Displacement of Protomeric Equilibria by Self-Association: Hydroxypyridine–Pyridone and Mercaptopyridine–Thiopyridone Isomer Pairs

Peter Beak,* Johnny B. Covington, Stanley G. Smith, J. Matthew White, and John M. Zeigler

Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801

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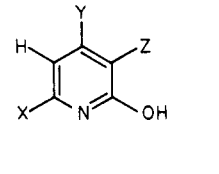
Values of both self-association and protomeric equilibrium constants are reported for 2-hydroxypyridine–2-pyridone, 4-hydroxypyridine–4-pyridone, and 2-mercaptopyridine–2-thiopyridone isomer pairs in different solvents. These results provide quantitative evidence for significant differences in the positions of protomeric equilibria for self-associated and monomeric species. The 2-substituted isomers are associated as well-known dimers while the 4-substituted systems form oligomers. In polar and hydrogen-bonding solvents self-association is substantially reduced. Sterically hindered 2- and 4-pyridones are less associated than unhindered systems. The implication of these results, that determinations and interpretations of protomeric equilibrium should take into account the possible dominance of self-association, is discussed.

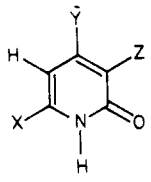
Evaluation of the effect of self-association on protomeric equilibria is essential for reliable interpretation of solution data.[1] In this report we detail evidence which establishes that self-association can have a dominating effect on the apparent solution protomeric equilibrium constants for 2- and 4-hydroxypyridine–pyridone and 2-mercaptopyridine–2-thiopyridone isomer pairs in nonpolar media.[2,3] We also report the effect of solvent and substituents on these associations. The implications of these observations are discussed as a matter of general concern for determinations and interpretations of positions of protomeric equilibria. In the preceding paper a quantitative model for the effect of molecular environment on these and related equilibria is developed.[4]

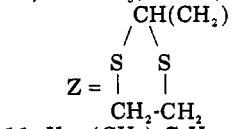
Thermodynamic and kinetic evidence for a strong hydrogen-bonding dimerization of 2-pyridone in solution has been reported and reviewed.[5-7] For example at a 0.01 M concentration in benzene, 2-pyridone is 85% dimerized.[8] Other pyridones have been less thoroughly investigated, but 2-thiopyridone is only slightly less associated than 2-pyridone,[8,9] and 4-pyridone is reported to be a trimer in chloroform.[10] As early as 1968 it was noted that self-association might affect protomeric equilibrium constants of hydroxypyridine–pyridone systems.[1,5,6,11-15] However, a quantitative assessment of the influence of intermolecular association on such protomeric equilibria has not been available previously.[3]

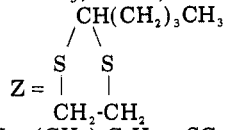
Results

Analytically pure samples of the isomer pairs **1–24** were used for protomeric and association studies. The syntheses of compounds **7–14** are described in the Experimental Section.



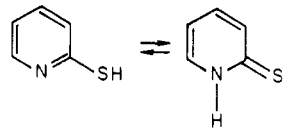


1, X = Y = Z = H
3, X = Cl; Y = Z = H
5, X = CH_3; Y = OCH_3; Z = H
7, X = CH_3; Y = H; Z = $CH{=}CH(CH_2)_2CH_3$
9, X = CH_3; Y = H; Z = 

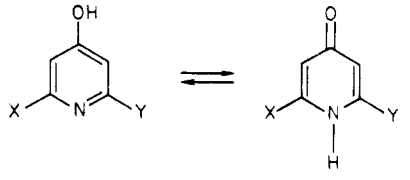
2, X = Y = Z = H
4, X = Cl; Y = Z = H
6, X = CH_3; Y = OCH_3; Z = H
8, X = CH_3; Y = H; Z = $CH{=}CH(CH_2)_2CH_3$
10, X = CH_3; Y = H; Z = 

11, X = $(CH_2)_2C_6H_4$-*p*-SC_6H_5; Y = H; Z = $CO_2C_{16}H_{33}$
13, X = $CH{=}CHC_6H_4$-*p*-SC_6H_5; Y = H; Z = $CO_2C_{16}H_{33}$

12, X = $(CH_2)_2C_6H_4$-*p*-SC_6H_5; Y = H; Z = $CO_2C_{16}H_{33}$
14, X = $CH{=}CHC_6H_4$-*p*-SC_6H_5; Y = H; Z = $CO_2C_{16}H_{33}$



15 **16**



17, X = Y = H
19, X = H; Y = Cl
21, X = Y = CH_3
23, X = Y = $C(CH_3)_3$

18, X = Y = H
20, X = H; Y = Cl
22, X = Y = CH_3
24, X = Y = $C(CH_3)_3$

(1) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977), and references cited therein.
(2) We have used these systems as prototypes in earlier gas-phase studies. P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
(3) For a preliminary report of some of the work detailed herein, see: (a) P. Beak, J. B. Covington, and S. G. Smith, *J. Am. Chem. Soc.*, **98**, 8284 (1976); (b) P. Beak, J. B. Covington, and J. M. Zeigler, *J. Org. Chem.*, **43**, 177 (1978).
(4) P. Beak, J. B. Covington, and J. M. White, *J. Org. Chem.*, preceding paper in this issue; P. Beak and J. B. Covington, *J. Am. Chem. Soc.*, **100**, 3961 (1978).
(5) H. Tieckelmann, *Chem. Heterocycl. Compd.*, **14**, 731 (1974).
(6) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1976, Supplement 1.
(7) For more recent work, see: K. A. Engdahl and P. Ahlberg, *J. Chem. Res. (S)*, 340 (1977); O. Bensaude, "Protons and Ions Involved in Fast Dynamic Phenomena", Elsevier, Amsterdam, 1978, pp 393–401, and references cited therein.
(8) M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Am. Chem. Soc.*, **87**, 892 (1965); G. G. Hammes and H. O. Spivey, *ibid.*, **88**, 1621 (1966).
(9) N. Kulevsky and W. Reineke, *J. Phys. Chem.*, **72**, 3339 (1968).
(10) R. A. Coburn and G. O. Dudek, *J. Phys. Chem.*, **72**, 3681 (1968).
(11) P. Beak, J. Bonham, and J. T. Lee, *J. Am. Chem. Soc.*, **90**, 1569 (1968).
(12) G. Simchen, *Chem. Ber.*, **103**, 398 (1970).
(13) S. T. King, W. C. Dilling, and N. B. Tefertiller, *Tetrahedron*, **28**, 5859 (1972).
(14) M. J. Cook, A. R. Katritzky, L. G. Hepler, and T. Matsui, *Tetrahedron Lett.*, 2685 (1976).
(15) J. Frank and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1428 (1976). The discrepancy between the results in this reference and our work have been discussed and attributed to self-association and the single-wavelength determinations used in the Frank and Katritzky work.

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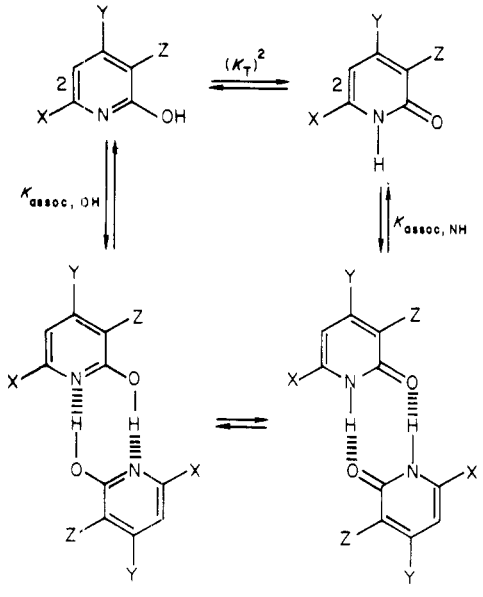
Table I. Changes in Ratios of Optical Densities at λ_{max} for Hydroxypyridine-Pyridone and Mercaptopyridine-Thiopyridone Chromophores

substr	concn, M	T,[a] °C	solvent	OD,[b] $\lambda_{max,NH}/\lambda_{max,OH}$
1-2[c]	5×10^{-5}		decane	>5
	5×10^{-5}	100	decane	1.7
	5×10^{-5}	130	decane	0.95
	5×10^{-5}	150	decane	0.88
	5×10^{-5}	160	decane	0.88
	1×10^{-5}		cyclohexane	>5
	3×10^{-6}		cyclohexane	>5
	2×10^{-6}		cyclohexane	1.3[d]
	8×10^{-7}		cyclohexane	1.0[d]
	4×10^{-7}		cyclohexane	1.0[d]
	3×10^{-7}		cyclohexane	0.77
	10^{-7}		cyclohexane	0.77
3-4[e]	5×10^{-2}		chloroform	4.4
	2×10^{-4}		chloroform	2.3
	4×10^{-5}		chloroform	2.3
15-16[f]	1×10^{-3}		cyclohexane	0.8
	1×10^{-5}		cyclohexane	0.04
	3×10^{-3}		chloroform	8.0
	1×10^{-4}		chloroform	1.5
	5×10^{-6}		chloroform	1.5

[a] Ambient temperature unless otherwise noted. [b] Errors are ±10%. [c] 300 and 275 nm. [d] 310 and 278 nm. [e] 305 and 278 nm. [f] 360 and 240 nm.

Scheme I



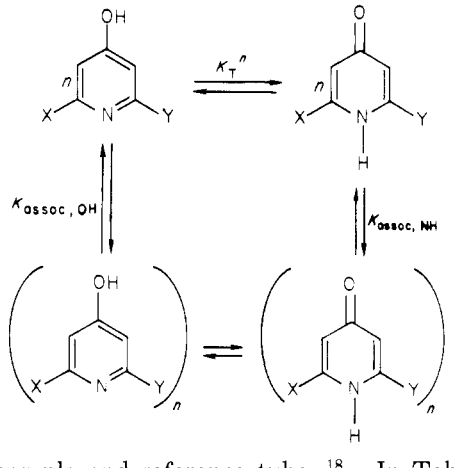
The ratios of the hydroxypyridine to pyridone and mercaptopyridine to thiopyridone chromophores were determined by the ultraviolet analyses used theretofore and developed by many workers from the pioneering work of Specker and Gawrosch.[2,16] For calculations of protomeric equilibrium constants (K_T) the assumption that the chromophores of the OCH_3 and NCH_3 compounds provide adequate models for free and associated OH and NH protomers was modified by inclusion of small shifts in λ_{max} for cases in which Dewar–Urch analysis[17] indicated better correlation was thus achieved. It should be noted that the extremely dilute solutions, down to 10^{-7} M, required for the investigation of 2-pyridone necessitated the construction of a spectrophotometer which allowed the use of 3-m sample and reference tubes.[18] In Table I the changing ratio in optical densities of λ_{max} for bands assigned to the NH and OH chromophores of the **1–2**, **3–4**, and **15–16** systems is listed as a function of temperature or concentration.[19]

Table II. Association of Hydroxypyridine-Pyridones from Vapor Pressure Osmometry

substr	concn, M	solvent	% associated[a] (type)
1-2	1×10^{-1}	chloroform	100 ± 4 (dimer)
	1×10^{-2}	chloroform	86 ± 6
	2×10^{-3}	chloroform	37 ± 6
	1×10^{-2}	chloroform	61 ± 5[b]
	4×10^{-1}	ethanol	23 ± 8
3-4	5×10^{-2}	chloroform	91 ± 2 (dimer)
	6×10^{-3}	chloroform	57 ± 6
	5×10^{-2}	chloroform	75 ± 5[b]
	5×10^{-2}	chloroform	69 ± 3[c]
5-6	1×10^{-2}	benzene	38 ± 3 (dimer)
	1×10^{-1}	tetrahydrofuran	55 ± 1
	1×10^{-2}	chloroform	100 ± 5
	5×10^{-2}	methylene chloride	86 ± 5
	1×10^{-2}	acetonitrile	3 ± 11
	1×10^{-1}	ethanol	50 ± 6
7-8	5×10^{-2}	methylene chloride	68 ± 9 (dimer)
9-10	5×10^{-2}	methylene chloride	63 ± 6 (dimer)
11-12	5×10^{-2}	methylene chloride	35 ± 7 (dimer)
13-14	5×10^{-2}	methylene chloride	21 ± 5 (dimer)
17-18	5×10^{-2}	chloroform	>98 (oligomer)[d]
	6×10^{-3}	chloroform	>90[e]
	4×10^{-4}	methylene chloride	>98[b,f]
	1×10^{-4}	ethanol	40[g]
19-20	3.9×10^{-3}	1,2-dichloroethane	40 (oligomer)[c,h]
21-22	1.5×10^{-4}	methylene chloride	>98 (oligomer)[b,i]
23-24	7×10^{-2}	chloroform	60 (oligomer)[j]
	2×10^{-2}	chloroform	30[k]
	4×10^{-2}	methylene chloride	60[l]

[a] Ambient temperature unless otherwise noted. [b] 37 °C. [c] 50 °C. [d] Average mol wt 870 ± 18. [e] Average mol wt 364 ± 78. [f] Average mol wt 540 ± 87. [g] Average mol wt 169 ± 3. [h] Average mol wt 163 ± 1. [i] Average mol wt 660 ± 66. [j] Average mol wt 339 ± 4. [k] Average mol wt 253 ± 3. [l] Average mol wt 345 ± 4.

Scheme II



Equilibrium constants for association (K_{assoc}) obtained, in most cases, by vapor-pressure osmometry are given as ratios of mole fractions according to the treatment described by Schrier[20] as shown in eq 1–4, where a = 1, 2,

$$aP \rightleftharpoons Pa \qquad (1)$$

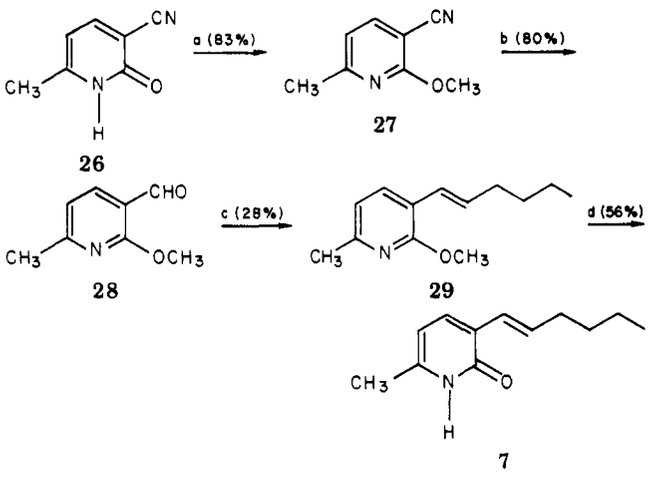
(16) H. Specker and H. Gawrosch, *Chem. Ber.*, **75**, 1338 (1942). For a review, see: S. F. Mason "Physical Methods in Heterocyclic Chemistry", Vol. II, A. R. Katritzky, Ed., Academic Press, New York, 1963.
(17) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).
(18) For details, see, J. B. Covington, Ph.D. Thesis, University of Illinois, 1978, available from University Microfilms, Ann Arbor, MI.
(19) The data are presented in this form in anticipation of our subsequent demonstration that a chromophore is comprised of more than one species.

Table III. Protomeric Equilibrium Constants and Association Constants for Hydroxypyridine-Pyridone Isomers

substr	solvent	K_T[a]	$K_{assoc,NH}$
1-2	cyclohexane	1.6 ± 0.5	(5.6 ± 1.7) × 10^6
	benzene	>5	(9.0 ± 1.0) × 10^4 [b]
	chloroform	>5	(2.5 ± 1.0) × 10^4 [c]
	chloroform	>5	(9.5 ± 1.0) × 10^3 [d]
	dioxane	>5	
3-4[e]	chloroform	0.45 ± 0.3	(7 ± 1) × 10^3
5-6	methylene chloride		(2.4 ± 1.0) × 10^4
	benzene		(1.5 ± 0.4) × 10^3
	tetrahydrofuran	>5	(5.2 ± 0.3) × 10^2
	ethanol	>5	(5.0 ± 2.0) × 10^2
	acetonitrile	>5	(5.7 ± 5.0) × 10
10	methylene chloride	>5	(3.6 ± 2.0) × 10^3
11-12	methylene chloride	0.6 ± 0.2	(5.3 ± 1.0) × 10^2
15-16	chloroform	2.6 ± 0.5	(2.7 ± 0.5) × 10^3
18	chloroform	>5	(3 ± 0.7) × 10^4
	methylene chloride	>5	(7.4 ± 2.4) × 10^4
	ethanol	>5	(6.0 ± 2.0) × 10
19-20	toluene		(6.9 ± 0.4) × 10^2
	1,2-dichloroethane		(9.6 ± 0.8) × 10^2
22	methylene chloride		(4.8 ± 1.0) × 10^4
23-24	chloroform	>1	(1.8 ± 0.5) × 10^2
	methylene chloride		(2.1 ± 0.2) × 10^2

[a] [NH]/[YH]. [b] Calculated from ref 8. [c] 27 °C. [d] 37 °C. [e] $K_{assoc,OH}$ = (7 ± 1) × 10^3.

Scheme III[a]



[a] a: (1) $(CH_3)_3O^+BF_4^-$, CH_2Cl_2, room temperature, 48 h; (2) 10% aqueous NaOH. b: (1) DIBAH, toluene, −78 °C; (2) saturated aqueous NH_4Cl; (3) 5% H_2SO_4; (4) 10% aqueous NaOH. c: (1) *n*-BuMgI, Et_2O, −10 °C; (2) $CH_3(PhO)_3P^+I^-$, HMPA, 75 °C, 2 h. d: $(CH_3)_3SiI$, $CHCl_3$, Δ, 24 h.

..., n, X_s = the stoichiometric mole fraction = $X_1 + 2X_2 + ... + aX_a$, X_e = the effective mole fraction = $X_1 + X_2 + ... + X_a$, and X_a = the mole fraction of aggregate a.

dimerization $$K_{assoc} = \frac{X_s - X_e}{(2X_e - X_s)^2} \quad (2)$$

oligomerization $$K_{assoc} = X_a/(X_1)^a \quad (3)$$

specific protomers $$K_{assoc,YH} = \frac{X_{YH}(\text{monomer})}{X_{YH}(\text{associated})} \quad (4)$$

It is important to note that by this analysis the equilibrium constants are dimensionless and suitable for thermodynamic analysis. Representative association results are collected in Table II, and equilibrium constants for association appear in Table III.

Discussion

2-Hydroxypyridines–2-Pyridones. The changes shown in Table I in the ratios of the chromophores for 2-hydroxypyridine (1) and 2 pyridone (2) and for 6-chloro-2-hydroxypyridine (3) and 6-chloro-2-pyridone (4) as a function of dilution are inexplicable if only two isomeric species are in equilibrium. On the other hand, those changes can be readily accommodated if monomeric and dimeric species contribute to the absorptions.

Qualitatively, inclusion of the well-known dimerization of 2-pyridone, shown as $K_{assoc,NH}$ in Scheme I, with the protomeric equilibrium, represented as K_T, provides a satisfactory model. The change in the ratios of chromophores is then explained if dilution shifts the associative equilibrium from the dimer, in which only the 2-pyridone chromophore is observable, to monomeric species, for which both chromophores are seen.[15] If Scheme I is correct, the ratios of monomeric 1 and 2 should reach a constant value on dilution; this appears to occur at 3 × 10^{-7} M in cyclohexane. The resulting K_T value of 1.6 ± 0.5 (Table III) is sensibly near the gas-phase value of 0.4 ± 0.2.[2] Analysis of the dilution data allows calculation of a $K_{assoc,NH}$ for 2-pyridone of 5.6 × 10^6 ± 1.7 × 10^6 (Table III) in cyclohexane.

The change in the ratios of the chromophores of 1–2 on heating of the decane solution is also rationalized by Scheme I. In this case thermal energy decreases the association, and the chromophore ratio appears to reach a constant value because the equilibrium constant is not appreciably affected by temperature.

Although 2-pyridone is too insoluble in cyclohexane to allow determination of the dilution and temperature dependence of the association constant by independent measurements, such studies could be carried out by vapor-pressure osmometry in chloroform.[8,9] The change in $K_{assoc,NH}$ for 1–2 in chloroform as a function of temperature allows calculation of a $\Delta G°_{assoc,NH}$ of −10 + 2 kcal/mol, a $\Delta H°_{assoc,NH}$ of −18.6 ± 1.5 kcal/mol, and a $\Delta S°_{assoc,NH}$ of −40 ± 4 eu for 2-pyridone in chloroform at 27–37 °C. The entropy value is close to the theoretical entropy of association of 26 eu attributable to the loss of translational degrees of freedom on dimerization.[21] While 2-hydroxypyridine might also exist as a dimer in concentrated solution, such a species would not be observed in our experiments if its stability were an order of magnitude less than that of the 2-pyridone dimer.

The association of 6-chloro-2-hydroxypyridine–6-chloro-2-pyridone, a system in which both 3 and 4 can be observed,[6,12,13,22] is particularly informative. The ratio of

(20) E. E Schrier, *J. Chem. Educ.*, **45**, 176 (1968).

(21) K. B. Wiberg, "Physical Organic Chemistry", Wiley, New York, 1964, Chapter 2. The difference between the calculated and observed values could be attributed to additional loss of motion in the dimerized species.

(22) A. R. Katritzky, F. A. Popp, and J. D. Rowe, *J. Chem. Soc. B*, 562 (1966); A. R. Katritzky, J. D. Rowe, and S. K. Roy, *ibid.*, 758 (1967); E. Spinner and J. C. B. White, *ibid.*, 991 (1966); E. M. Peresleni, M. Y. Uriskaya, V. A. Loginova, Yu. N. Sheinker, and L. N. Yukhortov, *Dokl. Akad. Nauk SSSR*, **183**, 1083, 1102 (1968).

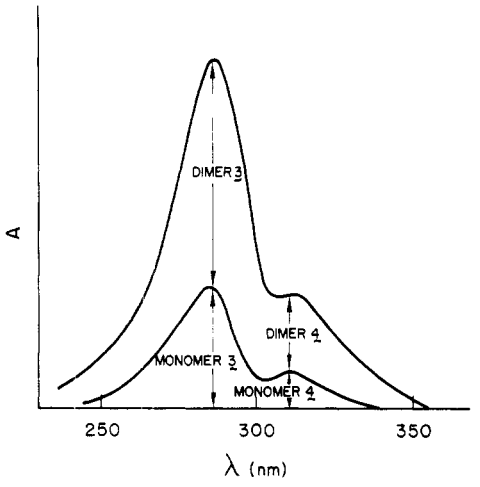


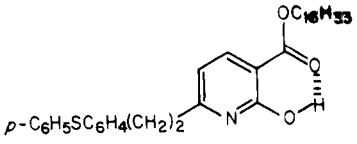
Figure 1. Ultraviolet spectrum of **3–4** in chloroform at a 10^{-2} M concentration.

the monomers, determined at high dilution, provides a basis from which analysis of the spectral and osmometric data at higher concentrations can be dissected into the protomeric and association constants. The data cannot be fit by a model in which only one dimer is present, and we propose the existence of at least two dimers as shown in Scheme I and Table III. The contributions to the ultraviolet spectra by the different protomers of Scheme I are shown in Figure 1. This rationale is the most economical model; however, it should be noted that although the data require at least two dimers, one of which must be a symmetrical dimer of **3**, the other could be the symmetrical dimer of **4** as shown or a mixed dimer of **3–4**. Our data does not, of course, exclude three dimers. The different dimers of **3–4** provide an interesting case of hydrogen bonding in different double potential wells.

The self-association association of 2-pyridone is known to be significantly affected by solvent. Free energies of association of **2** are 9 ± 1 kcal/mol in cyclohexane, 6 ± 1 kcal/mol in benzene, 5 ± 1 kcal/mol in chloroform, and 2 ± 1 kcal/mol in dioxane.[3a,8] A similar trend is shown by the decreasing association of 4-methoxy-6-methyl-2-pyridone (**6**) in the series benzene, tetrahydrofuran, ethanol, and acetonitrile as shown in Tables II and III. The two factors which seem important in determining these orders are the ability of the solvent to stabilize the different dipoles and to participate in hydrogen bonding.[4-7]

The effect of 3- and 6-substituents on self-association of 2-pyridones is illustrated by examination of the data in Tables II and III for the series **2**, **4**, **6**, **8**, **10**, **12**, and **14**.[24] The fact that 6-chloro-2-pyridone (**4**) is a factor of 3 less associated than is 2-pyridone (**2**) in chloroform and that 6-methyl-4-methoxy-2-pyridone (**6**) is a factor of 60 less associated than is **2** in benzene shows that 6-substitution can decrease association.[25] Comparison of the association of the 3-substituted 6-methyl-2-pyridones **8** and **10** with **6** in methylene chloride shows a further decrease in association due to additional substitution at the 3-position. The 3-carboalkoxy-6-alkyl-2-pyridones **12** and **14** also show further reduction in association relative to **10**.

The case of **11–12** can be used to illustrate the value of obtaining both association and protomeric equilibrium data in an analysis of equilibrium energetics. From ultraviolet spectra and vapor-pressure osmometry in methylene chloride and the assumption that the hydroxypyridine is the species **25**, as previously suggested for other



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3-carboxy-substituted 2-pyridones,[6,26] the values for K_T and $K_{assoc,NH}$ of 2.6 ± 0.5 and (5.3 ± 1.0) × 10^2 shown in Table III are obtained. Thus while the lower self-association of **11–12** does reflect a decrease in the association of the 2-pyridone protomer **12** relative to that of **10**, by a factor of 7, the shift of the protomeric equilibrium, by at least a factor of 8, is revealed only by the complete analysis.

2-Thiolpyridine–2-Thiopyridone. The ultraviolet spectra for **15–16** in cyclohexane and chloroform as shown in Table I change with concentration in a manner attributable to an association of **16** analogous to that described for **2** in Scheme I. While dilutions of 10^{-4} M are required to avoid the complications of self-association in the hydrocarbon solvent, the K_{assoc} for **6** (Table III) in chloroform suggests that the 10^{-3} M solutions normally used for ultraviolet spectroscopy would be suitable for study of monomeric species in most other solvents. At the higher concentrations used with other spectral methods, however, displacement of the apparent position of protomeric equilibrium in favor of the NH form could be caused by association. As shown in Table III, vapor-pressure osmometry shows **16** to be somewhat less associated than **2** as has been previously reported.[8,9]

4-Hydroxypyridines–4-Pyridones. Even at 10^{-7} M in cyclohexane the ultraviolet spectrum of the 4-hydroxypyridine (**17**) and 4-pyridone (**18**) system shows only the chromophore of **18**. This appears to be in contradiction to our estimate that **17** should be the overwhelming isomer in this equilibrium in nonpolar media.[1] However, in view of the demonstration that self-association can control the apparent value of K_T for 2-pyridones and the suggestion that 4-pyridone is associated,[10] we have reinvestigated the association of **18**. Limited solubility precluded measurements in cyclohexane, but we find **18** to be very strongly oligomerized in chloroform. For example at 0.025 M the modal association number is 7.[27] The model suggested by this result is shown in abbreviated form in Scheme II with the calculated association constants given in Table III. The extent of self-association of **18** in cyclohexane is presumably even more extensive than in chloroform. Thus, determination of the protomeric equilibrium constant between monomers from the ratios of the chromophores even in highly dilute hydrocarbon solution is not possible, and our estimate that monomeric **17** should be favored by at least 10^5 over monomeric **18** in the vapor phase or in hydrocarbon solution is not disproven.[1] An assumption of the model in Scheme II is that the equilibrium constant for the association of two monomeric species is the same as that for addition of a monomer onto an oligomer, i.e.,

(23) In reference 3a K_T was incorrectly given as the inverse. We are grateful to Professor O. Bensaude for calling this error to our attention.

(24) Compounds **7–14** were available from another study: J. M. Zeigler, Ph.D. Thesis, University of Illinois, 1979, available from University Microfilms, Ann Arbor, MI.

(25) A chloro group has a lower *A* value than does a methyl group, but both groups have similar van der Waals radii. E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, p 236; L. Pauling, "The Nature of the Chemical Bond", 3rd ed., Cornell University Press, Ithaca, NY, 1960, pp 257–64.

(26) T. Kitagawa, S. Mitzukami, and E. Hirai, *Chem. Pharm. Bull.*, **26**, 1403, (1978).

(27) While repetitive measurements do appear to show that the free energy of the hydrogen bond in **18** is somewhat greater than that of **2** in chloroform, the values are within experimental error, and our earlier statement[3b] regarding the somewhat greater aggregation of **18** is hereby corrected.

$K_{1,2} = K_{n,n+1}$. It seems possible that $K_{1,2} \leq K_{n,n+1}$ since such an order is found in amide association,[28] and hydrogen bonding should be more favorable in a molecule already polarized by prior association. Our attempts to measure the necessary constants for **19–20**, a system in which both isomers can be observed,[29] have not been successful.

The hydrogen-bonding oligomerization of **18** is high in chloroform and methylene chloride but is substantially reduced in ethanol as shown in Tables II and III. Once again the solvent effect can be rationalized, in part, in terms of the hydrogen-bonding ability of the solvent.

The effect of steric hindrance on the association of 4-pyridones can be assessed by the data for **18**, **22**, and **24** in methylene chloride shown in Tables II and III. While **18** and **22** are similarly oligomerized there is a 2 orders of magnitude reduction in the association of **24**. Apparently *tert*-butyl groups are needed in the 4-pyridones to provide sufficient steric hindrance around the position of hydrogen bonding to interfere with association.[30] It is pertinent that in cyclohexane the ultraviolet spectrum of **23–24** shows only the hydroxypyridine **23** to be present. That result provides support for our above contention that an unassociated 4-pyridone–4-hydroxypyridine in cyclohexane should favor the latter form in the absence of other perturbations.

Conclusions

The most important conclusion to be drawn from this work is that self-association of hydroxypyridine–pyridone and mercaptopyridine–thiopyridone isomers can significantly shift the apparent protomeric equilibrium between the isomers. In the case of 2-hydroxypyridine (**1**) and 2-pyridone (**2**) in cyclohexane the comparable energies of the monomeric protomers is obscured by the preferential self-association of **2** to the point that only the chromophore of the latter is observed unless the dilution is greater than 10^{-5} M. For 2-mercaptopyridine (**15**) and 2-thiopyridone (**16**) both isomers can be observed in cyclohexane and chloroform in dilute solutions, but the equilibrium constants calculated at higher concentrations would be erroneous if assigned to the isolated protomers. In the case of 4-hydroxypyridine (**17**) and 4-pyridone (**18**) in cyclohexane it appears that only an oligomer is seen, and the shift in the equilibrium constant relative to the monomeric species is estimated to be 5 orders of magnitude.

These observations are well precedented. The strong self-association of the pyridones is well-known[1-15] and consistent with associative structures of amides.[28,31] Also pertinent are the recent studies of Bensaude and Dubois, who find that the protomeric equilibrium of 2-hydroxypyridine–2-pyridones is shifted in favor of the amide by complexation with water or sodium ion.[32] Effects of self-association on the protomeric equilibrium of amides,[33] triazoles,[34] and thioamides[35] and on the photochemical reactivity of anilides[36] also have been noted.

Future determinations of protomeric equilibria, if undertaken to define structure–stability relationships under conditions which could involve self-association, will need to be analyzed carefully in terms of the species actually involved. The extreme dilutions required for observation of monomeric **1–2** and our inability to detect monomeric **17–18** in cyclohexane, along with earlier demonstrations of the phase dependence of such equilibria, may be taken to suggest again that care should be exercised in assignments of relative chemical binding energies of protomers from equilibrium constants in solution.[1,2,11] For situations in which association is a serious problem, indirect methods, such as calorimetric approaches,[1,14] may be more useful than direct measurement.

On the other hand, the present results also show that self-association of 2- and 4-pyridones can be minimized by the choice of solvent. The changes observed in the association energies in different solvents can be attributed to the ability of the solvent to engage in hydrogen bonding which can compete with self-association and to differential solution of the different dipoles of the associated and unassociated species.[4-7]

Substituents which can interfere with intermolecular hydrogen bonding also reduce the self-association of the hydroxypyridine–pyridone systems. Thus the effect of the 3-carboalkoxy substituent in the association of **12** relative to that of **8** and **10** is explained, in part, by the formation of an intramolecular hydrogen bond as shown in **25** and, in part, by steric repulsion of groups in the 3- and 6-positions of the 2-pyridone dimers. The planar and cyclic structures of the 2-pyridone dimers suggest that substitution would be more hindering for those cases than for the 4-substituted isomers.[37] The fact that 6-methyl substitution is effective in reducing association in the 2-pyridone system while 2,6-dimethyl substitution is ineffective in the 4-pyridone system bears out that model. However, it is clear that if steric buttressing is made sufficiently severe, as with 2,6-di-*tert*-butyl substitution, the 4-pyridone system does show reduced self-association.

It appears reasonable that the influence on protomeric and association energies of hydroxypyridine–pyridone isomers by the molecular environment extends to the corresponding protomeric equilibrium and associations of the nucleic acid bases. Attempts to assess these biologically important interactions on the basis of protomeric data from aqueous media should be highly suspect. Indeed, the present results extend our earlier concern about the inappropriate extrapolation of structural data between very different environments.[1] Clearly the thermodynamics of the hydrogen-bonding interactions which are central in the control of many biological processes may depend on the local molecular environment.

In summary, the present results show that self-associated species may have protomeric equilibrium constants which are substantially different from those of the unassociated molecules. These cases again illustrate the necessity of consideration of all pertinent data before conclusions about the energies of systems in protomeric equilibrium are

(28) In the case of oligomerization of amides it has been found that the equilibrium constant for association of two monomers is less than that for association of a monomer onto the chain. M. Davies and D. K. Thomas, *J. Phys. Chem.*, **60**, 767 (1956); L. L. Graham and C. Y. Chang, *ibid.*, **75**, 776 (1971).

(29) A. R. Katritzky, J. D. Rowe, and S. K. Roy, *J. Chem. Soc. B*, 758 (1967); Z. Talik, *Rocz. Chem.*, **36**, 1313 (1962).

(30) A similar effect of 8-methyl substitution in reducing intermolecular association of 4-quinolones has been reported previously and attributed to π hydrogen bonding. P. A. Claret and A. G. Osborne, *Spectrosc. Lett.*, **10**, 25 (1977); P. A. Claret and A. G. Osborne, *ibid.*, **9**, 157 (1976), and references cited therein.

(31) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, 1973, pp 279–89; R. B. Homer and C. D. Johnson, "The Chemistry of the Amides", J. Zabricky, Ed., Interscience, New York, 1970, pp 223–7.

(32) O. Bensaude, M. Chevrier, and J. E. Dubois, *Tetrahedron Lett.*, 222 (1978); *J. Am. Chem. Soc.*, **100**, 7055 (1978).

(33) H. O. Sieveking and W. Luttke, *Ann. Chim. (Paris)*, **12**, 189 (1977).

(34) S. Kubota and M. Uda, *Chem. Pharm. Bull.*, **24**, 955 (1975).

(35) E. Gentric, J. Lauranson, C. Roussel, and J. Metzer, *Tetrahedron Lett.*, 251 (1977).

(36) D. Masilamani, R. O. Hutchins, and J. Ohr, *J. Org. Chem.*, **41**, 3687 (1976).

(37) In contrast to the 2-pyridone dimers in which the rings should be in approximately the same plane for the 4-pyridone oligomers, there appears to be little reason for alignment of the rings.

drawn. It is also to be noted that by proper choice of solvent and high dilutions or by using sterically hindered systems monomeric species can be observed.

Experimental Section

^1H NMR spectra were recorded as solutions in chloroform-*d* ($CDCl_3$) or dimethyl-d_6 sulfoxide (Me_2SO-d_6), and all chemical shifts are relative to internal tetramethylsilane. Elemental analysis and microgram-quantity weighings were done by Mr. J. Nemeth and associates. Mass spectra were recorded on a Varian MAT CH-5 mass spectrometer by Mr. J. Carter Cook and associates.

Cyclohexane and *n*-decane were washed with several portions of concentrated sulfuric acid followed by 10% sodium bicarbonate and several washes with water. The solvents were dried over anhydrous magnesium sulfate and distilled from metallic sodium. Distilled in glass chloroform and dichloromethane were passed over basic aluminum oxide and dried only anhydrous magnesium sulfate. Spectrograde solvents were used as received.

Compounds **1–2**,[2] **3–4**,[2] **5–6**,[38] **15–16**,[2] **17–18**,[2] **19–20**,[29] **21–22**,[39] and **23–24**[40] have been previously described and were obtained from commercial sources or by standard procedures. Materials used for these studies had satisfactory spectral and analytical properties. Vapor pressure osmometric measurements were carried out on a Mechrolab Model 301A vapor pressure osmometer and on a Knauer vapor pressure osmometer at concentrations as low as 10^{-3} M. The instruments were calibrated with the appropriate solvent and naphthalene as a nonassociating standard. It was also shown that *N*-methylpyridones are not associated under the conditions of measurement.

Ultraviolet Spectra. Ultraviolet spectra (UV) at concentrations greater than 10^{-5} M were recorded on a Cary 14 spectrophotometer with cells having path lengths from 0.01 to 15 cm. Ultraviolet spectra at concentrations below 10^{-5} M were recorded on a variable path length spectrophotomer which was calibrated with naphthalene, 2-methoxypyridine (λ_{max} 275 nm), and 1-methyl-2-pyridone (λ_{max} 310 nm).

A sample of 2-pyridone at 1.3×10^{-5}–3×10^{-6} M in cyclohexane with 5-cm cells shows one band with λ_{max} = 300 (A = 1.6). At 1.5×10^{-6} M in 300-cm cells two bands are observed in the spectrum of the pyridone with λ_{max} at 300 nm (A = 1.3) and at 278 nm (A = 1.0). At 7.5×10^{-7} the two bands have λ_{max} at 300 nm (A = 0.70) and at 278 nm (A = 0.8). At the lowest concentration, 10^{-7} M, the bands are λ_{max} at 300 nm (A = 0.23) and at 278 nm (A = 0.3).

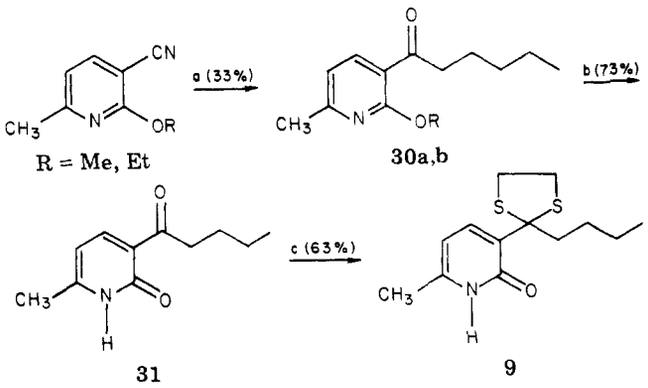
Variable-temperature studies of the ultraviolet spectrum of 2-pyridone were carried out in decane in the previously described 15-cm cell.[2]

A solution of 5×10^{-5} M 2-pyridone in decane at ambient temperature has a band at a λ_{max} of 300 nm (A = 0.64). At 100 °C the band centered at λ_{max} = 300 nm has a reduced absorbance of 0.47, and a second band with λ_{max} = 275 nm (A = 0.28) appears. The absorbances at elevated temperature are corrected for absorbances attributed to decomposition of impurities at the given temperature. Spectra recorded at 130, 150, and 160 °C show that above 130 °C the absorbance at λ_{max} = 275 nm is predominant. The ultraviolet spectrum of a solution allowed to cool to ambient temperature shows only an absorbance at λ_{max} = 300 nm (A = 0.62) after correction for the impurity absorbances.

The solution of 2-pyridone in decane was washed with five 2-mL portions of water, and a spectrum recorded of the water extract shows only an absorbance at λ_{max} = 300 (A = 0.5) identical with the spectrum of a fresh sample of 2-pyridone in water. A spectrum of the washed decane contained the absorbance of the impurities at λ_{max} = 260 nm (A = 0.18).

4-Methoxy-6-methyl-2-pyridone (6). To 50 mL of dry methanol was added 1.57 g (68.4 mmol) of sodium metal. When reaction was complete, 5.70 g (45.6 mmol) of 4-hydroxy-6-methyl-2-pyridone was added and the mixture heated to reflux, whereupon 25.47 g (136.8 mmol) of methyl tosylate was introduced. After 20 h at reflux, the mixture was allowed to cool to room temperature, the precipitated sodium tosylate was removed by filtration, and the clear filtrate was poured into 150 mL of 5% aqueous ammonia and stirred for 1 h. The resulting solution was then saturated with sodium chloride and extracted with methylene chloride, and the dried ($MgSO_4$) extract was evaporated in vacuo to yield fine white needles. Chromatography on silica gel with a 70:30 ethyl acetate–methanol mobile phase provided three fractions: **4** (25%), 2,4-dimethoxy-6-methylpyridine (6.7%), and 2-methoxy-1,6-dimethyl-4-pyridone (0.5%). Recrystallization of **4** four times from acetonitrile provided 1.08 g (18%) of pure **4**: mp 176–180 °C[41] (lit.[42] mp 172–173 °C); ^1H NMR δ 2.28 (s, CH_3), 3.77 (s, OCH_3), 5.75 (s, H_3 and H_5); IR 1655 cm^{-1} (C=O); UV λ_{max} 225 (ϵ 2600), 285 (5200); mass spectrum (10 eV), m/e 139 (M^+). Anal. ($C_7H_9NO_2$) C, H, N.

Scheme IV[a]



[a] a: (1) *n*-BuLi, THF, 0 °C; (2) 6 N aqueous H_2SO_4; (3) 10% aqueous KOH. b: $(CH_3)_3SiI$, $CHCl_3$, Δ. c: $HS(CH_2)_2SH$, $CHCl_3$, Δ, $BF_3 \cdot OEt_2$.

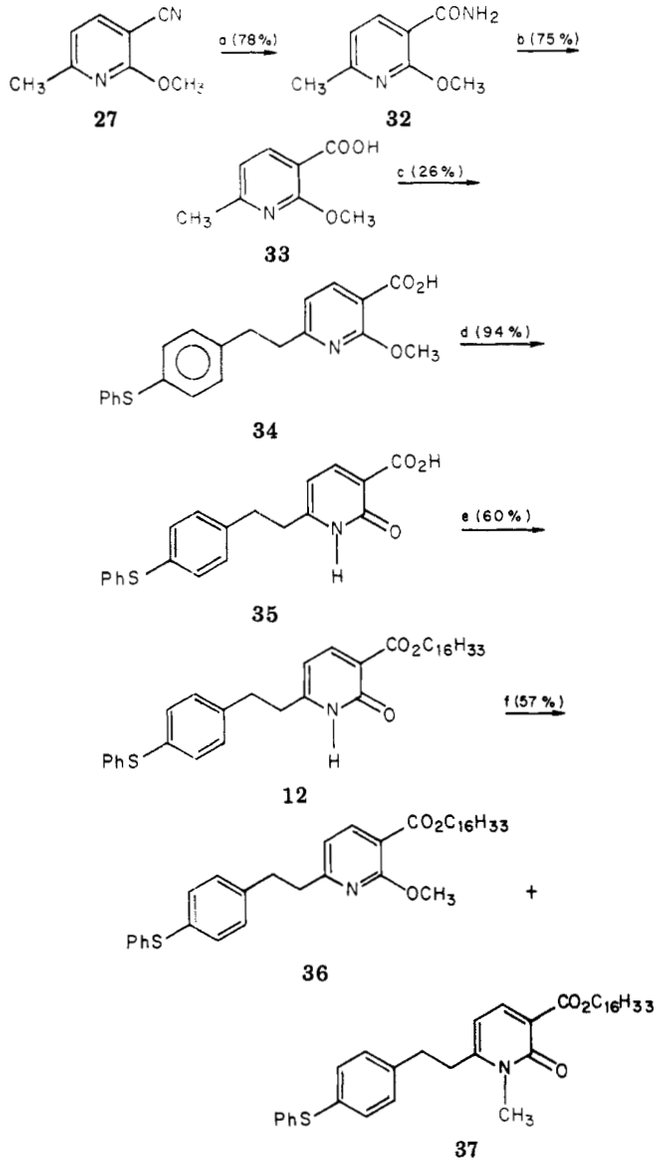
Synthesis. Syntheses of compounds **7**, **4**, **11**, and **13** were carried out as outlined in Schemes III–VI. In the synthetic procedures which follow the schemes, the phrase "extractive workup" refers to washing of an organic extract with dilute aqueous acid or base as necessary for the removal of basic or acidic impurities or reagents, respectively, followed by a wash with saturated NaCl solution.

2-Methoxy-3-cyano-6-methylpyridine (27). A dichloromethane slurry of 59.9 g (0.446 mol) of **26**[43] and 69.33 g (0.469 mol) of trimethyloxonium fluoborate was stirred at room temperature under a dry N_2 atmosphere for 48 h. At the end of this time excess 10% aqueous NaOH was added, and the organic phase was separated, washed with saturated aqueous NaCl solution, and dried over K_2CO_3. The solvent was removed at reduced pressure and the resulting crude product recrystallized from hexane–ethanol to afford 54.2 g (83%) of pure **27** as lustrous, white plates: mp 83–84 °C (lit.[44] mp 81.5 °C); ^1H NMR (CCl_4) δ 2.52 (s, 3 H, CH_3), 4.03 (s, 3 H, OCH_3), 6.73 (d, J = 8 Hz, 1 H, H-5), 7.69 (d, J = 8 Hz, 1 H, H-4); IR (Nujol mull) 2222 (C≡N), 1122 cm^{-1} (OCH_3). Anal. ($C_8H_8N_2O$) C, H, N.

2-Methoxy-6-methylpyridine-3-carboxaldehyde (28). A solution of 23.05 g (0.156 mol) of the nitrile **27** in dry toluene was cooled to −78 °C and treated dropwise with 23.23 g (0.163 mol) of neat diisobutylaluminum hydride (Ventron). After completion of the addition, the resulting bright yellow solution was allowed to stir at −78 °C for 30 min and then at ambient temperature for 3 h. Excess reducing agent was destroyed by addition of 100 mL of saturated aqueous NH_4Cl solution followed by stirring of the reaction mixture for 30 min at ambient temperature. The imine produced by the reduction was cleaned by addition of 100 mL of 5% aqueous H_2SO_4 to the above mixture followed by stirring for 5 min. Adjustment of the pH to 9 by addition of 10% aqueous KOH solution and extractive workup with toluene followed by

(38) P. Beak, *Tetrahedron*, **20**, 831 (1964), and references cited therein.
(39) P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. B*, 1226 (1967).
(40) H. C. van der Plas and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, 81, 841 (1962).
(41) The broad melting point appears to be due to the formation of dimorphic crystals from acetonitrile. A remelted sample has a melting point of 180–181 °C.
(42) H. M. Woodburn and M. Hellman, *Recl. Trav. Chim. Pays-Bas*, **70**, 813 (1951).
(43) L. J. Binovi and H. G. Arlt, Jr., *J. Org. Chem.*, **26**, 1656–75 (1961).
(44) R. P. Mariella and A. J. Havlik, *J. Am. Chem. Soc.*, **74**, 1915–6 (1952).

Scheme V[a]



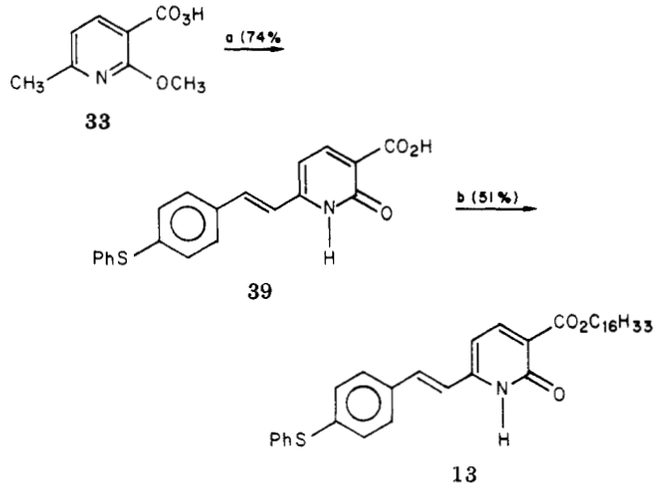
[a] a: 30% H_2O_2, 25% aqueous NaOH, EtOH, 50–60 °C. b: (1) 10% aqueous KOH; (2) H_3O^+. c: (1) 2 equiv of LDA, THF–hexane, −78 °C; (2) 4-(phenylthio)benzyl chloride; (3) H_3O^+. d: $(CH_3)_3SiI$, $CHCl_3$, room temperature, 18 h. e: (1) $(CH_3)_4N^+OH^-$, EtOH; (2) n-$C_{16}H_{33}OTs$, HMPA, 60 °C. f: $(CH_3O)_2SO_2$, K_2CO_3, DMF, room temperature.

removal of solvent at reduced pressure gave a slightly yellow oil. Sublimation at 90 °C and 0.5 mmHg afforded 18.5 g (80%) of **28** as a colorless solid: mp 44–45 °C; ^{1}H NMR (CCl_4) δ 2.50 (s, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 6.75 (d, J = 8 Hz, 1 H, H-5), 7.91 (d, J = 8 Hz, 1 H, H-4), 10.21 (s, 1 H, CHO); IR (Nujol mull) 2770 (aldehyde CH), 1695 cm^{-1} (aldehyde C=O). Anal. ($C_8H_9NO_2$) C, H, N.

2-Methoxy-3-[1-(*E*)-pentenyl]-6-methylpyridine (29). An ethereal solution of n-butylmagnesium iodide was prepared in the usual fashion from 196 mg (8.04 mmol) of magnesium turnings and 1.23 g (6.70 mmol) of 1-iodobutane. After the solution was cooled to −10 °C, it was treated dropwise with a solution of 1.00 g (6.70 mmol) of the aldehyde **28** in 8 mL of ether. The resulting mixture was allowed to stir for 16 h at room temperature and then quenched by addition of a few milliliters of saturated aqueous $NH_4^+Cl^-$ solution. Extractive workup with diethyl ether provided 1.16 g (84%) of the desired secondary carbinol product as a yellow oil. This material was indicated to be 85% pure with a single contaminant of the starting aldehyde **28** by ^{1}H NMR.

The crude carbinol was dehydrated in a hexamethylphosphoramide (HMPA) solution of 560 mg (2.71 mmol) of the

Scheme VI[a]



[a] a: (1) 2 equiv of LDA, THF–hexane, −78 °C; (2) 4-(phenylthio)benzaldehyde; (3) 1.1 equiv of TsOH; H_2O, toluene, Δ; (4) glacial AcOH, Δ. b: (1) $(CH_3)_4N^+OH^-$, MeOH; (2) n-$C_{16}H_{33}OTs$, HMPA, 60 °C.

alcohol and 2.45 g (5.41 mmol) of methyltriphenoxyphosphonium iodide at 75 °C for 2 h.[45] After the mixture was cooled to ambient temperature, the very dark reaction mixture was diluted with about 3 volumes of 10% NaOH solution and extracted with several portions of cyclohexane. The usual extractions were followed by removal of the solvent and distillation of the residue in a Kugelrohr apparatus at 0.5 mmHg with an air-bath temperature of 115–120 °C to afford 170 mg (33%) of **29** as a colorless oil: ^{1}H NMR (CCl_4) δ 0.93 (br t, J = 6 Hz, 3 H, CH_2CH_3), 1.10–1.70 (sextet, J = 6 Hz, 2 H, C-4 CH_2CH_3), 2.13 (q, J = 6 Hz, 2 H, =CHCH_2), 3.87 (s, 3 H, OCH_3), 5.96 (dt, J = 15, 6 Hz, 1 H, =CHCH$_2$), 6.38 (br d, J = 15 Hz, CH=CH), 6.46 (d, J = 8 Hz, H-5), 7.31 (d, J = 8 Hz, 1 H, H-4); IR (neat) 975 cm^{-1} (trans, olefinic CH deformation).

3-[1-(*E*)-Pentenyl]-6-methyl-2-pyridone (7). A chloroform solution of 170 mg (0.899 mmol) of **29** and 145 μL (1.12 mmol) of iodotrimethylsilane was heated at reflux under a dry N_2 atmosphere for 24 h. At the end of this time, the mixture was allowed to cool and then quenched by pouring it into an equal volume of methanol. The solvent was removed at reduced pressure. The residue was dissolved in dichloromethane, and the usual extractive workup followed. Removal of the solvent gave a yellow solid which was recrystallized from hexane to afford 90 mg (56%) of **7** as a colorless solid: mp 102–103 °C; ^{1}H NMR (CCl_4) δ 0.97 (t, J = 6 Hz, 3 H, CH_2CH_3), 1.49 (sextet, J = 6 Hz, 2 H, C-4 CH_2CH_3), 2.15 (dt, J = 6, 4 Hz, 2 H, =CHCH_2), 2.39 (s, 3 H, 6-CH_3), 5.86 (d, J = 8 Hz, 1 H, H-5), 6.25 (d, J = 15 Hz, 1 H, olefinic proton α to ring), 6.39 (dt, J = 15, 4 Hz, 1 H, olefinic proton β to ring), 7.20 (d, J = 8 Hz, 1 H, H-4); IR (Nujol mull) 1650 (lactam C=O), 978 cm^{-1} (trans olefinic CH deformation); UV (CH_2Cl_2) λ_{max} 250 nm (ϵ 6000), 332 (800). Anal. ($C_{11}H_{15}NO$) C, H, N.

Mixture of 2-Methoxy-3-pentanoyl-6-methylpyridine (30a) and 2-Ethoxy-3-pentanoyl-6-methylpyridine (30b). A dry THF solution of 5.50 g (36.5 mmol) of a 60:40 mixture of 2-methoxy-3-cyano-6-methylpyridine (**27**) and its 2-ethoxy homologue (prepared analogously to **27** from **26** by using a mixture of trimethyl- and triethyloxonium fluoborate) was cooled to 0 °C and 16.47 mL of 2.44 M n-butyllithium in hexane (40.2 mmol) added dropwise over about 10 min. The resulting very dark red mixture was stirred at 0 °C for 30 min and subsequently at room temperature for 1 h. The reaction was then cautiously quenched by slow addition of 6 N H_2SO_4, and the two-phase mixture so produced was heated to 50–60 °C and vigorously stirred for 2 h. The mixture was then made basic by addition of 10% aqueous KOH solution, hexane was added, the layers were separated, and the aqueous phase was extracted twice with THF–hexane. Extractive workup followed by removal of the organic solvent gave

(45) R. O. Hutchins, M. G. Hutchins, and C. A. Milewski, *J. Org. Chem.*, **37**, 4190–2 (1972).

a reddish brown oil which was then further purified by medium-pressure liquid chromatography on silica gel using 80:20 hexane–ether as the mobile phase. This yielded 2.50 g (33%) of a yellow oil which was shown by ^{1}H NMR to be an 85:15 mixture of **30a** and **30b**, respectively.

3-Pentanoyl-6-methyl-2-pyridone (31). The mixture of **30a** and **30b** (2.41 g, 11.63 mmol) was heated with 3.02 mL (23.3 mmol) of iodotrimethylsilane at reflux in dry $CHCl_3$ for 16 h under an N_2 atmosphere. After a workup similar to that used for **7**, crude pyridone **31** was obtained. Recrystallization from aqueous ethanol gave 1.64 g (73%) of **31** as cream-colored crystals: mp 183–185 °C; ^{1}H NMR ($CHCl_3$) δ 0.94 (br t, J = 6 Hz, 3 H, CH_2CH_3), 1.20–1.90 (m, 4 H, $CH_2CH_2CH_2CH_3$), 2.47 (s, 3 H, 6-CH_3), 3.13 (br t, J = 6 Hz, 2 H, $COCH_2$), 6.23 (d, J = 8 Hz, 1 H, H-5), 8.17 (d, J = 8 Hz, 1 H, H-4), 13.5 (br s, 1 H, NH); IR (Nujol mull) 1669 (ketone C=O), 1645 cm^{-1} (lactam C=O).

2-(6-Methyl-2-pyridon-3-yl)-2-*n*-butyl-1,3-dithiolane (9). Pyridone ketone **31** (0.531 g, 2.75 mmol) was heated in refluxing chloroform for 24 h with 1.30 g (13.76 mmol) of ethanedithiol in the presence of a catalytic amount of boron trifluoride etherate. Extractive workup followed by removal of solvent provided a slightly yellow solid. Recrystallization from acetonitrile afforded 467 mg (63%) of the dithioketal **9** as colorless, fibrous needles: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (br t, $J \simeq$ 6 Hz, 3 H, CH_2CH_3), 1.22 (m, 4 H, $CH_2CH_2CH_3$), 2.33 (s, 3 H, 6-CH_3), 2.59 (br t, 6 Hz, 2 H, S_2—C—CH_2), 3.18 (m, A_2B_2, 4 H, $(SCH_2)_2$), 5.97 (d, J = 8 Hz, 1 H, H-5), 7.83 (d, J = 8 Hz, 1 H, H-4), 13.0 (br s, 1 H, NH); IR (Nujol mull) 1642 cm^{-1} (lactam C=O); UV (CH_2Cl_2) λ_{max} 237 nm (ϵ 6100), 310 (10 000). Anal. ($C_{13}H_{19}NOS_2$) C, H, N, S.

2-Methoxy-6-methylpyridine-3-carboxamide (32). To a solution of 4.86 g (32.8 mmol) of **27** in a mixture of 40 mL of 95% ethanol and 15 mL of 25% aqueous NaOH was added with stirring 16.73 mL (164 mmol) of 30% H_2O_2 in a single portion. The reaction temperature was held below 60 °C by occasional cooling in an ice bath until the initial moderately strong exotherm and accompanying O_2 evolution had subsided. The temperature of the mixture was then held at 55 °C for 3 h. After this time the mixture was allowed to cool and was neutralized by addition of concentrated HCl, and the precipitated product was then collected by filtration. Recrystallization of this crude product from water gave 3.90 g (78%) of **32** as a colorless solid: mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3 H, 6-CH_3), 4.10 (s, 3 H, OCH_3), 6.85 (d, J = 8 Hz, 1 H, H-5), 8.37 (d, J = 8 Hz, 1 H, H-4); IR (Nujol mull) 3425, 3135 (amide NH), 1667 cm^{-1} (C=O). Anal. ($C_8H_{10}N_2O_2$) C, H, N.

2-Methoxy-6-methylpyridine-3-carboxylic Acid (33). Heating 3.74 g (2.25 mmol) of **32** at reflux in 10 mL of 10% aqueous KOH for 3 h followed by acidification to pH 4 gave a flocculent precipitate of **33**, as 2.83 g (75%) of an analytically pure white solid: mp 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3 H, 6-CH_3), 4.15 (s, 3 H, OCH_3), 6.92 (d, J = 8 Hz, 1 H, H-5), 8.30 (d, J = 8 Hz, 1 H, H-4); IR (Nujol mull) 3300–2500 (br, COOH OH), 1686 cm^{-1} (C=O). Anal. ($C_8H_9NO_3$) C, H, N.

2-Methoxy-6-[2-(4′-phenylthio)phenethyl]pyridine-3-carboxylic Acid (34). A THF–hexane solution of lithium diisopropylamide (LDA) was prepared at −78 °C from 7.46 g (73.7 mmol) of diisopropylamine and 30.20 mL of 2.44 M *n*-butyllithium in hexane (73.7 mmol). To this was added dropwise, at −78 °C, a THF solution of the acid **33** (5.87 g, 35.1 mmol), giving a bright yellow-orange solution. After completion of the addition, the mixture was allowed to stir at −78 °C for 30 min, whereupon a solution of 4-(phenylthio)benzyl chloride[25,46] (8.24 g, 35.1 mmol) was added in a single portion and the cooling bath removed. After being stirred for 5 h at room temperature, the reaction was quenched by addition of a few drops of water.

The yellow solution was acidified to pH 4 by addition of 10% HCl solution and hexane added. Extractive workup of the resulting solution provided a yellow oil. When this oil was cooled to −20 °C for 24 h, yellow crystals were obtained; these were isolated by filtration and washed well with benzene to afford 4.4 g of crude **34**. Two recrystallizations from benzene–hexane and three from methanol gave 3.28 g (26%) of pure **34**, mp 127–128 °C. The crude product oil could also be purified by medium-pressure liquid chromatography on silica gel, affording essentially the same yield of the desired product. The major side product in this reaction was identified as 1,2-bis[4-(phenylthio)phenyl]-ethane. For **34**: ^{1}H NMR ($CDCl_3$) δ 3.07 (br s, 4 H, Ar—$(CH_2)_2$—pyr), 4.14 (s, 3 H, OCH_3), 6.88 (d, J = 8 Hz, 1 H, H-5 of pyridine ring), 7.00–7.40 (m, 9 H, Ar H of Ar—S—Ar moiety), 8.31 (d, J = 8 Hz, 1 H, H-4 of pyridine ring); IR (Nujol mull) 3400–2100 (br) (COOH OH), 1689, 1667 cm^{-1} (COOH C=O). Anal. ($C_{21}H_{19}NO_3S$) C, H, N, S.

6-[2-(4′-Phenylthio)phenethyl]-2-pyridone-3-carboxylic Acid (35). A dry chloroform solution of 3.28 g (8.98 mmol) of **34** and 2.69 mL (20.2 mmol) of iodotrimethylsilane was stirred under a dry N_2 atmosphere at room temperature for 18 h. The resulting bright red solution was poured into excess methanol and the solvent removed in vacuo from that mixture. The residue was taken up in 95% ethanol and the solution treated with 10% aqueous $NaHSO_3$ until the color of I_2 was fully dissipated. The mixture was then heated to the boiling point and water added to dissolve some precipitated inorganic salts. As the mixture cooled, colorless crystals of product separated which were collected by filtration and air-dried to provide 2.95 g (94%) of analytically pure **35** as colorless crystals: mp 189–191 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.97 (s, 4 H, Ar—$(CH_2)_2$—pyr), 6.51 (d, J = 8 Hz, 1 H, H-5 of pyridone ring), 7.29 (m, 9 H, Ar H of Ar—S—Ar), 8.26 (d, J = 8 Hz, 1 H, H-4 of pyridone ring); IR (Nujol mull) 3300–2600 (br) (COOH OH), 1739 (COOH C=O), 1642 cm^{-1} (lactam C=O). Anal. ($C_{20}H_{17}NO_3S$) C, N, S.

***n*-Hexadecyl 6-[2-(4′-Phenylthio)phenethyl]-2-pyridone-3-carboxylate (12).** The acid **35** (2.95 g, 8.39 mmol) was dissolved in a minimum amount of hot methanol, and 2 drops of 1% ethanolic phenolphthalein were added. This mixture was then titrated to the end point with methanolic tetramethylammonium hydroxide (Aldrich). The alcoholic solvent was then removed in vacuo and replaced with 75 mL of dry HMPA. Solid *n*-hexadecyl tosylate (3.50 g, 8.81 mmol) was added and the mixture stirred at 60 °C for 24 h. At the end of this time the mixture was poured into 400 mL of ice water and the resulting cream-colored emulsion worked up by extracting with THF–benzene to afford an oil. Purification of this oil was accomplished by medium-pressure liquid chromatography (LC) on silica gel employing 90/8/2 chloroform/hexane/ethanol as the mobile phase. Crystallization of the product fractions from hexane gave 2.82 g (60%) of analytically pure **12**: mp 65.5–66.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (br t, $J \simeq$ 6 Hz, 3 H, terminal CH_3 of hexadecyl chain), 1.26 (br s, 28 H, interior methylenes of the hexadecyl chain), 2.98 (br s, 4 H, Ar—$(CH_2)_2$—pyr), 4.23 (br t, $J \simeq$ 6 Hz, 2 H, CO_2CH_2), 6.15 (d, J = 8 Hz, 1 H, H-5 of pyridone ring), 7.21 (br s, 9 H, Ar H of Ph—S—Ph), 8.07 (d, J = 8 Hz, 1 H, H-4 of pyridone ring); IR (Nujol mull) 1748 (ester C=O), 1647 (lactam C=O), 1269, 1121 cm^{-1} (ester CO); UV (cyclohexane) λ_{max} 215 nm (ϵ 23 600), 235 (19 100), 254 (16 400), 300 (16 400); mass spectrum (70 eV) m/e (% of base) 577 (9.45), 576 (24.21), 575 (M^+, 61.4), 333 (41.3), 224 (12.9), 201 (20.21), 200 (100). Anal. ($C_{36}H_{49}NO_3S$) C, H, N, S.

***n*-Hexadecyl 2-Methoxy-6-[2-(4′-phenylthio)phenethyl]-pyridine-3-carboxylate (36) and *n*-Hexadecyl 6-[2-(4′-Phenylthio)phenethyl]-1-methyl-2-pyridone-3-carboxylate (37).** A mixture of 198 mg (0.34 mmol) of **12**, 2.5 g (18 mmol) of potassium carbonate, and 0.5 mL (0.5 mmol) of dimethyl sulfate was stirred for 18 h at room temperature in dimethylformamide solution. At the end of this time, the reaction mixture was diluted with water and worked up extractively with diethyl ether to provide an oil which NMR indicated to be a 2:3 mixture of **36** and **37**, respectively. These were separated into two bands by preparative TLC on silica gel using 1:1 hexane–ether as the developer.

The high-R_f component was eluted from the plate with chloroform. After removal of the solvent, an oil was obtained which was crystallized from ethyl acetate to afford 51 mg (25%) of **36**: mp 39–40 °C; ^{1}H NMR (CCl_4) δ 0.92 (br t, $J \simeq$ 6 Hz, 3 H, terminal CH_3 of hexadecyl chain), 1.28 (br s, 28 H, interior methylenes of hexadecyl chain), 3.00 (br s, 4 H, Ar—$(CH_2)_2$—pyr), 3.95 (s, 3 H, OCH_3), 4.19 (br t, $J \simeq$ 6 Hz, 2 H, CO_2CH_2), 6.60 (d, J = 8 Hz, 1 H, H-5 of pyridone ring), 7.15 (br s, 9 H, Ar H of Ar—S—Ar), 7.93 (d, J = 8 Hz, 1 H, H-4 of pyridone ring); UV (CH_2Cl_2) λ_{max} 229 nm (sh), 259 (ϵ 7600), 284 (8200). Anal. Calcd for $C_{37}H_{51}NO_3S$:

(46) G. Cavallini, E. Massarani, D. Nardi, L. Mauri, and F. Tencovi, *Farmaco, Ed. Sci.*, 19, 964–71 (1964).

C, 75.34; H, 8.71. Found: C, 74.66; H, 8.99.

The component of low R_f was eluted with ethyl acetate; reduction in volume of the resulting solution gave 65 mg (32%) of **37**: mp 59–60 °C; ^{1}H NMR (CCl_4) δ 0.96 (br t, $J \simeq 6$ Hz, 3 H, terminal CH_3 of hexadecyl chain), 1.33 (br s, 28 H, interior methylenes of hexadecyl chain), 2.90 (br s, 4 H, Ar—$(CH_2)_2$—pyr), 3.47 (s, 3 H, NCH_3), 4.16 (br t, J = 6 Hz, 2 H, CO_2CH_2), 5.86 (d, J = 8 Hz, 1 H, H-5 of pyridone ring), 7.23 (br s, 9 H, Ar H of Ar—S—Ar), 7.80 (d, J = 8 Hz, 1 H, H-4 of pyridone ring); UV (CH_2Cl_2) λ_{max} 245 nm (ϵ 7600), 273, 345 (6300). Anal. ($C_{37}H_{51}NO_3S$) C, H.

6-[(4′-Phenylthio)-(*E*)-styryl]-2-pyridone-3-carboxylic Acid (39). The LDA dilithiation of 4.57 g (27.3 mmol) of carboxylic acid **38** was performed in a manner analogous to that employed for the preparation of **34**. The dilithiated species was then trapped by addition at −78 °C of a THF solution of 5.86 g (27.3 mmol) of 4-(phenylthio)benzaldehyde.[24,47] The reaction mixture was allowed to warm to room temperature and stirred for 2 h. After the mixture was quenched with a few drops of water and acidified to pH 3 with 10% aqueous HCl, extractive workup provided a yellow solid which was indicated by ^{1}H NMR to be composed of 85% of the desired secondary carbinol. This material was not purified but was, instead, dehydrated directly by heating with 6.0 g (31.5 mmol) of toluenesulfonic acid monohydrate in toluene at reflux with continuous removal of the water formed. The orange solid obtained was taken up in hot glacial acetic acid and decolorized with carbon. The solids obtained on cooling were washed with water followed by recrystallization of the crude material from glacial acetic acid to give 2-pyridone **39**. The yield of yellow plates, mp 270–271 °C dec, was 7.1 g (74% overall from **38**): ^{1}H NMR (Me_2SO-d_6) δ 6.95 (d, J = 8.4 Hz, 1 H, pyridone H-5), 7.05 (d, J = 15.6 Hz, 1 H, olefinic proton α to pyridone ring), 7.40 (AA′BB′ q, J = 8.4 Hz, 4 H, disubstituted Ar H), 7.40 (s, 5 H, 5 Ar H), 7.78 (d, J = 15.6 Hz, 1 H, olefinic H α to phenyl ring), 8.30 (d, J = 8.4 Hz, 1 H, pyridone H-4); IR (Nujol mull) 3400–2400 (br, COOH OH), 1742 (COOH C=O), 1632 (lactam C=O), 973 (trans olefinic CH deformation); mass spectrum (70 eV), m/e (% of base) 351 (8.61), 350 (24.76), 349 (M^+, 100). Anal. ($C_{20}H_{15}NO_3S$) C, H, N, S.

(47) H. H. Szmant, J. M. Segedi, and J. Dudek, *J. Org. Chem.*, 18, 745–7 (1953).

***n*-Hexadecyl 6-[(4′-Phenylthio)-(*E*)-styryl]-2-pyridone-3-carboxylate (13).** Esterification of 4.80 g (13.7 mmol) of **39** was accomplished by alkylation of the corresponding tetramethylammonium salt with 5.74 g (14.4 mmol) of hexadecyl tosylate in HMPA in a manner analogous to that employed for the corresponding saturated system **35**. The crude product so obtained was purified by medium-pressure LC on silica gel employing 70/25/5 chloroform/hexane/ethyl acetate as the mobile phase. The fractions containing **13** were combined, and the solvent was removed at reduced pressure. The resulting yellow solid was crystallized from hexane to afford 4.00 g (51%) of pure **13** as bright yellow, matted needles: mp 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (br t, $J \simeq 6$ Hz, 3 H, terminal CH_3 of hexadecyl chain), 2.29 (br s, 38 H, interior methylenes of hexadecyl chain), 4.27 (t, J = 6 Hz, 2 H, CO_2CH_2), 6.57 (d, J = 8.4 Hz, 1 H, pyridone H-5), 6.86 (d, J = 15.4 Hz, 1 H, CH=$CHC_6H_4C_6H_5$), 7.10–7.73 (m, 9 H, Ar H of Ar—S—Ar), 7.85 (d, J = 15.4 Hz, 1 H, CH=$CHC_6H_4SC_6H_5$), 8.13 (d, J = 8.4 Hz, 1 H, pyridone H-4); IR (Nujol mull) 1751, 1736 (ester C=O), 1631 (lactam C=O), 1282, 1149 (ester CO), 989 cm^{-1} (trans olefinic CH deformation); UV (cyclohexane) λ_{max} 219 nm (ϵ 15 500), 254 (14 400), 373 (35 300); mass spectrum (70 eV), m/e (% of base) 575 (17), 574 (40.3), 573 (M^+, 100), 332 (64.7). Anal. ($C_{36}H_{47}NO_3S$) C, H, N, S.

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Registry No. 1, 72762-00-6; **2**, 142-08-5; **3**, 73018-09-4; **4**, 17228-61-4; **5**, 72917-96-5; **6**, 72982-87-7; **7**, 72917-97-6; **8**, 73035-73-1; **9**, 72917-98-7; **10**, 72983-37-0; **11**, 72917-99-8; **12**, 73035-74-2; **13**, 72918-00-4; **14**, 73035-75-3; **15**, 73018-10-7; **16**, 2637-34-5; **17**, 626-64-2; **18**, 108-96-3; **19**, 17368-12-6; **20**, 17228-67-0; **21**, 13603-44-6; **22**, 7516-31-6; **23**, 72918-01-5; **24**, 72918-02-6; **26**, 4241-27-4; **27**, 72918-03-7; **28**, 72918-04-8; **29**, 72918-05-9; **30a**, 72918-06-0; **30b**, 72918-07-1; **31**, 72918-08-2; **32**, 72918-09-3; **33**, 72918-10-6; **34**, 72918-11-7; **35**, 72918-12-8; **36**, 72918-13-9; **37**, 72918-14-0; **38**, 38116-61-9; **39**, 72918-15-1; 4-hydroxy-6-methyl-2-pyridone, 3749-51-7; 2,4-dimethoxy-6-methylpyridine, 40334-96-1; 2-methoxy-1,6-dimethyl-4-pyridone, 40334-98-3; 2-ethoxy-3-cyano-6-methylpyridine, 54957-81-2; 4-(phenylthio)benzyl chloride, 1208-87-3; 1,2-bis[4-(phenylthio)-phenyl]ethane, 72918-16-2; *n*-hexadecyl tosylate, 6068-28-6; 4-(phenylthio)benzaldehyde, 1208-88-4.

π-Complexed β-Arylalkyl Derivatives. 6. Effect of Electron-Withdrawing Substituents on the Acetolysis of 2-[π-(Aryl)chromium tricarbonyl]-2-methyl-1-propyl Methanesulfonates[1]

Robert S. Bly,* Ester K. Ni, Albert K. K. Tse, and Easley Wallace

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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The π-(arene)chromium tricarbonyl complexes of *m*-methoxy- and *p*-chloro-substituted 2-[π-(phenyl)chromium tricarbonyl]-2-methyl-1-propyl (neophyl) methanesulfonates have been prepared and their acetolysis rates determined. At 99.5 °C, the complexes are, respectively, 1.1 and 1.6 times as reactive as their noncomplexed counterparts. The *p*-chloroneophyl complex yields, after oxidative decomplexation of the product mixture with Ce(IV), 54% 3-(*p*-chlorophenyl)-2-methyl-2-propyl acetate, 34% 3-(*p*-chlorophenyl)-2-methyl-1-propene, and 12% 1-(*p*-chlorophenyl)-2-methyl-1-propene. No nonaryl-migrated products are observed. The acetolysis rates of *p*-methoxy-, *m*-methoxy-, *p*-methyl-, *m*-methyl-, and *p*-chloroneophyl complexed and noncomplexed methanesulfonates at 99.5 °C are well correlated by the Yukawa–Tsuno relations: $\log (k/k_0)_{complex} = -3.39[\sigma + 0.47(\sigma^+ - \sigma)] - 0.03$ and $\log (k/k_0)_{noncomplex} = -1.97[\sigma + 0.18(\sigma^+ - \sigma)] - 0.16$. The meaning of these correlations is discussed, and it is concluded that in addition to its strong inductive electron withdrawal, π-tricarbonylchromium acts amphoterically to donate or withdraw electrons by resonance. From a comparison of the relative acetolysis rates of the *p*- and *m*-methoxy complexes, it is suggested that the π-tricarbonylchromium probably does not act via direct d-orbital participation to accelerate the solvolysis rates of the complexes.

In a previous paper in this series[2] we reported that the acetolysis rates at 75 °C of the π-(arene)chromium tricarbonyl complexes of 2-phenyl-2-methyl-1-propyl (neophyl) and *p*-methoxy-, *p*-methyl-, and *m*-methylneophyl

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