Solvent Effects on the Tautomerism of *t*-Butyl 2-Picolyl and *t*-Butyl Quinaldyl Ketones

R. Roussel, M. Oteyza de Guerrero, P. Spegt and J. C. Galin

Centre de Recherches sur les Macromolécules 6, rue Boussingault,
67083 Strasbourg, France
Received October 15, 1981

The tautomeric equilibria (constant K_T) of *t*-butyl 2-picolyl ketone (ketone $\leftrightharpoons$ enol) and of *t*-butyl quinaldyl ketone (ketone $\leftrightharpoons$ enamine) in semi-dilute solution (0.3 mole.l^{-1}) were studied by ^{1}H-nmr and uv spectroscopy as a function of solvent polarity, for a set of twenty-five different solvents including apolar, dipolar aprotic as well as amphiprotic ones. The contribution of electrostatic field effects (π^*), of solute-solvent hydrogen bonding interactions (α) and of solvent cavitation effects (δ_h) were estimated separately and critically discussed, using multiparametric regression analysis and empirical polarity parameters, according to the "Solvatochromic Comparison Method" developed by Taft, *et al.* For both heterocyclic ketones, the hydrogen bond donor power of the solvent (α) is the major factor of the K_T variations, as a result of preferential solvation of the ketonic tautomer.

Introduction.

In the course of our studies on the reaction of a series of heterocyclic organo-lithium reagents on polymethylmethacrylate and on the specific properties of the derived copolymers, we were faced with he problem of the tautomerism of some keto-β-heterocyclic structures, especially 2-picolyl and quinalkyl ketones (1-3). As part of the important field of the tautomerism of heterocyclics (4), the tautomerism of such structures has already been investigated for low molecular weight compounds, mostly for the identification of the tautomers. We have focused our attention on the analysis of the prototropic equilibrium in solution with special emphasis on the influence of the solvent polarity, because of the scarcity of quantitative data in this particular area. As a matter of fact, comparison between the solvent dependence of the tautomerism of low molecular weight model compounds and of macromolecules labelled with identical structures may provide a useful strategy for testing the polarity of the microenvironment of polymeric chains in solution (3,5). This factor does contribute in a significant way to the reactivity of macromolecules in solution (6), and it still remains to be measured quantitatively. In the present communication, the experimental results we obtained for the tautomerism of *t*-butyl 2-picolyl ketone (A) and *t*-butyl quinalkyl ketone (C) in solution will be discussed according to recent trends in the field of solvent polarity effects on chemical processes (7).
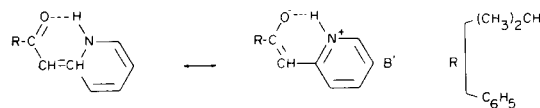
Results.

Nature of the Tautomers and Determination of the Tautomeric Equilibrium Constant.

For a long time, nmr and uv spectroscopy has allowed the identification of the conjugated tautomeric forms, *i.e.* chelated enol B (8-10) and chelated enamine D (8,11), for the heterocyclic ketones A and C respectively.
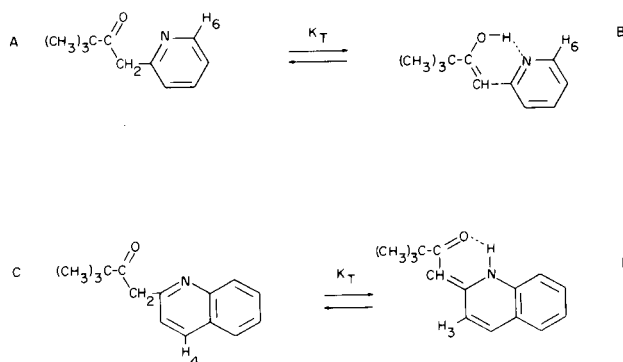
Chelation is a major but not the only factor of the tautomer B and D stability, since enolization does occur, but to a much lower extent, for 4-picolyl and 4-methylquinolyl ketones where chelation is excluded (8,10). The possibility of a low fraction of non chelated enol or enamine cannot be thus completely ruled out. According to Klose and Uhlemann (12), 2-picolyl ketones may exist in the form of a pyridinium enolate B' in carbon disulfide solution:

This zwitterionic structure is merely a canonical form of the enamine one which has also been quoted by Wolfe, *et al.* (13), but apparently as the result of a misunderstanding of Mondelli and Merlini's conclusions (8). Moreover, the enaminic structure has been rejected by Katrizky, *et al.* (4) in their recent critical survey of the tautomerism of heterocycles. Consideration of this controversial problem is out of the scope of the present work, and only a single ketone A $\leftrightharpoons$ enol B equilibrium is taken into account in the following discussion.

The determination of the tautomerism constant K_T rests

Table I

'H-NMR Patterns of the Various Tautomers (a,b)

	-CO·CH$_2$	-CH	-H$_6$	-H$_3$	-H$_4$	-OH	-NH
A	(s) 4.02		(m) 8.32				
B		(s) 5.44	(m) 8.22			(s) 15.0	
C	(s) 4.20				(m) 8.25		
D		(s) 5.55		(m) 6.95			(s) 14.15

(a) Chemical shifts δ in ppm at 28°C, for a solute concentration $\cong$ 0.3 mole.l^{-1}, (s) singlet, (m) multiplet. (b) The t-butyl group may be split into two well separated singlets in some solvents, and especially in aromatic ones: δ_B - δ_A = 0.30 and δ_D - δ_C = 0.33 ppm in benzene for instance.

upon the quantitative analysis of the well resolved 'H-nmr spectra, as described in literature (8-11). The average values of the chemical shifts of some characteristic hydrogen atoms are collected in Table I. The accuracy of K_T is about ± 6% in the best cases ($K_T \cong$ 1), but it decreases drastically when one tautomer is highly predominant, and may be lower than 20% as for a molar fraction higher than 0.90.

The uv spectra in dilute solution, for solute molar fraction lower than 0.01, are characterized by two main absorption bands, in good agreement with literature data (8,11). At higher wavelength λ_2, the absorption related to the $\pi \rightarrow \pi^*$ transition of the conjugated chromophores appears as a single band with a well defined maximum at 318 nm for the enol B, and as a more complex band showing three maxima at 405, 420 and 445 nm with relative intensities in the nearly constant ratios 0.81:1.00:0.69, for the enamine D. Because of chelation, these absorption bands show only a slight hypsochromic shift when increasing the solvent polarity: λ_2 (B) = 319 and 313 nm in hexane and trifluoroethanol respectively, for instance. At lower wavelength λ_1, the observed bands, mainly to the $\pi \rightarrow \pi^*$ transition of the heterocyclic nucleus, show a poorly defined peak at λ = 264 ± 6 nm for A,B and a broad absorption with successive maxima at about 276, 291, 302, 314 and 322 nm for C,D. The overall (A,B) absorption band is shifted from 270 to 258 nm when going from a non polar solvent like hexane to a very strong hydrogen bond donor solvent like trifluoroethanol. At a constant total concentration of solute c, the tautomeric equilibrium may be easily modified using various binary mixtures of two solvents of sufficiently different polarities, like dioxane and acetonitrile for instance. For t-butyl 2-picolyl ketone, increasing acetonitrile fraction shifts the equilibrium towards the ketonic form, and the lack of any isosbestic point and the simultaneous decrease of both λ_1 and λ_2 bands clearly show that the conjugated tautomer B does contribute to the complex absorption at the shorter wavelength. Following the same approach as Llor and Cortijo (14), and assuming no significant changes of molar absorptivities with the solvent polarity, it may be easily shown that:

$$D_2 = D_1 \left[\epsilon_2/(\epsilon_1' - \epsilon_1) \right] - c \, \ell \, \epsilon_1 \epsilon_2/(\epsilon_1' - \epsilon_1)$$

where D_1 and D_2 are the absorbances at λ_1 and λ_2; ϵ_1 the molar absorptivity of the ketonic tautomer at λ_1; ϵ_1' and ϵ_2 the molar absorptivities of the conjugated tautomer at λ_1 and λ_2 respectively; ℓ the optical length. This linear relationship, illustrated in Figure 1, allows only the determination of a reasonable value of $\epsilon_1 : \epsilon_1$ = 2870 l.mole^{-1}.cm^{-1} versus ϵ_1 2-picoline = 2450 l.mole^{-1}.cm^{-1} at λ = 262 nm in dioxane. On the other hand, comparison of uv and 'H-nmr
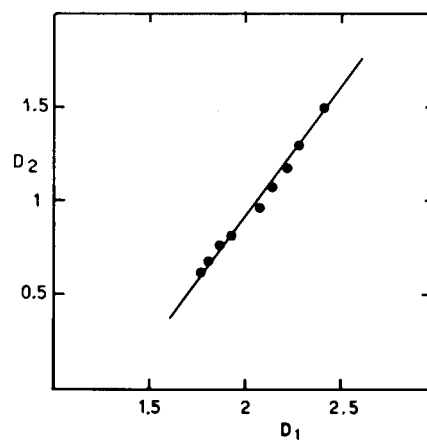

Figure 1. The uv spectrum of t-butyl 2-picolyl ketone (4.6 × 10^{-3} mole.l^{-1}) in dioxane-acetonitrile binary solvents. Variations of the long wavelength absorbance $D_2(\lambda_2$ = 317 nm) with the short wavelength absorbance $D_1(\lambda_1$ = 263 nm) for various solvent compositions (the volume fraction of acetonitrile is increased stepwise by increment of 0.1).

data obtained at the same concentration of 10^{-2} mole.l^{-1} in dimethylsulfoxide solution leads to the following values:

ϵ_2(B) = 7500 ± 370, ϵ_2(D) = 9900 ± 500 l.mole^{-1}.cm^{-1} practically independent of temperature within the range of 25-110°C. Beer's law is well obeyed within the concentration range of 4 × 10^{-4}-4 × 10^{-2} mole.l^{-1}, and the tautomeric equilibria may be thus safely considered as independent of concentration for these dilute solutions. The uv measurements however are very sensitive to the residual water content of the solvents: for insufficiently dried solvents, it may be of the same order of magnitude

as the solute concentration, and preferential solvation water-ketonic tautomers — see Discussion — may lead to strongly underestimated K_T values. Influence of preferential or specific hydration upon tautomeric equilibria has been recently reemphasized by Dubois, *et al.* (15). Moreover, the independence of the molar absorptivities of the conjugated chromophores with respect to solvent polarity is not quite ascertained. In these conditions, K_T values were derived from ^{1}H-nmr spectrometry in most cases.

Concentration Effects on the Tautomeric Equilibria.

The experimental results related to carbon tetrachloride and dimethylsulfoxide solutions at 28° are illustrated in Figures 2 and 3.

Concentration effects mainly result from differences between solvent and solute relative polarities, and possible self-association of a given tautomer may also contribute to the observed equilibrium (16). Dilution with carbon tetrachloride, less polar than the solutes, is expected to favour the less polar chelated tautomers B and D, whereas opposite effects should occur in dimethylsulfoxide solution.
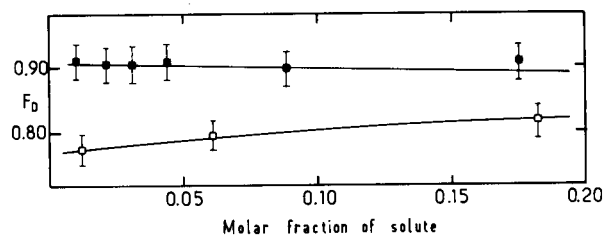

Figure 3. Influence of dilution on the t-butyl quinaldyl ketone tautomerism at 28°. Varations of the enamine fraction F_D with the total molar fraction of the solute in carbon tetrachloride (■) and dimethylsulfoxide (□) solutions.

These equilibrium shifts actually occur in the case of t-butyl 2-picolyl ketone (figure 2), but in the case of t-butyl quinaldyl ketone and for a molar fraction lower than 0.2 (upper limit of solubility), concentration effects are drastically levelled off (Figure 3). On the other hand, vapor phase osmometry measurements performed at 30° on carbon tetrachloride solutions have shown that t-butyl 2-picolyl ketone is essentially monomeric for molar frac-
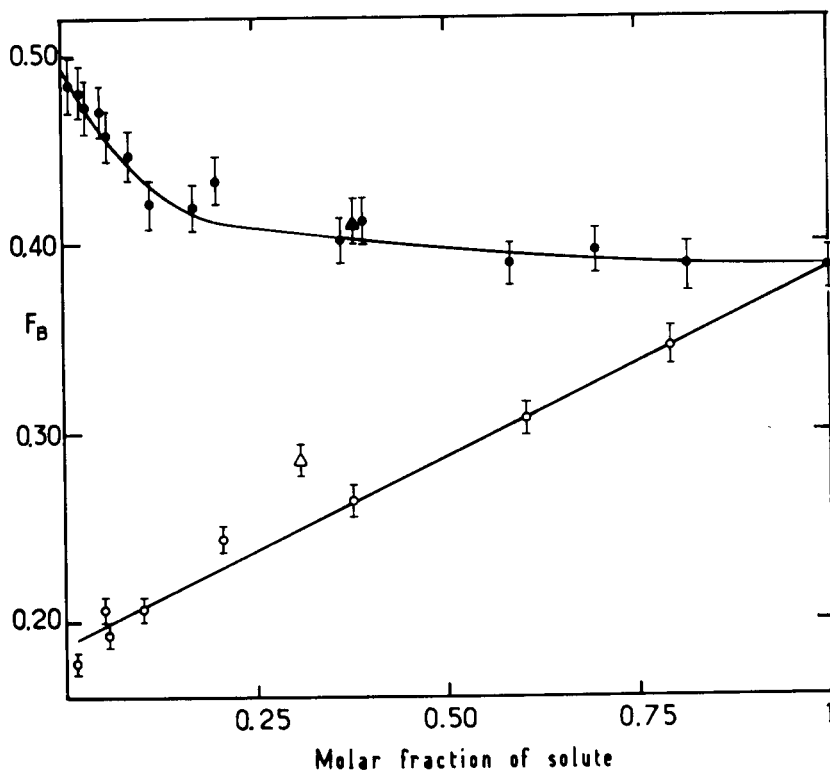

Figure 2. Influence of dilution on the t-butyl 2-picolyl ketone tautomerism at 28°. Variations of the enol fraction F_B with the total molar fraction of the solute in carbon tetrachloride (●) and dimethylsulfoxide (O) solutions. ▲ and △ literature data (10).

tions lower than 0.1 (M exp. = 180 ± 6 versus M Theor. = 177.3): the observed dilution behaviour cannot be thus correlated with the concentration dependence of any self-association equilibrium. Finally, at higher dilution for solute molar fraction lower than 1×10^{-3}, the tautomeric equilibria of both heterocyclic ketones are no more affected by concentration effects (see uv measurements in the preceeding section).

Solvent Effects on the Tautomeric Equilibria.

Some K_T values, restricted to carbon tetrachloride, chloroform and dimethylsulfoxide solutions, have already shown that the tautomeric equilibria are shifted to the more polar ketonic forms A and C when increasing solvent polarity (8,10). Since chelation is a major factor of the enol B and of the enamine D stability, it may be anticipated that protic and amphiprotic solvents able to block the chelation sites will strongly favour the ketonic forms. As a limiting case, they are indeed the only tautomers observed in trifluoroacetic acid, in good agreement with literature data (8): $\epsilon(A) = 7100$ l.mole^{-1} at $\lambda_1(A) = 263$ nm, and $\epsilon(C) = 10400$ l.mole^{-1}.cm^{-1} at $\lambda_1(C) = 319$ nm for the protonated ketonic tautomers. The K_T values we measured in

a number of solvents of different polarities (28°, solute concentration of about 0.3 mole.$^{-1}$) are collected in Table III. Solvents were characterized according to Taft et al. (17), as non hydrogen bonding NHB, hydrogen bond acceptor HBA, hydrogen bond donor HBD, and amphiprotic hydrogen bond acceptor-donor HBA-D solvents. All the physical constants and the various empirical polarity parameters of the solvents were taken from literature compilations quoted in the text.

Thermodynamics of the Tautomerism of t-Butyl 2-Picolyl Ketone.

Within the temperature range 25-110°, the uv spectrum changes of both heterocyclic ketones in dimethylsulfoxide solution (10^{-2} mole.l^{-1}) are reversible, showing that no degradation occurs in these conditions. An increase in temperature shifts the equilibria towards the ketonic tautomers, as illustrated by the experimental data collected in Table III for t-butyl 2-picolyl ketone.

The linearity of the plot $Ln K_T = f(1/T)$ is very good, allowing the determination of the enthalpy $\Delta H°$, the entropy $\Delta S°$ and the change in free energy $\Delta G°$ of the tautomeric conversion A → B: see table III. Enolization is exo-

Table II

Ketonic Fractions of t-Butyl 2-Picolyl Ketone F_A and t-Butyl Quinaldyl Ketone F_C in Various Solvents at 28°
(Solute Concentration ≅ 0.3 mole.l^{-1})

No.	Solvent	Solvent type	Ketone Fraction F_A	F_C
0	Bulk		0.614 (d)	
1	Hexane	NHB	0.408	
2	Triethylamine	HBA		0.115
3	Carbon tetrachloride	NHB	0.527 (e)	0.113
4	Benzene (a)	NHB-HBA	0.587	0.130
5	Dioxane	HBA	0.640	0.169
6	Methylpivalate	HBA	0.555	
7	Ethylacetate	HBA		0.172
8	1,2-Dimethoxyethane	HBA	0.649	
9	Chloroform (b)	NHB-HBD	0.744 (f)	0.152
10	Pyridine	HBA	0.694	0.185
11	Hexamethylphosphoramide	HBA		0.185
12	Methylenechloride	NHB	0.745	
13	Acetone	HBA	0.752	0.220
14	Dimethylformamide	HBA	0.770	
15	t-Butyl alcohol	HBA-D	0.790	0.256
16	Dimethylsulfoxide	HBA	0.793 (g)	0.244
17	Acetonitrile (b)	HBA-D	0.840	0.320
18	Nitromethane (b)	HBA-D		0.351
19	Propylenecarbonate	HBA	0.828	0.362
20	Ethanol	HBA-D		0.388
21	N-Methylformamide	HBA-D	0.933	
22	Methanol	HBA-D	0.950	0.474
23	Ethyleneglycol	HBA-D	0.948	
24	Formamide	HBA-D	0.956	
25	Trifluoroethanol (c)	HBD	1.000	0.588

(a) Usually weak HBA, but sometimes NHB solvent. (b) Weak HBD with strong HBA solutes. (c) No HBA properties even with strong HBD solutes. (d) $F_A = 0.585$ at 33° (10). (e) $F_A = 0.588$ at 33° for 50% vol/vol solution (10). (f) $F_A = 0.741$ and 0.730 for 50% (10) and 25% (13) vol/vol solution. (g) $F_A = 0.714$ for 50% vol/vol solution (10).

thermic, and its entropy decrease is closely related to the chelated structure of the enol and to the "planarization" of the molecule. Within the temperature range investigated, the tautomeric equilibirium of *t*-butyl 2-picolyl ketone is entropy controlled.

Table III

Temperature Effects on the Tautomeric Equilibrium of *t*-Butyl 2-Picolyl Ketone in Dimethylsulfoxide Solution (10^{-2} mole.l^{-1})

Temperature °C	28	50	70	90	110
Ketone Fraction F_A	0.747	0.768	0.787	0.805	0.814
$\Delta G°$ kcal.mole.$^{-1}$.K^{-1}	0.648	0.768	0.891	1.020	1.120

$\Delta H° = -1.10 \pm 0.05$ kcal.mole.$^{-1}$, $\Delta S° = -5.9 \pm 0.2$ cal.mole.$^{-1}$ K^{-1}

Discussion.

A decade ago Katritzky, *et al.* (18) pointed out that quantitative description of solvent effects on chemical processes using a single polarity parameter was highly questionnable, since all types of solute-solvent interactions have been taken into account simultaneously. As a more rigorous and quantitative approach, linear multiparametric equations have been thus proposed by many authors (7,17-21). They correlate a given property X of a given chemical system which both specific and non specific polarity parameters of the solvents, according to empirical relations of the following general form:

$$X = X_0 + qQ + yY + pP + eE + nN$$

where X_0 is the value of the given property X in the gas phase; Q is related to the energy of solvent cavitation; Y and P are measurements of the solvent polarization and polarizability respectively; E and N are measures of the Lewis acidity or electrophilicity and of the Lewis basicity or nucleophilicity; q, y, p, e, and n are the partial regression coefficients which allow the determination of the sensitivity of the property X with respect to every solvent polarity parameter. In his recent "Solvatochromic Comparison Method", Taft *et al.* (17) suggested the following simplified form for most cases:

$$X = X_o + s\pi^* + a\alpha + b\beta$$

where π^*, α and β are empirical parameters measuring the polarity-polarizability ($\pi^* \rightarrow$ Y and P), the hydrogen bond donating power ($\alpha \rightarrow$ E, HBD solvents) and the hydrogen bond accepting power ($\beta \rightarrow$ N, HBA solvents) of the solvent respectively. These approaches may be criticized from two complementary view-points (7). The separation of solvent effects into various additive contributions is somewhat arbitrary, since different solute-solvent interactions mechanisms may cooperate in a non independent way. Moreover, the choice of the best parameter for every type of interactions is critical because of the multiplicity of

the corresponding empirical parameters, and because of their sensitivity to more than one of the multiple facets of solvent polarity (see further discussion below). Nevertheless, a continuously increasing number of various chemical processes is currently analyzed successfully by this method, and especially some heterocyclic tautomeric equilibria (22,23). We have thus tentatively interpreted our experimental data according to the same methodology.

Solvent Polarity-Polarisability Effects (SPPE).

According to Koppel and Palm (19), non specific solute-solvent interactions may be readily taken into account by the two additive functions: polarity function $Y = (\epsilon-1)/(2\epsilon + 1)$ (kirkwood-Onsager theory for electrostatic field effects) and polarizability function $P = (n^2-1)/(n^2 + 2)$ (Lorentz-Lorenz expression) where ϵ and n are the dielectric constant and the refractive index of the solvent respectively. Linear regression analysis on the experimental results versus Y and P only show, as a general trend, a strong decrease of Ln K_T with increasing SPP effects, but no significant correlation may be drawn out. Correcting the polarity function Y by the molar volume of the solvent V_m, as suggested by Powling and Bernstein in their early studies of tautomeric equilibria (24), and omitting trifluoroethanol as a particular case (see further) lead to poor linear relationships:

$$A \rightleftharpoons B \begin{cases} \text{Ln } K_T = 0.4775 - 0.2995 \left(\frac{\epsilon-1}{2\epsilon+1} V_m^{-1} \times 10^3 \right), \\ R(18 \text{ solv.}) = 0.928 \end{cases}$$

$$C \rightleftharpoons D \begin{cases} \text{Ln } K_T = 2.253 - 0.1869 \left(\frac{\epsilon-1}{2\epsilon+1} V_m^{-1} \times 10^3 \right), \\ R(16 \text{ solv.}) = 0.903 \end{cases}$$

Addition of the polarizability term P does not offer a definite advantage. Inclusion of the solute polarizability as suggested by Abraham (25) would probably improve the correlations, but such refinements, which require a precise knowledge of the solute molecular geometry and of the bond dipole moments, are out of scope of the present work. Because of dielectric saturation which does occur for solvents of moderate polarity ($\epsilon > 15$), Taft and Abboud (26) have recently derived an improved dielectric constant function $\theta(\epsilon)$ in place of the classical Kirkwood-Onsager's one:

$$\theta(\epsilon) = \frac{3\epsilon \text{ Ln } \epsilon}{\epsilon \text{ Ln } \epsilon - \epsilon + 1} - \frac{6}{\text{Ln } \epsilon} - 2$$

This new $\theta(\epsilon)$ function leads to amended and statistically acceptable correlations illustrated in Figure 4.

$$A \rightleftharpoons B \begin{cases} \text{Ln } K_T = 0.0868 - 0.2659 \left[\theta(\epsilon) V_m^{-1} \times 10^3 \right], \\ R(18 \text{ solv}) = 0.934 \end{cases}$$

$$C \rightleftharpoons D \begin{cases} \text{Ln } K_T = 2.085 - 0.1856 \left[\theta(\epsilon) V_m^{-1} \times 10^3 \right], \\ R(16 \text{ solv}) = 0.922 \end{cases}$$

The better correlations (R = 0.99) corresponding to the dashed lines of Figure 4 have not true physical meaning, since they involve a completely arbitrary classification of the solvents.
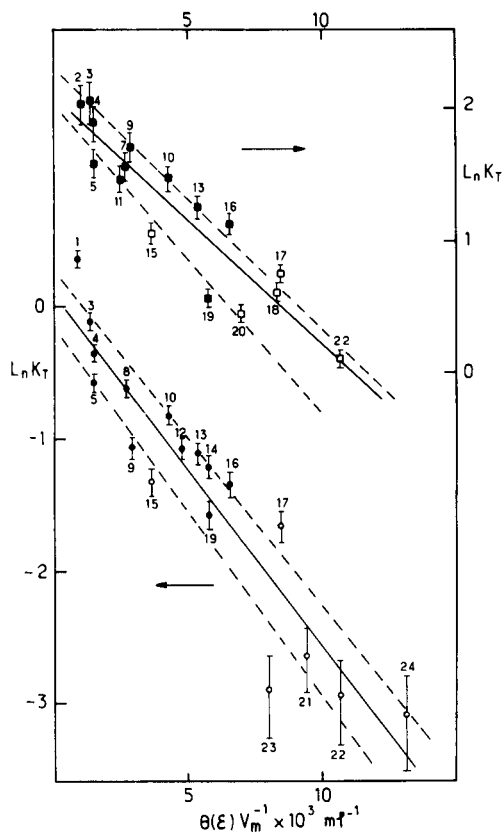

Figure 4. Variations of the tautomerism constants K_T in solution (0.3 mole.l^{-1}, 28°) with the Abboud-Taft modified expression $\theta(\epsilon).V_m^{-1}$.

The numbers refer to solvent classification of Table II. NHB or HBA solvents: ● and ■ for t-butyl 2-picolyl and quinaldyl ketones respectively. HBD or HBA-D solvents: O and □ for t-butyl 2-picolyl and quinaldyl ketones respectively.

In spite of its empirical character, the spectroscopic π^* scale of solvent polarity recently developed by Taft et al. (17,27,28) may afford the definite advantage of taking into account SPP effects through a single parameter which probes directly the cybotactic region of the solvent at a molecular level, whereas dielectric constant is merely a macroscopic property of the bulk of the solvent (29). Figure 5 clearly shows that the π^* parameter is worse than the $\theta(\epsilon)V_m^{-1}$ function for the analysis of K_T variations when the solvents are considered all together, but it clearly points out the specific behaviour of HBD and HBA-D solvents, including acetonitrile and nitromethane.
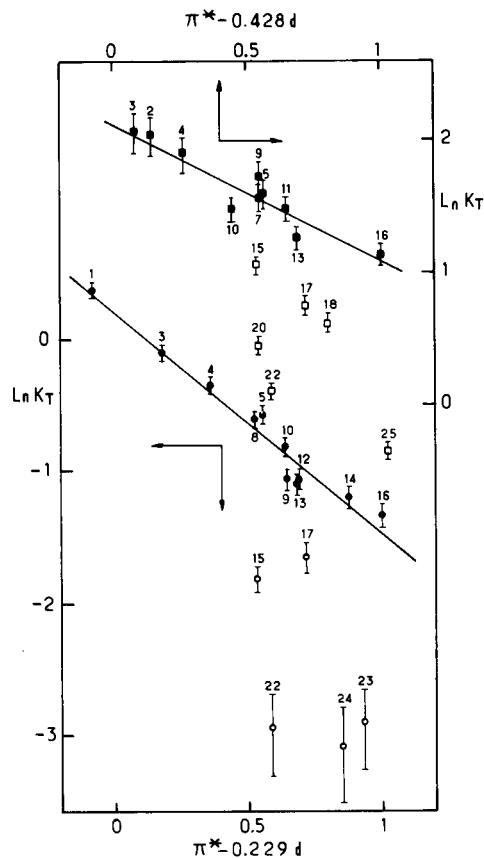

Figure 5. Variations of the tautomerism constants K_T in solution with the empirical polarity parameter π^*. Same symbols as in Figure 4.

Thus, as suggested by Taft et al. (17,28), for NHB and HBA solvents, significant correlations may be drawn out and progressively improved considering families of similar polarizability characteristics, or introducing a correction factor for polarizability effects (δ = 0.5 and 1.0 for polychlorinated aliphatic and for aromatic solvents respectively) when the aprotic solvents are considered all together. This is clearly the case of t-butyl 2-picolyl ketone, but less quantitative agreement is in fact observed for t-butyl quinaldyl ketone, as illustrated below:

Aliphatic, non polychlorinated aprotic solvents
$$A = B \quad Ln \ K_T = 0.2297 - 1.647 \ \pi^*,$$
$$R(6 \ solv.) = 0.984$$
$$C = D \quad Ln \ K_T = 2.119 - 0.9585 \pi^*,$$
$$R(6 \ solv.) = 0.194$$

Aprotic solvents
$$A = B \quad Ln \ K_T = 0.2095 - 1.681(\pi^* - 0.229 \delta),$$
$$R(11 \ solv.) = 0.976$$
$$C = D \quad Ln \ K_T = 2.116 - 1.026(\pi^* - 0.428 \delta),$$
$$R(10 \ solv.) = 0.944$$

Because of the too weak number of polychlorinated aliphatic and of aromatic solvents under investigation, the

polarizability correction factor has to be considered merely as an adjustable parameter which allows a better fit of the experimental data, and the coefficient of the δ term would require more accurate determination to allow a meaningfull comparison of the influence of solvent polarizability on the two tautomeric equilibria.

SPP effects, as considered within theories of electrostatic field effects, are of definite importance in the position of the tautomeric equilibria, and this is reemphasized by the fact that, for the aliphatic non polychlorinated solvents, the dielectric constant function $\theta(\epsilon)$ and the solvatochromic parameter π^* are both very nearly proportional to their molecular dipole moments (26,27). On the other hand, in spite of the apparent greater value and of the theoretical background of the $\theta(\epsilon)$ function, the empirical π^* parameter is of major interest since it clearly points out the similar behaviour of NHB and HBA solvents and the specific behaviour of the HBD ones.

Solute-solvent Specific Interactions.

The use of the single Dimroth-Reichardt polarity parameter E_T (7,30) leads to good linear correlations $Ln\ K_T = f(E_T)$ for all the solvents under investigation, as illustrated in Figure 6.

$$A \leftrightharpoons B \quad Ln\ K_T = 4.033 - 0.1235\ E_T\ ,\ R(18\ solv.) = 0.991$$
$$C \leftrightharpoons D \quad Ln\ K_T = 5.010 - 0.0898\ E_T\ ,\ R(17\ solv.) = 0.981$$

This merely means that the various types of solute-solvent interactions do influence the tautomeric equilibria with the same statistical weight as for the solvatochromy of the phenol-betaine dye selected as reference solute in the empirical E_T scale. Nevertheless, the E_T parameter has not necessarily a universal value: binary solvent mixtures, where preferential or selective solvation phenomena may occur to a different extent for the tautomers and for the reference dye, are not expected to lead systematically to analogous linear correlations $Ln\ K_T = f(E_T)$. For instance this is the case of *t*-butyl 2-picolyl ketone in carbon tetrachloride-dimethylsulfoxide mixtures (31), where significant deviation to linearity is actually observed within the whole range of solvent composition, suggesting stronger preferential solvation by dimethylsulfoxide: Figure 7. On the other hand, no significant preferential solvation occurs in dioxane-acetonitrile mixtures, as illustrated in Figure 8, by the nearly linear variations of $Ln\ K_T$ with the molar fraction of acetonitrile (unfortunately E_T data are not available for this particular binary solvent).
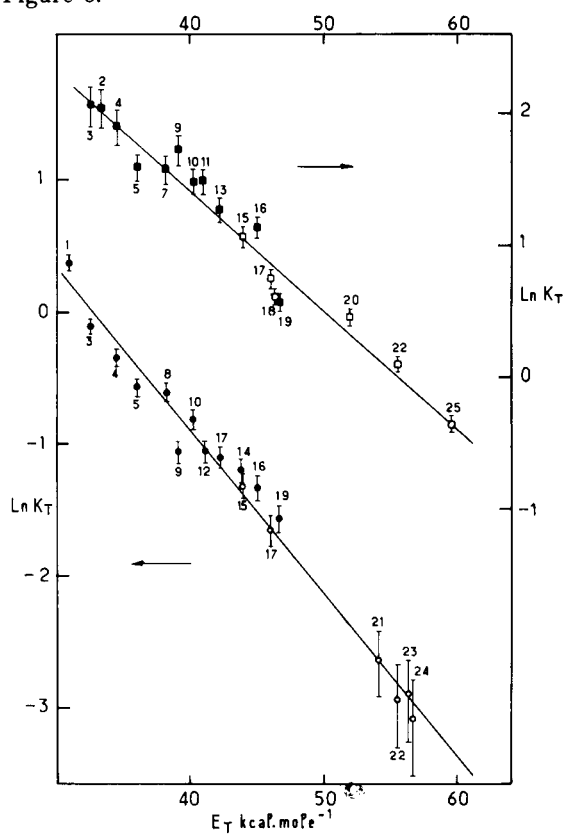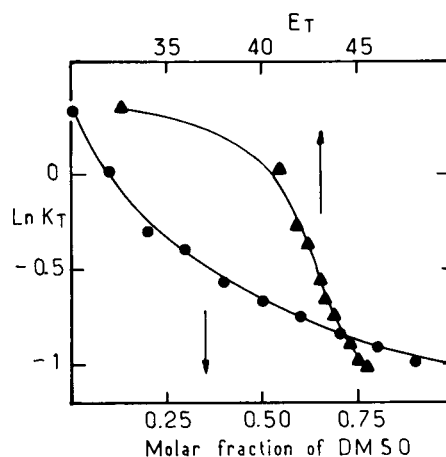

Figure 6.   Variations of the tautomerism constants K_T in solution with the Dimroth-Reichardt polarity parameter E_T. Same symbols as in Figure 4.

Figure 7.   Tautomerism of *t*-butyl-2-picolyl ketone (6.7 × 10^{-3} mole.l^{-1}) in carbon tetrachloride-dimethylsulfoxide binary mixtures. Variations of the tautomerism constant with solvent composition or its E_T parameter.

It is now well recognized that if E_T is essentially a measure of the Lewis acidity for protic solvents, it actually combines non specific SPP effects and hydrogen bonding specific interactions when the various types of solvents are considered all together (32,33). The decomposition of E_T according to Koppel and Palm to derive the solvent electrophility parameter E (19) has been critically discussed by Kamlet and Taft (34), who suggested a better correlation
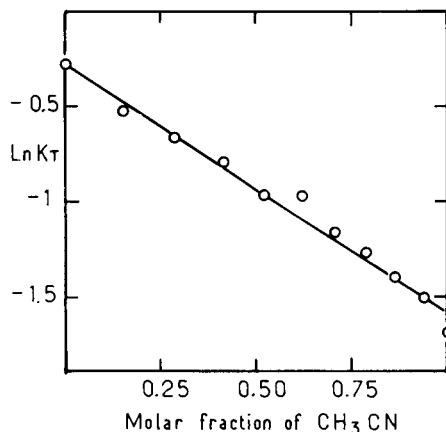
Figure 8. Tautomerism of *t*-butyl 2-picolyl ketone (4.6 × 10^{-3} mole.l^{-1}) in dioxane-acetonitrile binary mixtures. Variations of the tautomerism constant with the solvent composition.

between E_T, π^* and α (33), α being a solvachromic electrophilicity parameter which measures directly the HBD acidity of the solvent (32). Stepwise regression analysis over all the experimental results yields good linear correlations, as illustrated in Figure 9.

$$A \rightleftharpoons B \quad \begin{cases} \text{Ln } K_T = 0.2095 - 1.681(\pi^* - 0.229\delta) - 2.160\alpha, \\ R(16 \text{ solv.}) = 0.993 \end{cases}$$

$$C \rightleftharpoons D \quad \begin{cases} \text{Ln } K_T = 2.116 - 1.026(\pi^* - 0.428\delta) - 1.426\alpha, \\ R(15 \text{ solv.}) = 0.977 \end{cases}$$
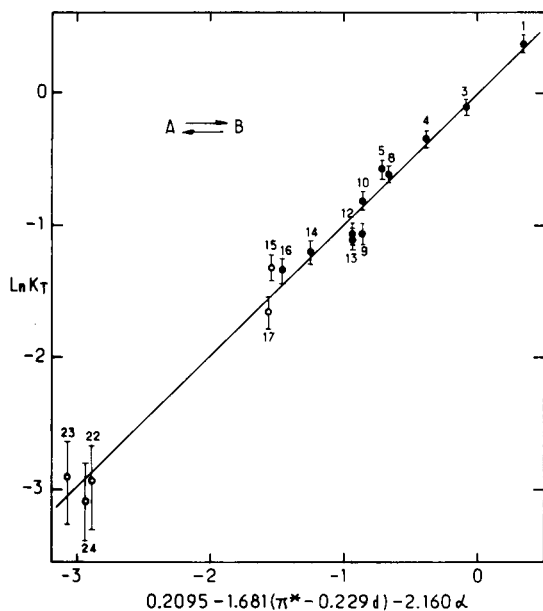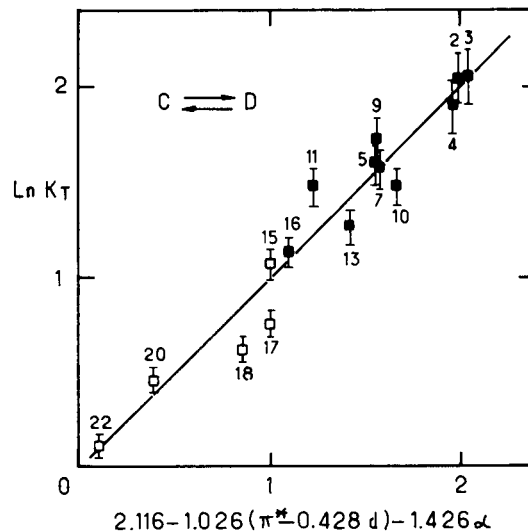

Figure 9. Stepwise regression analysis of the variations of the tautomerism constants K_T in solution with the solvatochromic polarity parameters π^* and α: observed versus calculated Ln K_T values. Same symbols as in Figure 4.

Solvent effects as a whole are more important for *t*-butyl 2-picolyl ketone, but statistical analysis of the partial regression coefficients (20) points out that the two tautomeric equilibria depend mainly and to the same extent on the HBD power of the solvent: it contributes for 62 and 63% to the variations of Ln K_T in the case of *t*-butyl 2-picolyl and *t*-butyl quinaldyl ketones, respectively. The decrease of K_T when increasing the HBD power of the solvent is easily understandable, taking into account the high probability of strong specific hydrogen bonding interactions between the solvent and the ketonic tautomers on their two HBA sites, the carbonyl group and the heterocyclic nitrogen atom. Moreover the HBA behaviours of 2-picoline and quinaldine towards HBD and HBA-D solvents are similar (35). On the other hand, analysis of the results along the same line using Gutmann's Acceptor Number AN (36) is also expected to be successful, since AN is linearly correlated with E_T for a number of solvents (36), and corresponds actually to a linear combination of π^* and α (33). Nevertheless, this cannot afford any clear advantage, and correlations with AN are in fact worse than with E_T (AN values are not available for solvents 2, 7, 15, 23 and 25):

$$A \rightleftharpoons B \text{ Ln } K_T = 0.2926 - 0.0832 \text{ AN}, R(16 \text{ solv.}) = 0.963$$

$$C \rightleftharpoons D \text{ Ln } K_T = 2.054 - 0.0475 \text{ AN}, R(13 \text{ solv.}) = 0.798$$

Finally, taking into account the previous conclusions, the possibility of any influence of the solvent basicity seems very improbable. Introduction of a basicity parameter like the Gutmann's Donor Number DN (36), as suggested by Krigowski and Fawcett (20), the B parameter of Koppel and Palm (19), or the β parameter of Taft *et al.* (37,38), does not yield any significant improvement of the correlation Ln K_T = f(E_T). This feature does not necessarily imply the lack of any specific solute-solvent interactions with

HBA solvents, since both the ketonic (acidic $COCH_2$ heterocycle methylenic group) and the conjugated (enol OH or enamine NH functions) forms may behave as weak HBD solutes: it merely means that preferential solvation of a given tautomer does not occur to a sufficient extent in HBA solvents.

Cavity Effects.

Cavity effects are directly related to the energy necessary to create a cavity in the bulk of the solvent to accomodate a solute molecule. They may be of definite importance especially for non polar and electroneutral chemical processes, and for structured solvents like the highly associated protic ones. The Hildebrand solubility parameter (39,40), δ_H, defined as the square root of the cohesive energy density ($\delta_H^2 = (\Delta Hv - RT)/V_m$), is a measure of the total molecular cohesion per ml of solvent in the liquid state. Its interest as a solvent "polarity" parameter has been pointed out by Herbrandson and Neufeld (41), and it has been recently reemphasized by Dack (42). For instance, the solvent dependence of the tautomerism of some azo-dyes has been quantitatively interpreted in terms of δ_H for both protic and aprotic solvents

(43). Regression analysis on our experimental data for all solvents except trifluoroethanol leads to the following correlations, illustrated in Figure 10.

$$A \rightleftharpoons B \ Ln \ K_T = 2.180 - 0.3051 \ \delta_H \ , \ R(18 \ solv.) = 0.932$$

$$C \rightleftharpoons D \ Ln \ K_T = 4.433 - 0.2970 \ \delta_H \ , \ R(16 \ solv.) = 0.964$$

They may be favorably compared with those previously obtained using the polarity function $\theta(\epsilon)V_m^{-1}$. Here again, the apparent better correlations ($R = 0.99$) corresponding to the dashed lines of Figure 10 have no true physical meaning, since they are derived from a completely arbitrary classification of the solvents. On the other hand, the use of the standard free energy of vaporisation of the solvent to estimate cavity effects, as recently suggested by Mayer (21), does not allow to draw out any statistically acceptable correlation; it tends however to point out stronger deviations from the monotonous decrease of $Ln \ K_T$ with ΔG vap. for the associated HBA-D solvents. A similar trend is observed when substituting the internal pressure P_i of the solvent of the δ_H parameter, since hydrogen-bonding contributions to the total molecular cohesion of the protic solvents are not included in P_i (42). The rather fairly good correlations $Ln \ K_T = f(\delta_H)$ suggest that solvent cavitation is a major factor of the tautomeric equilibria under study. This could be tentatively interpreted as a result of the differences in molecular geometry between the "ordered" structure of the conjugated and the "planarized" chelated forms and the more flexible structures of the ketonic ones. Such conformational differences and their impact on the solvation shell may be at the origin of the solvent cavity effects.

Consideration of solute-solvent interactions, not included in δ_H, could perhaps improve the previous correlations. Multiparameter regression analysis using the so called "three dimensional solubility parameter" (39,40), which resolves the cohesive energy density into non polar dispersion forces, dipolar interactions and hydrogen bonding interactions, fails to lead to any reasonable correlation. On the other hand, Taft *et al.* (44) recently suggested that δ_H may be introduced as an additive term to their "Solvatochromic Equation". Regresssion analysis of the K_T values with δ_H, π^* and α leads to the following correlations, illustrated in Figure 11:

$$A \rightleftharpoons B \begin{cases} Ln \ K_T = 0.4777 - 0.0364\delta_H - 1.5181(\pi^* - d\delta) - 1.9374\alpha \\ R(16 \ solv.) = 0.993 \end{cases}$$

$$C \rightleftharpoons D \begin{cases} Ln \ K_T = 3.0315 - 0.1124\delta_H - 0.7213(\pi^* - d\delta) - 0.9461\alpha \\ R(15 \ solv.) = 0.987 \end{cases}$$

According to f statistics (45), it may be shown that the probabilities that the two parameter regression analysis (π^*, α) may be rejected in favor of the three parameter ones are of 54.7 and 99.5% for A → B and C → D, respectively. The cavity effects, the polarity-polarizability effects and
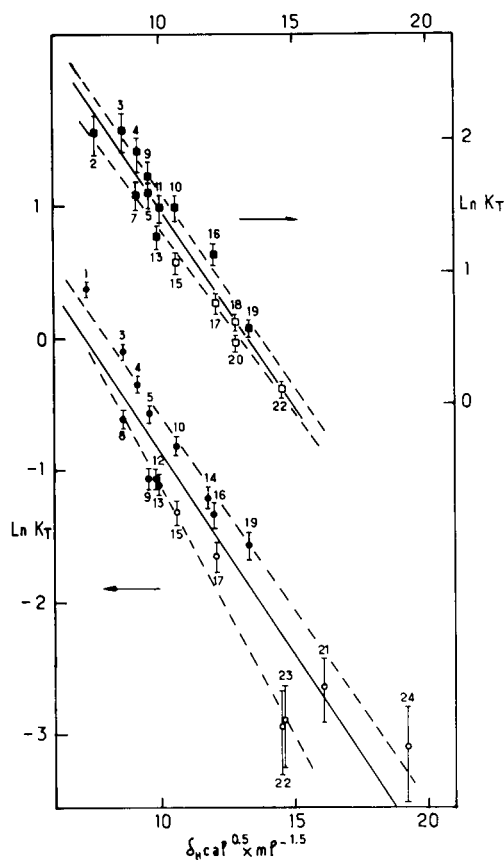

Figure 10. Variations of the tautomerism constants K_T in solution with the Hildebrand solubility parameter δ_H. Same symbols as in Figure 4.
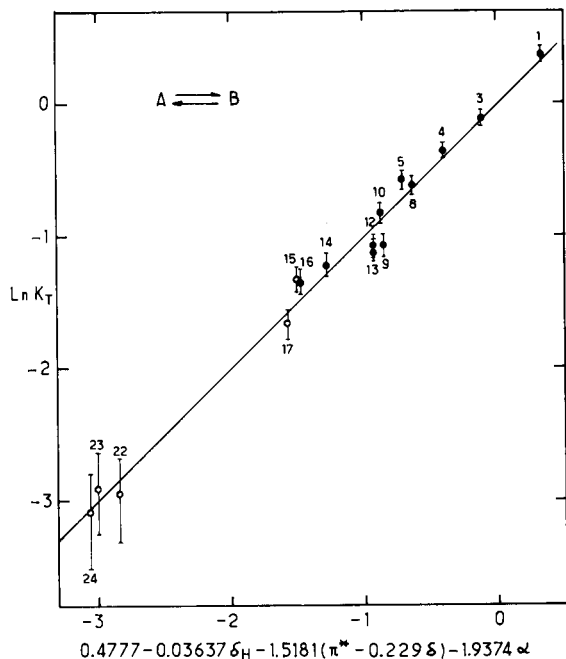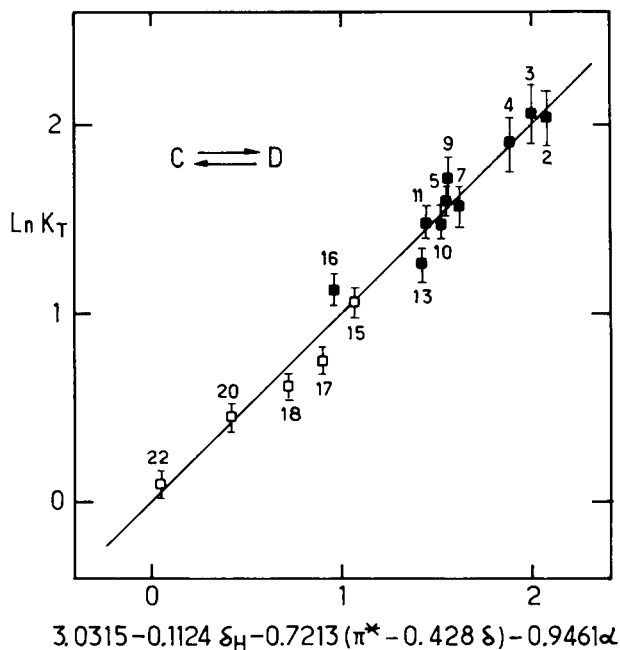
Figure 11. Stepwise regression analysis of the variations of the tautomerism constants K_T in solution with the polarity parameters δ_H, π^* and α: observed versus calculated Ln K_T values. Same symbols as in Figure 4.

the HBD power of the solvents would account respectively for 9, 36 and 55% of the observed K_T variations in the case of t-butyl 2-picolyl ketone, and for 30, 26 and 44% in the case of t-butyl quinaldyl ketone. Hydrogen-bonding in-

teractions remain always the major factor of the two tautomeric equilibria, but cavity effects, which are nearly negligible for A, become of the same importance as polarity-polarizability effects for C: this feature may be tentatively correlated with the more important cavity requirements of the bulkier enaminic D structure.

Conclusions.

Physically different interpretations of a given experimental data set through regression analysis may merely arise from some fortuitous correlation between the various polarity parameters of the solvents under investigation. Omitting trifluoroethanol and methylpivalate, for the twenty three solvents we used, poor but yet statistically significant correlations may be drawn out between the three polarity parameters $\theta(\epsilon)_m^{-1}$, E_T and δ_H for instance:

$$\delta_H = -4.033 + 0.3557\,E_T, \qquad R(23\ \text{solv}) = 0.928$$

$$\delta_H = 7.198 + 0.7998\,(\theta(\epsilon)V_m^{-1} \times 10^3),\ R(23\ \text{solv.}) = 0.939$$

On the other hand, Taft et al. (44) have pointed out only a very bad correlation (R = 0.886) between δ_H and π^* for seventeen aliphatic "select" solvents. In spite of the ambiguity implied by these correlations, solvent effects on the tautomerism of t-butyl 2-picolyl and t-butyl quinaldyl ketones may be rationalized at best in terms of solvent cavity effects δ_H, and of polarity π^* and hydrogen bond donating power α of the medium, within the general framework of the "Solvatochromic Comparison Method" recently developed by Taft et al. The three parameter regression analysis of the K_T variations does allow an excellent fit of all the experimental data, taking into account, as a major factor, specific hydrogen bonding interactions between the ketonic tautomers and the HBD or HBA-D solvents. These interactions rest on very sound spectrometric observations and cannot thus be neglected.

On the other hand, from a thermodynamic point of view, extrapolation of the previous correlations may also afford a rough estimate of the free energy difference between the isolated tautomers in the gas phase (virtual state for crystalline t-butyl quinaldyl ketone which melts at 65°). This estimation, in spite of its inherent unaccuracy, is of great interest since it is closely related to the relative chemical binding energies of the tautomers in equilibrium (46). The evaluated values $\Delta G^\circ{}_{vap} \in (A \rightarrow B) \cong -0.3$ and $\Delta G^\circ{}_{vap} \in (C \rightarrow D) = -1.8$ kcal.mole^{-1} would obviously require an independant and direct measurement in the gas phase, but their difference clearly points out the much greater stability of the chelated enamine D with respect to the chelated enol B, the ketonic structures A and B are taken as references. The nature of the molecular environment is a decisive factor of the tautomeric equilibria (K_T is decreased by a factor of about ten when going from the vapor phase to solution in HBA-D solvents), but much

stronger solvation effects have already been observed with K_T changes of several orders of magnitude, as for the system 4-hydroxypyridine/4-pyridone for instance (46).

EXPERIMENTAL

Synthesis.

The heterocyclic ketones A and C were prepared by reaction of methylpivalate on 2-picolyl and quinaldyl lithium respectively, according to known procedures (47,48) as described elsewhere (2). Purification of A by vacuum distillation and of C by recrystallization in methanol-water mixtures produces analytical samples: their uv and ¹H-nmr spectra were in excellent agreement with those expected (see Results).

Anal. Calcd. for $C_{11}H_{15}ON$ (A): C, 74.54; H, 8.53; O, 9.03; N, 7.90. Found: C, 74.30; H, 8.58; O, 9.18; N, 8.03.

Anal. Calcd. for $C_{15}H_{17}ON$ (C): C, 79.26; H, 7.54; O, 7.04; N, 6.16. Found: C, 79.19; H, 7.43; O, 7.16; N, 6.27.

¹H-NMR Spectroscopy.

Deuterated solvents (CEA) were used after drying over molecular sieves 4 Å. Hydrogenated solvents were purified and dried according to literature procedures (49), and finally distilled on a Cadiot teflon spinning band column and stored over molecular sieves 4 Å. Their residual water content (Karl-Fisher titration) was generally less than 20 ppm. The ¹H-nmr spectra were run in solution (TMS as internal reference) on a Perkin-Elmer R-32 and on a Cameca-250 apparatus operating in the Fourier transform mode within the range 25-110° for the more dilute solutions (solute molar fraction < 0.01). According to our experience, the equilibrium was not reached instantaneously after the dilution process, and the measurements were systematically and safely performed after at least 15 hours annealing of the solutions at room temperature, and 1 hour annealing at the selected measurement temperature. Quantitative analysis of the well resolved spectra (see Results) leads directly to the various tautomer fractions with a reproducible accuracy of about ± 3%.

UV Spectrometry.

Measurements were performed at room temperature (Beckmann-Acta) or at higher temperatures regulated within ± 0.5° up to 110° (Cary-14). The thermal variations of the concentration were corrected using $\alpha = 8.8 \times 10^{-4}$ ml.g⁻¹.deg⁻¹ as thermal expansion coefficient of dimethylsulfoxide (49).

Vapor Phase Osmometry.

Measurements were performed on a Knauer apparatus, after calibration with recrystallized triphenylmethane as reference.

Acknowledgment.

The authors gratefully acknowledge Dr. R. Graff for some ¹H-nmr spectra (Cameca 250) run at the "Service Général de RMN de l'Université L. Pasteur, Strasbourg" and Mrs. H. Bellisent for her efficient technical assistance during the experimental work. They are greatly indebted to a referee for drawing their attention to a recent publication of Taft *et al.* (44) which proved to be of great interest for a better interpretation of the experimental results.

REFERENCES AND NOTES

(1) J. J. Bourguignon, R. Roussel, P. Spegt and J. C. Galin, "Modified Polymers Their Preparation and Properties", 4th Bratislava IUPAC Sponsored International Conference, Preprint Vol 1, p 9, July, 1975.

(2) M. Oteyza De Guerrero, Thesis, Strasbourg, September, 1977.

(3) J. C. Galin, in "Modification of Polymers", *A. C. S. Symp. Ser.*, **121**, 119 (1979).

(4) 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.

(5) P. Strop, F. Mikes and J. Kalal, *J. Phys. Chem.*, **80**, 694 (1976).

(6) H. Morawetz, *J. Polym. Sci.-Polym. Symp.*, **62**, 279 (1978) and *J. Macromol. Sci-Chem.* **A-13**, 311 (1979).

(7) C. Reichardt, "Solvent Effects in Organic Chemistry", Verlag Chemie, Weinheim, 1979.

(8) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).

(9) G. Klose and K. Arnold, *Mol. Phy.*, **11**, 1 (1966).

(10) K. R. Wursthorn and E. H. Sund, *J. Heterocyclic Chem.*, **9**, 25 (1972).

(11) M. Yamazaki, K. Hoda and M. Hamana, *Chem. Pharm. Bull.*, **18**, 908 (1970).

(12) G. Klose and E. Uhleman, *Tetrahedron*, **22**, 1373 (1966).

(13) R. P. Cassity, L. T. Taylor and J. P. Wolfe, *J. Org. Chem.*, **43**, 2286 (1978).

(14) J. Llor and M. Cortijo, *J. Chem. Soc., Perkin Trans. II*, 1111 (1977).

(15) O. Bensaude, M. Chevrier and J. E. Dubois, *Tetrahedron Letters*, **25**, 2221 (1978).

(16) P. Beak, J. B. Covington, S. G. Smith, J. M. White and J. M. Zeigler, *J. Org. Chem.*, **45**, 1354 (1980).

(17) M. J. Kamlet, J. L. M. Abboud and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 6027 (1977).

(18) F. W. Fowler, A. R. Katritzky and R. J. D. Rutherford, *J. Chem. Soc. B*, 460 (1971).

(19) I. A. Koppel and V. A. Palm, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, eds, Plenum Press, London, 1972, p 207.

(20) T. M. Kirgowski and W. R. Fawcett, *J. Am. Chem. Soc.*, **97**, 2143 (1975).

(21) U. Mayer, *Monatsch. Chem.*, **109**, 421 (1978); ibid., **109**, 775 (1978).

(22) R. J. Highet and Feng-Te E. Chou, *J. Am. Chem. Soc.*, **99**, 3538 (1977).

(23) P. Beak, J. B. Covington and J. M. White, *J. Org. Chem.*, **45**, 1347 (1980).

(24) J. Powling and H. J. Bernstein, *J. Am. Chem. Soc.*, **73**, 4353 (1951).

(25) R. J. Abraham, *J. Phys. Chem.*, **73**, 1192 (1969) and references cited therein.

(26) J. L. M. Abboud and R. W. Taft, *J. Phys. CHem.*, **83**, 412 (1979).

(27) J. L. M. Abboud, M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **99**, 8325 (1977).

(28) M. J. Kamlet, T. N. Hall, J. Boykin and R. W. Taft, *J. Org. Chem.*, **44**, 2599 (1979).

(29) For a critical discussion of the quantitative analysis of the solvent polarity using parameters involving model processes or cybotactic probes, see also B. R. Knauer and J. J. Napier, *J. Am. Chem. Soc.*, **98**, 4395 (1976).

(30) C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, **4**, 29 (1965); ibid., **18**, 98 (1979).

(31) Z. B. Maksimovic, C. Reichardt and A. Spiric, *Z. Anal. Chem.*, **270**, 100 (1974). E_T values were obtained by interpolation on the published curves E_T = f(binary solvent composition).

(32) R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.*, **98**, 2886 (1976).

(33) R. W. Taft and M. J. Kamlet, *J. Chem. Soc., Perkin Trans. II*, 1723 (1979).

(34) M. J. Kamlet and R. W. Taft, ibid., 349 (1979).

(35) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", M. Dekker, Inc, New York, 1974, p 291.

(36) V. Gutmann, "The Donor-Acceptor Approach to Molecular Interactions", Plenum Press, New York, 1978, p 17.

(37) M. J. Kamlet, A. Solomonovici and R. W. Taft, *J. Am. Chem. Soc.*, **101**, 3734 (1979).

(38) M. J. Kamlet, M. E. Jones, R. W. Taft and J. L. Abboud, *J. Chem. Soc., Perkin Trans. II*, 342 (1979).

(39) C. Hansen and A. Beerbower, "Kirk-Othmer Encyclopedia of Chemical Technology", Suppl. Vol, 2nd Ed, A. Stauden, ed, 1971, p 889.

(40) A. F. M. Barton, *Chem. Rev.*, **75**, 731 (1975).

(41) H. F. Herbrandson and F. R. Heufeld, *J. Org. Chem.*, **31**, 1140 (1966).

(42) M. R. J. Dack, *Chem. Soc. Rev.*, **4**, 211, (1975).

(43) R. L. Reeves, M. S. Maggio and L. F. Costa, *J. Am. Chem. Soc.*, **96**, 5917 (1974).

(44) M. J. Kamlet, P. W. Carr, R. W. Taft and M. H. Abraham, *J. Am. Chem. Soc.*, **103**, 6062 (1981).

(45) S. Ehrenson, *J. Org. Chem.*, **44**, 1793 (1979).

(46) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).

(47) N. N. Goldberg, L. B. Barkley and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(48) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(49) J. A. Riddick and W. B. Bunger, "Organic Solvents", Wiley Interscience, New York, 1970.