solution was washed with 10% NaOH and analyzed by GLC. The results are reported in Tables IV–VI.

i. Isopropylation of Pyridine by *i*-PrI and Diazonium Salt in Me_2SO. A solution of 1.6 mmol of *p*-chlorobenzenediazonium tetrafluoroborate in 3 mL of Me_2SO was added dropwise with stirring over a period of 30 min to a mixture of 35 mmol of heteroaromatic base, 7 mmol of CF_3COOH, 4 mmol of *i*-PrI, 0.5 mmol of Cu powder, and 0.05 mmol of $Cu(OAc)_2$ in 10 mL of Me_2SO at 40 °C. The solution was diluted with 30 mL of water, made basic with 10% NaOH, extracted with EtOAc, and analyzed by GLC. The results are reported in Table I.

All the reaction products have been identified by comparison with authentic samples previously obtained by similar procedures.[6]

Relative Rates. The relative rates shown in Tables IV, VI, and VII were determined by the competitive method, using pairs of heteroaromatic bases according to the procedures reported in the tables and analyzing the reaction products by GLC.

Isotope Effect. The isotope effects shown in Table VIII were determined by the competitive method, using equimolecular amounts of pyridine and deuteriated pyridine according to the procedures reported in the table. The α- and γ-isomers (as mixtures of deuteriated and nondeuteriated derivatives) were isolated by silica gel chromatography (eluent hexane–EtAc, 7:3) and analyzed by mass spectrometry, checking the reliability of the method starting from the known mixtures of the pure isomers obtained from pyridine and deuteriated pyridine.

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Registry No. 2-THF·, 19426-60-9; Ph·, 2396-01-2; Me·, 2229-07-4; *n*-Pr·, 2143-61-5; *i*-Pr·, 2025-55-0; *n*-Bu·, 2492-36-6; *t*-Bu·, 1605-73-8; $PhCH_2$·, 2154-56-5; D_2, 7782-39-0; pyridine conjugate acid, 16969-45-2; quinaldine conjugate acid, 41229-56-5; lepidine conjugate acid, 41229-57-6; 3-cyanopyridine conjugate acid, 53760-43-3; 4-cyanopyridine conjugate acid, 37449-63-1; 1,4-dioxan-2-yl, 4598-47-4.

Carbanions: Electron Transfer vs. Proton Capture. 8. Use of Sterically Protected Aromatic Nitro Compounds as Base-Resistant, One-Electron Oxidants

Robert D. Guthrie,* Christa Hartmann, Richard Neill, and Dale E. Nutter

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

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The behavior of two sterically protected nitroarenes, 2,4,6-tri-*tert*-butylnitrobenzene and 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydro-9-nitroanthracene, was studied in the presence of strong bases. These compounds are resistant to the oxygen-base-promoted reactions observed with nitrobenzene, but they retain the capacity to oxidize carbon bases such as 9-methoxyfluorenide and triphenylmethide ions. Alkyllithium compounds are converted to alkyl radicals but phenyllithium does not react. Unexpectedly, the radical anions formed when these nitro compounds serve as oxidants undergo slow denitration to the corresponding aryl radicals.

Nitroarenes are useful as oxidants in strongly basic media[1,2] because they combine resistance to base and nucleophile attack with ease of one-electron reduction. For nitroarenes unsubstituted in the 2- or 6-positions, strong bases can remove a proton ($A_{xh}D_H$)[3] to produce a nitro-stabilized phenyl anion. Minimal conditions for this reaction to occur with nitrobenzene are potassium *tert*-butoxide in *tert*-butyl alcohol at 50 °C,[4] suggesting a pK_a in the high twenties.[5] While this reaction is usually reversible and nondestructive, a more serious complication arises when the hydrogen-bonding stabilization of *tert*-butyl alcohol is removed. In tetrahydrofuran (THF), potassium *tert*-butoxide at 25 °C, nucleophilic attack at a ring carbon is followed by proton removal to produce a dianion finally giving alkoxy-substituted nitroarene and 2 equiv of radical anion ($A_N + A_{xh}D_H + 2T$).[3,6]

It seemed reasonable that replacement of ring hydrogens, particularly those ortho and para to the nitro group, with nonacidic, bulky alkyl groups would increase the resistance of nitroarenes to attack by bases and nucleophiles. Of course such substituents, when positioned ortho to the nitro group, interfere with the radical-anion stabilizing coplanarity of the $NO_2^{\bullet-}$ group and the aromatic ring. The reduction potential of 2,4,6-tri-*tert*-butylnitrobenzene is $E_{1/2} = -1.50$ V vs. SCE in acetonitrile[7] as compared to nitrobenzene, $E_{1/2} = -1.15$ V[8] under the same conditions.

(1) For a review, see: Guthrie, R. D. In "Comprehensive Carbanion Chemistry", Buncel, E.; Durst, T. Eds.; Elsevier: Amsterdam, 1980, pp 197–269.

(2) Preceding papers in this series are: (a) Guthrie, R. D.; Hrovat, D. A; Prahl, F. G.; Swan, J. *J. Org. Chem.* **1981**, *46*, 498–501. (b) Guthrie, R. D.; Cho, N. S. *J. Am. Chem. Soc.* **1979**, *101*, 4698–4705.

(3) "A" and "D" indicate associative and dissociative processes respectively. "T" indicates electron transfer. "A" and "D" symbols are subscripted in various ways to indicate the apportionment of electrons. "A_N" thus indicates bond formation between a core atom (for a substitution reaction this is the atom at which substitution takes place) and a nucleophile. "D_H" represents bond breaking between a proton and a core atom. "A_{xh}" is bond formation between a proton and a generalized base (x). Lower case subscripts indicate that no core atom is involved in the bond being made or broken. "+" Signs indicate a new (nonconcerted) reaction step ($S_N2 = A_ND_N$, $S_N1 = D_N + A_N$). Commission on Physical Organic Chemistry, IUPAC, Pure and Applied Chemistry, in press. A primitive version of this system was published earlier: Guthrie, R. D. *J. Org. Chem.* **1975**, *40*, 402–407.

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(5) This is a localized anion so the pK_a should be greater in polar, nonhydroxylic medium.

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(7) Geske, D. H.; Ragle, J. L.; Bambenek, M. A.; Blach, A. L. *J. Am. Chem. Soc.* **1964**, *86*, 987–1002.

(8) Maki, A. H.; Geske, D. H. *J. Chem. Phys.* **1960**, *33*, 825–832; *J. Am. Chem. Soc.* **1961**, *83*, 1852–1860.

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