Polar Effects in Free Radical Reactions. Induced Decompositions of Peroxo Compounds in the Substitution of Heteroaromatic Bases by Nucleophilic Radicals

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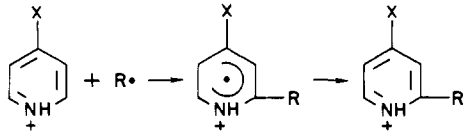
Abstract: The decomposition of benzoyl and lauroyl peroxides and potassium peroxydisulfate in various solvents leads to the selective substitution at position 2 of the protonated lepidine by the nucleophilic free radicals generated in the reactions ($\cdot CH_2OH$, dioxanyl, $\cdot CON(CH_3)_2$, $CHON(CH)_3CH_2\cdot$, $(CH_3)_2\dot{C}H$, cyclohexyl, and $n\text{-}C_{11}H_{23}\cdot$). The remarkable induced decomposition of the peroxides, observed in all cases, is rationalized by the intermediacy of a strongly nucleophilic pyridinyl radical, which undergoes a ready and selective rearomatization and consequently contributes to the great synthetic interest of the homolytic substitution of protonated heteroaromatic bases by nucleophilic free radicals.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered free radicals has recently attracted increasing synthetic and theoretical interest, becoming one of the most important methods for aromatic substitution.[1] Polar effects play a dominant role in determining the reactivity and selectivity[1-3] of these reactions leading sometimes also to the ipsosubstitution.[4]

Another important factor which can strongly affect the success of the substitution is the rearomatization step of the radical adduct **1** (eq 1). In contrast to free radical substitution of carbocyclic



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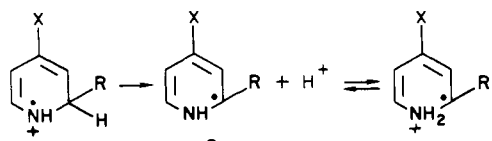
aromatic compounds which often leads to considerable amounts of side products, the reaction with heteroaromatic compounds is very selective with a large variety of radical sources and nucleophilic radicals. The question arises why the rearomatization of the intermediate adduct is not selective in benzene series when the same radical sources and identical reaction conditions are employed as with protonated heteroaromatic bases. A determining factor must be the oxidizability of the radical adduct intermediates, as reflected in the redox or ionization potentials; however, this factor should contribute more to the selectivity of reactions involving the benzene adduct than to those involving the pyridine adduct.

A possible explanation[5] is provided by the irreversible loss of an α-proton of the radical adduct **1** (eq 2) leading to the formation of the pyridinyl radical **2**, which is much more oxidizable than a cyclohexadienyl radical. When peroxides are used as the radical source, such a process should be reflected in a remarkable induced decomposition of the peroxide.



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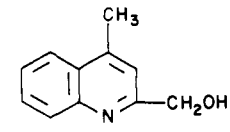
Results

In order to simplify kinetic investigation and product analysis lepidine, which has only one position susceptible to attack by nucleophilic free radicals, has been chosen as a model substrate for this study.

Reactions with Benzoyl Peroxide. The decomposition of benzoyl peroxide in methanol, dioxane, and DMF in the presence of protonated lepidine gives rise to substitution of the hydrogen atom at position 2 by the radicals deriving from hydrogen abstraction from the corresponding solvent molecules leading respectively to compounds **3-6**. DMF gives two products, **5** and **6**. In order



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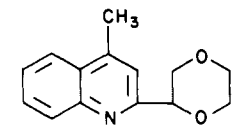

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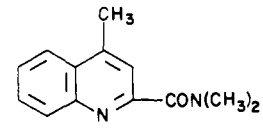

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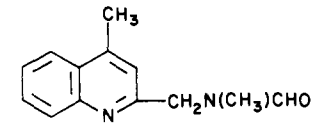

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to check the oxidizability of the intermediate radical and its influence on the relative quantity of compounds **5** and **6**, experiments were carried out in the presence of an increasing amount of Fe(III) salt. It was observed that considerable amounts of *N*-methylformamide are formed by demethylation of DMF at high Fe(III) salt concentration. The results are reported in Table II. It is noteworthy that the reaction involving cyclohexyl iodide is quite selective, giving 2-cyclohexyl-4-methylquinoline (**7**) as the only reaction product of lepidine and substantial amounts of benzoic acid and iodobenzene (Table I). With use of cyclohexane as solvent, compound **7** is the only product derived from lepidine.

The rates of decomposition of benzoyl peroxide in the presence or in the absence of lepidine were determined iodometrically, and the results are summarized in Table III. The reactions in the presence of lepidine are in all cases inhibited by the presence of oxygen.

Reaction with Lauroyl Peroxide. The thermal decomposition of lauroyl peroxide in acetonitrile solution in the presence of

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Table I. Reaction Products for the Substitution of Lepidine with Benzoyl Peroxide in Various Solvents

solvent	reagents, mmol: lepidine	CF_3COOH	benzoyl peroxide	T, °C	time, h	reaction products, mmol: recovered lepidine	substituted lepidine	benzoic acid
methanol (30 mL)	1.26	1.29	1.30	65	32	0.28	0.96 (**3**)	1.31
dioxane (25 mL)	1.08	1.17	1.08	60	18	0.13	0.84 (**4**)	1.02
dimethylformamide (27 mL)	1.10	1.17	1.11	60	24	0.36	0.08 (**5**) 0.55 (**6**)	1.33
cyclohexyl iodide,[a] 15 mmol in 25 mL of acetonitrile	1.15	1.17	1.06	80	9	0.57	0.58 (**7**)	0.94
chloroform (35 mL), cyclohexane (13 mL)	2.10	2.10	1.05	72	10	1.26	0.84 (**7**)	1.18

[a] 0.90 mmol of iodobenzene is also formed.

Table II. Influence of $FeOH(OAc)_2$ Concentration in the **6**:**5** Ratio in the Reaction of Lepidine (1 mmol), Benzoyl Peroxide (1 mol), and CF_3COOH (1 mmol) in Dimethylformamide (25 mL)

$FeOH(OAc)_2$, mmol	% conversion of lepidine	% of **5**	% of **6**	**6**:**5**
0	67	11.1	89.9	8
0.009	41	15.9	84.1	5.3
0.043	33	27.0	73.0	2.7
0.086[a]	27	38.5	61.5	1.6

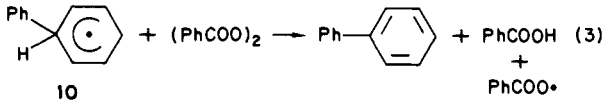
[a] 0.56 mmol of *N*-methylformamide is determined by GLC.

protonated lepidine very cleanly gives 2-undecyl-4-methylquinoline (**8**); substantial amounts of dodecanoic acid are also formed. The results are summarized in Table IV. Also in this case the reaction is inhibited by oxygen.

Reaction with Peroxydisulfate. The thermal decomposition of $K_2S_2O_8$ in the presence of potassium isobutyrate, isobutyric acid, and lepidine provides 2-isopropyl-4-methylquinoline (**9**). The kinetics were followed by the Kolthoff and Carr procedure.[6] The results are summarized in Table V.

Discussion

Benzoyl Peroxide. Benzoyl peroxide is one of the most widely studied sources of phenyl radical used in homolytic aromatic phenylation. Although the induced decomposition (eq 3) is the main cause of the rearomatization of the cyclohexadienyl radical **10**, this reaction step is not sufficiently fast to make this process selective as is observed by the formation of major amounts of dimerization and disporportionation products of the radical **10** when the reaction is performed at initial concentrations of benzoyl peroxide in benzene lower than 0.1 M.[7] The decomposition rate



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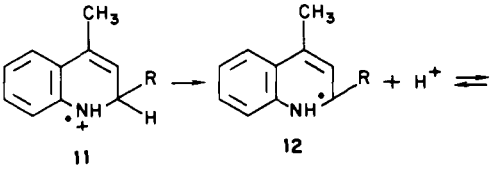
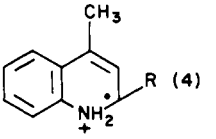
of benzoyl peroxide in solvents, such as methanol, dioxane, and DMF, is also increased by induced decomposition, due to the nucleophilic character of the radicals arising from hydrogen abstraction. However, when the reaction is performed in the presence of protonated lepidine, the radicals deriving from the solvents selectively do attack at position 2 of lepidine (Table I) leading to compounds **3**–**6**. In this process a further increase of the decomposition rate of benzoyl peroxide (Table III) and the formation of, at least, 1 mol of benzoic acid per mol of benzoyl peroxide are observed. This reaction pattern is in contrast with that of homolytic phenylation of benzene in which the amount of benzoic acid formed is always considerably lower and does therefore suggest that the radical adduct of lepidine **11** is rearomatized by an induced decomposition of benzoyl peroxide, which is strictly related to the nucleophilic character of the inducing radical. Thus, to explain kinetics and product results we must admit that the intermediate **11** does not directly react with benzoyl peroxide, but is converted into an extremely nucleophilic radical before giving rise to the induced decomposition. A plausible species which would reasonably explain these results is a pyridinyl radical (**12**) formed by the loss of the proton in the α-position of the intermediate **11** (eq 4). Several facts support this hypothesis:





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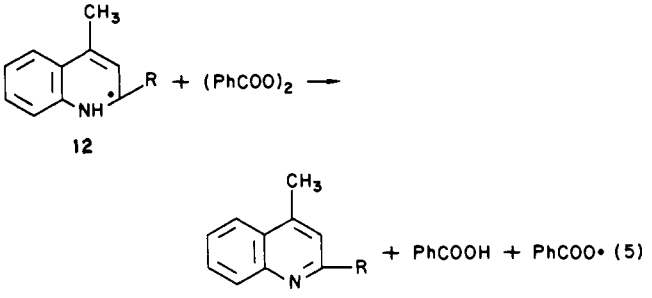
(i) it is well documented that amino radical cations produced by chemical or electrochemical processes can lose a proton from the α C–H bonds;[8] (ii) pyridinyl radicals, such as **12**, are very weakly basic[9] compared to the corresponding dihydropyridines[10] and in not strongly acidic medium the unprotonated radical must be present in significant amount at the equilibrium (eq 4); (iii) electrochemical techniques have made possible the measurement[11] of reliable one-electron reduction potentials of pyridinyl radicals, which emphasize their reducing properties; and (iv) the ionization potentials (5.4–6.1 eV) for α-aminoalkyl radicals are the lowest observed for any organic or organometallic species.[12]

Thus the induced decomposition of benzoyl peroxide by the strongly nucleophilic radical 12 (eq 5) is well explained by the kinetic and product results. Methanol and dioxane have only



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one type of C–H bond, and no problem of selectivity arises in hydrogen abstraction. DMF has two types of C–H bonds, and both are involved in the hydrogen abstraction leading to the two compounds **5** and **6** (Table I) (eq 6). Both radicals **13** and **14**

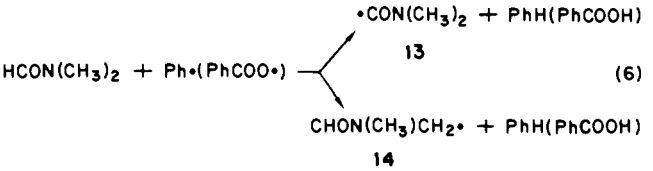

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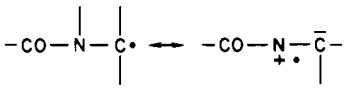
Table III. Apparent First-Order Rate Constants (k) for the Decomposition of Benzoyl Peroxide

solvent	[lepidine], mol L^{-1}	[CF_3COOH], mol L^{-1}	[benzoyl peroxide], mol L^{-1}	T, °C	10^4k, s^{-1}
dioxane	0.084	0.084	0.084	60	2.76
			0.084	60	0.62
	0.042	0.042	0.042	80	17.80
			0.042	80	2.76
methanol	0.042	0.042	0.042	60	1.62
			0.042	60	0.19
dimethylformamide	0.042	0.042	0.042	60	2.45
			0.042	60	0.95
acetonitrile			0.042	81	1.43
cyclohexyl iodide (0.42 M) in acetonitrile	0.042	0.042	0.042	81	6.70
			0.042	81	1.59
cyclohexane (35 mL), chloroform (13 mL)	0.044	0.044	0.022	72	1.06
cyclohexane (35 mL), chloroform (13 mL)			0.022	72	0.19

Table IV. Products and Rate Constants (k, s^{-1}) for the Reaction of Lauroyl Peroxide and Lepidine in Acetonitrile (5 mL) at 81 °C

reagents, mmol			reaction product **8**, mmol	dodecanoic acid, mmol	10^4k
lepidine	lauroyl peroxide	CF_3COH			
2.1	1.04	2.1	0.72	1.01	39.1
	1.04				7.7

have a clear-cut nucleophilic character, but the polar effect of the α-nitrogen atom is opposite for the two radicals. We have previously discussed[1c,d] the effect of α-alkoxy and amino groups on the nucleophilicity of alkyl and carbonyl radicals. Thus α-alkoxy and α-*N*-amidoalkyl radicals –O—C· and –CO—N—C· are more nucleophilic than the corresponding alkyl radicals because they are π-type radicals and oxygen and nitrogen (eq 7) have an electron-releasing effect. Acyl radicals are nucleophilic, mainly



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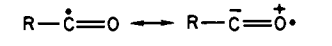
because of the resonance structure of eq 8 and the stability of acyl cations in a transition state with charge-transfer character (eq 9). Carbonyls, on the contrary to alkyls, are σ-type radicals and



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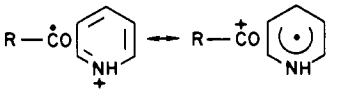

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contributing structures like eq 7 are not important with alkoxy (ROCO) and aminocarbonyl (R_2NCO) radicals so that only electron-withdrawing inductive effects of the oxygen or nitrogen atoms are operating and a clear reduction of nucleophilicity occurs compared with that of acyl radicals.

The different reactivity, caused by the σ or π nature, of the radicals **13** and **14** is clearly revealed by the results of Table II, in which increasing amounts of Fe(III) salt are used. The ratio of products **5**:**6** increases as the concentration of Fe(III) salt increases, but at the same time the lepidine conversions decrease. This behavior is explained by the competitive oxidation of the π radical **14** (eq 10) which is faster than that of the σ radical **13** (eq 11). The formation of substantial amounts of *N*-methylformamide (**15**) supports this interpretation. The couple alkyl

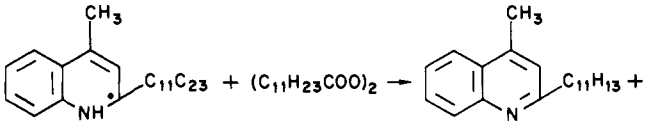
$$CHON(CH_3)CH_2\cdot + Fe^{3+} \rightarrow CHON(CH_3)CH_2^+ + Fe^{2+} \xrightarrow{H_2O} \underset{\mathbf{15}}{CHONHCH_3} + CH_2O + H^+ \quad (10)$$

$$\cdot CON(CH_3)_2 + Fe^{3+} \rightarrow {}^+CON(CH_3)_2 + Fe^{2+} \xrightarrow{H_2O} CO_2 + (CH_3)_2{}^+NH_2 \quad (11)$$

iodides and benzoyl peroxide constitute a selective source of alkyl radicals because the rate of iodine abstraction by the phenyl radical (eq 12) is very high, namely close to the diffusion-controlled limit (1.2×10^9 M^{-1} s^{-1}),[13] which is 3–4 orders of magnitude higher than that of hydrogen abstraction. In order to have a homogeneous reaction medium when cyclohexane was used it was necessary to add chloroform as cosolvent; chloroform does not interfere in the reaction of lepidine as **7** was found to be the only reaction product.

$$Ph\cdot + I\text{–}C_6H_{11} \rightarrow Ph\text{–}I + C_6H_{11}\cdot \quad (12)$$

Lauroyl Peroxide. The induced decomposition of decanoyl peroxide in the alkylation of protonated quinoline has previously been observed by us[14] in acetic acid and more recently confirmed,[15] but a satisfactory explanation of the induced decomposition has not been given so far. Acetonitrile proved to be a more suitable solvent: the decomposition of lauroyl peroxide in the presence of protonated lepidine in acetonitrile gives high yields of **8** and dodecanoic acid; at the same time a remarkable induced decomposition of the peroxide (eq 13) (Table IV) is observed and the reaction is inhibited by the presence of oxygen.



$$C_{11}H_{23}\cdot + CO_2 + C_{11}H_{13}COOH \quad (13)$$

Peroxydisulfate. Simple primary and secondary alkyl radicals do not induce decomposition of peroxydisulfate. Since **9** is the only product formed when a solution of isobutyric acid and potassium isobutyrate is oxidized by peroxydisulfate in the presence of lepidine, a reasonable explanation of the results displayed in Table V is based on the chain-induced decomposition of peroxydisulfate by a pyridinyl radical (eq 14). This mechanism is

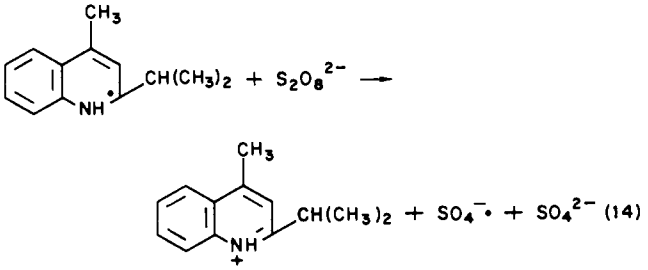


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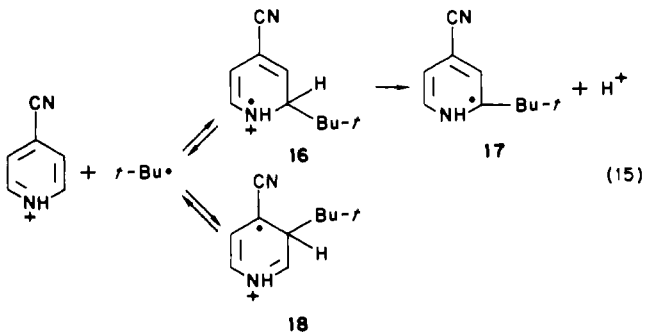
Table V. Products and Rate Constants (k, s^{-1}) in the Decomposition of Peroxydisulfate in the Presence of Isobutyric Acid, Potassium Isobutyrate, and Lepidine in 40 mL of Water at 75 °C

reagents, mmol				% of conversion to **9**	
lepidine	$K_2S_2O_8$	COOH	KOH	based to $K_2S_2O_8$	10^4k
1.05	1.05	8.4	4.2	34	1.89
	1.05	8.4	4.2		0.85
2.10	1.05	11.4	4.2	46	7.45
	1.05	11.4	4.2		0.87
2.10	0.52	11.4	4.2	40	4.26
	0.52	11.4	4.2		0.84
2.10	0.26	11.4	4.2	34	1.98

in accordance with the results previously[2b] obtained in *tert*-butylation of 4-cyanopyridine by pivalic acid and peroxydisulfate. The change of selectivity in the presence of Cu(II) salt is explained by the reversibility of the addition of the *tert*-butyl radical to the pyridine ring (eq 15). The radical **16** by loss of an α proton gives



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the strongly nucleophilic radical **17**, which induces the fast decomposition of the peroxydisulfate minimizing the effects of the reversibility. On the contrary the radical **18**, which cannot give an α-aminoalkyl radical, is much less oxidazable and thus the equilibrium of eq 18 is shifted toward **17**. Cu(II) salts are very effective oxidants of carbon-centered radicals[16] so that both radicals **16** and **18** are effectively oxidized increasing the amount of product arising from **18**. Thus the rate of the rearomatization step can also affect significantly the positional selectivity.

Conclusions

The great interest of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is strictly related to polar effects. These effects strongly affect not only the reactivity and the selectivity of the addition of the free radical to the heterocyclic ring, as previously established,[1] but also the rearomatization of the radical adduct. The key step in this process consists of the intermediate formation of strongly nucleophilic radicals, of the pyridinyl type (2, 12), which can then be involved in the induced decomposition of the peroxo compounds, and in any case are easily rearomatized by mild oxidants. This behavior, quantitatively investigated with lepidine, was found to be qualitatively similar in the case of several heteroaromatic bases (pyridines, diazines, imidazoles, thiazoles, purine bases, etc.).

Experimental Section

Analytical GLC was performed with a Carlo Erba 4200 or Dani 3600 instrument equipped with flame ionization detectors (2-m columns packed with 10% OV 101 on Chromosorb W HP DMSC (80–100 mesh) and 10% Carbowax 20 M on Chromosorb W DMSC). Quantitative TLC analyses were performed at 280 nm (Hg lamp) on HPTLC (Merk); peak areas were determined with a Spectra Physics SP 4100 integrator.

Materials. Lepidine was distilled before the use. Benzoyl and lauroyl peroxide were crystallized and analyzed by iodometric titration (99.5–99.8%). Methanol was distilled on Mg and stored on molecular sieves under N_2. Dioxane, cyclohexane, dimethylformamide, cyclohexyl iodide, and acetonitrile were distilled and then passed through activated alumina before each experiment.

Kinetics with Benzoyl Peroxide. Reactions were conducted under dry oxygen-free nitrogen in vessels equipped with reflux condensers and magnetic stirrer and immersed in a thermostat bath at the temperatures reported in Table III. Samples of appropriate size (1–5 mL) were withdrawn at intervals and their peroxide contents determined iodometrically. Each peroxide estimation was carried out in duplicate, and each run was duplicated. Apparent first-order rate constants were obtained from the initial slopes of the graphs of the logarithm of the peroxide concentration against time. The results are summarized in Table III.

Reaction Products with Benzoyl Peroxide. In a 50-mL flask, equipped with magnetic stirrer and reflux condenser, were introduced the reagents (in the amounts reported in Table I). The solution was flushed with N_2, and the flask was immersed in a thermostat bath at the temperatures and for the time reported in Table I. The solution was then diluted with 50 mL of water, made basic with 10% NaOH, and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with water (10 mL), dried, and analyzed. The solution from methanol (compound **3**) was quantitatively analyzed on HPTLC plates by using calibration curves for starting and the final product obtained from five solutions of the same volume and containing different amounts of the two products. The solutions from reactions with dioxane, cyclohexane, DMF, and cyclohexyl iodide (compounds **4**–**7**) were quantitatively analyzed by GLC using quinoxaline as internal standard.

The compounds **4**–**7** were identified by silica gel chromatography isolation and comparison TLC, GLC, IR, NMR, and MS) with authentic samples prepared by different procedures[17] previously developed by us (**3**,[17a] **4**,[17a] **5**,[17b] **6**,[17b] **7**[17c]).

The alkaline solution was acidified and extracted with CH_2Cl_2 (4 × 10 mL); the resulting extract was dried ($MgSO_4$), filtered and allowed to evaporate, and the residual benzoic acid (mp 120–121 °C) was weighed.

The results are reported in Table I.

The Table II are reported the results obtained with DMF under similar conditions with the only difference being variable amounts of $FeO-H(Ac)_2$.

Kinetics with Lauroyl Peroxide. The kinetics was conducted as described for benzoyl peroxide. Plots of the logarithm of the peroxide concentration against time gave good straight lines for 70% conversions. The reaction conditions and the results are reported in Table IV.

Reaction Products with Lauroyl Peroxide. In a 50-mL flask, equipped with reflux condenser and magnetic stirrer, were introduced the reagents (in the amounts reported in Table IV). The solution was flushed with N_2, and the flask was immersed in a bath at 81 °C for 2 h. The solution was then diluted with 60 mL of water, made basic with 10% NaOH, and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were quantitatively analyzed by GLC using quinoxaline as the internal standard.

The 2-undecyl-4-methylquinoline (**8**) has been isolated as an oil by silica gel chromatography (eluent hexane:ethyl acetate 9:1) and identified by NMR spectrum (5 aromatic H at δ 7–8.1 indicating that positions 2 and 4 are substituted, 2 H centered at δ 2.8, CH_2 bonded to the heteroaromatic ring, 3 H at δ 2.6, 4-CH_3, 18 H centered at δ 1.2, 9 CH_2, and 3 H at δ 0.8, CH_3 of the undecyl group) and MS which shows the molecular ion peak at m/e 297 and significant fragments at m/e 282, 268, 254, 240, 226, 212, 198, 184, 170, 156. Anal. Calcd for $C_{21}H_{31}N$: C, 84.84; H, 10.44; N, 4.71. Found: C, 84.66; H, 10.51; N, 4.76.

The alkaline solution was acidified with sulfuric acid and extracted with CH_2Cl_2 (4 × 10 mL); the resulting extract was dried ($MgSO_4$), filtered, and evaporated, and the residual dodecanoic acid (mp 45 °C) was weighed.

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Kinetics with $K_2S_2O_8$. Reactions were conducted under dry oxygen free nitrogen in vessels equipped with a magnetic stirrer and immersed in a thermostat bath at 75 °C. Samples were withdrawn at intervals, and their peroxide contents were determined according to the procedure of Kolthoff and Carr.[6] Each peroxide estimation was carried out in duplicate, and each run was duplicated.

Good straight lines were obtained plotting the logarithm of the $K_2S_2O_8$ concentration against time for the initial 70% conversions. The apparent first-order rate constants obtained from the initial slopes of the graphs and the reaction conditions are reported in Table V.

Reaction Products with $K_2S_2O_8$. In a 100-mL flask, equipped with a magnetic stirrer, were introduced the reagents (in the amounts reported in Table V). The solution was flushed with N_2, and the flask was immersed in a bath at 75 °C for 4 h and then made basic with 10% NaOH and extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were quantitatively analyzed by GLC using quinoxaline as the internal standard.

The 2-isopropyl-4-methylquinoline (**9**) has been isolated by silica gel chromatography and identified by comparison (TLC, GLC, IR, NMR, and MS) with an authentic sample.[18] The results are reported in Table V.

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Registry No. **3**, 33787-85-8; **4**, 33787-74-5; **5**, 30721-98-3; **6**, 30721-99-4; **7**, 56947-80-9; **8**, 91879-70-8; **9**, 91879-71-9; $(CH_3)_2CH\cdot$, 2025-55-0; $C_{11}H_{23}\cdot$, 55101-35-4; $K_2S_2O_8$, 7727-21-1; $(CH_3)_2CHCO_2H$, 79-31-2; $HOCH_2\cdot$, 2597-43-5; $(CH_3)_2NCO\cdot$, 23686-93-3; $OHCN(CH_3)CH_2\cdot$, 17526-06-6; $FeOH(OAc)_2$, 10450-55-2; dioxane, 123-91-1; dioxanyl radical, 4598-47-4; lepidine, 491-35-0; lepidine conjugate acid, 41229-57-6; lauroyl peroxide, 645-66-9; methanol, 67-56-1; dimethylformamide, 68-12-2; cyclohexyl iodide, 626-62-0; cyclohexane, 110-82-7; cyclohexyl radical, 3170-58-9; benzoyl peroxide, 94-36-0; potassium isobutyrate, 19455-20-0.

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Host–Guest Complexation. 32. Spherands Composed of Cyclic Urea and Anisyl Units[1,2]

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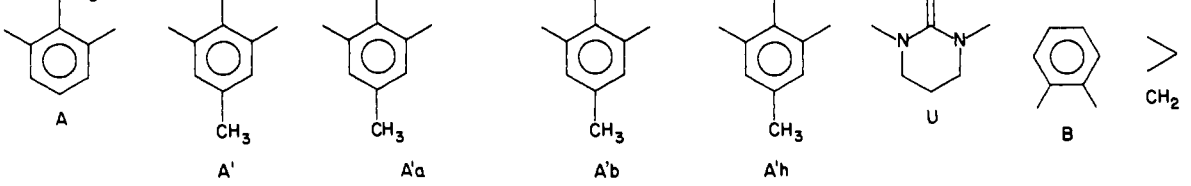
Abstract: Five new spherands and three new hemispherands containing cyclic urea units have been designed and synthesized, and their binding properties have been examined. Formally, these macrocycles are composed by attaching to one another the following units: 2,6-disubstituted anisyl, or A; 2,6-disubstituted 4-methylanisyl, or A′; N,N-disubstituted tetrahydro-2-pyrimidinone, or U; 2,6-disubstituted 1-(allyloxy)-4-methylbenzene, or A′a; 2,6-disubstituted 1-(benzyloxy)-4-methylbenzene, or A′b; 2,6-disubstituted 4-methylphenol, or A′h; 1,2-disubstituted benzene, or B; and CH_2 groups. Host structures and key



intermediates are visualized by line formulas in which adjacent letters indicate bonded units. The macroring acts as a semirigid support structure for the convergently arranged carbonyl and methoxy groups. Key ring-closing reactions involve urea NH group substitution of $ArCH_2Br$ in $(CH_2)_4O$–NaH under high dilution. Treatment of $U(A'UH)_2$ with $(BrCH_2)_2B$ gave $U(A'UCH_2)_2B$ (**1**, 7%), of $A(AUH)_2$ with $(BrCH_2)_2B$ gave $A(AUCH_2)_2B$ (**2**, 11%), of $A(AUH)_2$ with $(BrCH_2)_2A'$ gave $A(AUCH_2)_2A'$ (**3**, 32%), of $A'b(A'UH)_2$ with $(BrCH_2)_2A'a$ gave $A'b(A'UCH_2)_2A'a$ (**4**, 41%), deallylation of which with Pd–EtOH–TsOH gave $A'b(A'UCH_2)_2A'h$ (**5**, 25%), of $U(A'CH_2Br)_2$ with $(HU)_2A'$ gave $U(A'CH_2U)_2A'$ (**6**, 60%), and of $A'b(A'CH_2Br)_2$ with $(HU)_2A'b$ gave $A'b(A'CH_2U)_2A'b$ (**7**, 41%), which was hydrolytically debenzylated to give $A'h(A'CH_2U)_2A'h$ (43%), methylation of which produced $A'(A'CH_2U)_2A'$ (**8**, 71%). These compounds were generally purified as their NaBr complexes, which were decomplexed by crystallizing the free host from MeOH–H_2O mixtures by MeOH evaporation (a phase-transfer process). Crystal structures of complexes $A(AUCH_2)_2A'\cdot NaBr\cdot H_2O$ (**3**·NaBr·H_2O) and $A(AUCH_2)_2A'\cdot CsClO_4\cdot H_2O$ (**3**·$CsClO_4$·H_2O) are discussed. Association constants (K_a) between host and guest to give complexes were determined by extracting picrate salts (guests) from D_2O into $CDCl_3$ in the absence and presence of hosts at 25 °C. The rates of extraction were essentially instantaneous on the human time scale. The free energies for complexation for the seven hosts with picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ were determined. These $-\Delta G°$ values (kcal mol^{-1}) ranged from a high of ~18.3 ($U(A'UCH_2)_2B$ (**1**)) for Li^+ to a low of 7.2 ($U(A'CH_2U)_2A'$ (**6**)) for $(CH_3)_3CNH_3^+$. Interesting structural recognition factors ($K_a^G/K_a^{G'}$) for a host distinguishing between two similar guests (G and G′) are as follows: Li^+/Na^+, $U(A'UCH_2)_2B$ (**1**), 30; Na^+/Li^+, $A'b(A'CH_2U)_2A'b$ (**7**), 3400; Na^+/K^+, $A(AUCH_2)_2B$ (**2**), 2300; K^+/Na^+, $A(AUCH_2)_2A'$ (**3**), 3; K^+/Rb^+, $A'b(A'UCH_2)_2A'a$ (**4**), 110; Rb^+/Cs^+, $A'b(A'UCH_2)_2A'a$ (**4**), 25; Cs^+/Rb^+, $U(A'UCH_2)_2B$ (**1**), 2; $NH_4^+/CH_3NH_3^+$, $A(AUCH_2)_2A'$ (**3**), 9; $CH_3NH_3^+/NH_4^+$, $U(A'UCH_2)_2B$ (**1**), 1.7; $CH_3NH_3^+/t$-$BuNH_3^+$, $A'b(A'UCH_2)_2A'a$ (**4**), 4600; t-$BuNH_3^+/CH_3NH_3^+$, $U(A'UCH_2)_2B$ (**1**), 6. Correlations between the structures of hosts and guests and their free energies of binding are interpreted in terms of the principles of complementarity and of preorganization. In general, these hosts exist as a mixture of conformers equilibrating rapidly on the human time scale but slowly on the ^1H NMR time scale. When guest is added, they produce a single complex instantaneously on the human time scale.

Complexes as we use the term are composed of hosts (convergently arranged binding sites) and guests (divergently arranged binding sites) held together in solution in a definite structural relationship. Since each binding site provides at most a few

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