Equilibrium Addition of Nucleophiles to Carbon–Nitrogen Double Bonds. Kinetics of the Addition of Propanethiol to Benzylideneanilines in Non-aqueous Solutions

By **Yoshiro Ogata** * and **Atsushi Kawasaki**, Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

Rate constants for the addition of propanethiol to benzylideneanilines in methanol–acetonitrile (90 : 10 v/v) have been determined by following the reaction spectrophotometrically and by estimation of equilibrium constants. Electron-releasing groups (R^1 or R^2) in strongly basic Schiff's bases such as $R^1C_6H_4CH{=}NPh$ and $PhCH{=}NC_6H_4R^2$ and electron-withdrawing groups (R^2) in weakly basic Schiff's bases such as p-$NO_2C_6H_4CH{=}NC_6H_4R^2$ increase the second-order rate constants. These facts together with the occurrence of acid and base catalysis suggest a change in mechanism from acid catalysed addition of the thiol to the more basic Schiff's bases to attack of the thiolate ion on the unprotonated less basic Schiff's bases. The kinetic solvent isotope effects, $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$, and the equilibrium solvent isotope effects, $K^{\mathrm{MeOH}}/K^{\mathrm{MeOD}}$, are 1·5 and 0·50 for *N*-benzylidene-*m*-chloroaniline and 1·4 and 0·52 for *N*-*p*-nitrobenzylidene-*m*-chloroaniline, respectively. The nucleophilic reactivity of the thiolate ion toward azomethine is compared with that of methoxide.

In contrast to extensive studies on the addition of nucleophiles to carbonyl compounds,[1] additions to carbon–nitrogen double bonds have been little studied except for the addition of water, which is the first step in the hydrolysis of Schiff's bases, where the equilibrium constant is quite small and attacks by both hydroxide ion and water on protonated Schiff's bases occur.[2,3] Addition of hydrogen cyanide to Schiff's bases is substantially irreversible and is not base catalysed,[4] while addition of alcohols is base catalysed.[5] The observed negative Hammett ρ values for the overall rate constants suggest acid catalysed or pH independent reactions involving protonated Schiff's bases [2-4] whereas positive ρ values would favour base catalysed or uncatalysed reactions involving unprotonated Schiff's bases.[5] Measurements on equilibrium and rate constants for the addition of thiols have been reported recently.[6] The present paper describes rate studies on the reversible addition of propanethiol to benzylideneanilines (1)—(17) in methanol–acetonitrile (90 : 10 v/v) to form simple adducts. The reaction mechanism is discussed in terms of the observed acid and base catalysis together with substituent, solvent, and solvent isotope effects.

RESULTS

Adducts.—Some adducts of thiols to Schiff's bases were reported to be isolable but others are not.[6a] In our case, the expected adducts of propanethiol to benzylideneanilines are not stable enough to be isolated in pure form. The crude adducts decomposed to the thiol and Schiff's bases on heating below their m.p.s. However, adduct formation was confirmed by means of n.m.r. and u.v. spectra (see Experimental section). The stoicheiometry of addition is supported by the constancy of the *K* values calculated on the basis of equation (1) with variation of the concentrations of the thiol. Oakes and Stacy [6b] also have reported simple adduct formation under mild conditions, but sulphide formation takes place by a free radical mechanism under reflux conditions. Sulphide formation under mild conditions (below 35°) has not been detected.

$$\mathrm{R^1C_6H_4CH{=}NC_6H_4R^2 + PrSH \rightleftharpoons R^1C_6H_4CH(SPr){-}NHC_6H_4R^2} \qquad (1)$$

	R^1	R^2		R^1	R^2
(1)	p-NO_2	m-NO_2	(10)	H	m-OMe
(2)	p-NO_2	m-Cl	(11)	H	H
(3)	p-NO_2	p-Cl	(12)	H	p-Me
(4)	p-NO_2	H	(13)	H	p-OMe
(5)	p-NO_2	p-Me	(14)	p-Cl	H
(6)	p-NO_2	p-OMe	(15)	m-Me	H
(7)	H	m-NO_2	(16)	p-Me	H
(8)	H	m-Cl	(17)	p-OMe	H
(9)	H	p-Cl			

Equilibrium Constants.—Since the reaction is reversible, equilibrium constants are necessary for the evaluation of rate constants. The equilibrium constants *K* shown in Table 1 for the addition of thiol to Schiff's bases increase upon introducing an electron-withdrawing group in the benzylidene and the aniline rings. The constants are *ca.* 10^3 times larger than those for the addition of methanol.[5] The values of log *K* show a much better correlation with σ^+ than with σ, in agreement with the observations of Oakes and Stacy.[6b] The observed ρ^+ values are 0·78 (r = 0·988) at 20° for *N*-(substituted benzylidene)anilines, similar to the value of 0·86 reported by Oakes and Stacy [6b] for the addition of butanethiol at 24°, 1·19 (r 0·998) at 20° for *N*-benzylidene(substituted anilines) (*cf.* ρ^+ 1·25 calculated from Oakes and Stacy's data † for butanethiol), and 1·24 (r 0·989) at 15°, 1·28 (r 0·995) at 25°, and 1·32 (r 0·997) at 35° for *N*-*p*-nitrobenzylidene(substituted anilines). The analogous correlation with σ^+ for the aniline ring as well as for the benzylidene ring was also observed in the addition of methanol.[5] The polar effect of substituents in the aniline ring is larger than that in the benzylidene ring.

---

† Oakes and Stacy [6b] did not show any ρ values for the equilibrium data of the addition of butanethiol to *N*-benzylidene (substituted anilines). However, Hammett plots of their data in methanol at 24° give a ρ^+ value of *ca.* 1·25 and show a better correlation with σ^+ rather than σ constants.

[1] E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, 1968, **90**, 6154.

[2] A. Bruylants and E. F. Medicis, 'The Chemistry of the Carbon–Nitrogen Double Bond,' ed. S. Patai, Interscience, London, 1970, p. 465.

[3] R. L. Reeves, *J. Org. Chem.*, 1965, **30**, 3129.

[4] Y. Ogata and A. Kawasaki, *J. Chem. Soc.* (*B*), 1971, 329; *J.C.S. Perkin II*, 1972, 1792.

[5] Y. Ogata and A. Kawasaki, *J. Org. Chem.*, 1974, **39**, 1058.

[6] (*a*) G. W. Stacy, R. I. Day, and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 3869; (*b*) T. R. Oakes and G. W. Stacy, *ibid.*, 1972, **94**, 1594.

Rate Constants.—Since a large excess of propanethiol was used, the reaction was pseudo-first order and reversible. The first-order rate constant k_{obs} was determined spectrophotometrically. Forward second-order rate constants k_f were calculated as described in the Experimental section, and are listed in Table 1. In contrast to the correlation of the equilibrium constants with σ^+, the rate constants k_f, based on the concentrations of the thiol, show a correlation with σ. The ρ values are $-1·91$ (r 1·00) at 20° for N-(substitited benzylidene)anilines and $-1·61$ (r 0·948) at 20° for N-benzylidene(substituted anilines). However, plots of log k_f *versus* σ with N-p-nitrobenzylidene(substituted anilines) consist of two lines crossing at $\sigma = 0$. For (1)—(4) ($\sigma > 0$) the ρ values are 2·07 (r 0·999) at 15°, 2·81 (r 0·994) at 25°, and 2·68 (r 0·993) at 35°. The ρ value for (4)—(6) is *ca.* 0, and varies slightly with solvent acidity.

TABLE 1

Equilibrium and rate constants for the addition of propanethiol to substituted benzylideneanilines in methanol–acetonitrile (90 : 10 v/v)

Compound	T/°C	$[PrSH]_0$/M	K/l mol^{-1} [a]	10^3k_f/ mol^{-1} s^{-1}
(1)	15	0·0074	153	53
	25	0·0011—0·011	120 ± 2	183 ± 32
	35	0·0074	99	292
(2)	15	0·018	110 ± 1	12·0
	25	0·0037—0·018	56 ± 2	30 ± 1
	35	0·018	38	54
(3)	15	0·037	55	4·7 ± 0·1
	25	0·0037—0·074	30 ± 2	7·3 ± 0·8
	35	0·037	19	13·3
(4)	15	0·074	25	1·9
	25	0·055—0·18	12·4 ± 0·6	1·7 ± 0·2
	35	0·074	9·9	4·0
(5)	15	0·11	12·5	1·6
	25	0·055—0·18	6·5 ± 0·1	2·7 ± 0·2
	35	0·11	4·3	3·9
(6)	15	0·18	2·8 ± 0·1	1·45 ± 0·03
	25	0·037—0·18	1·7 ± 0·1	3·5 ± 0·3
	35	0·18	1·2	3·8
(7)	20	0·11—0·12	25 ± 1	3·4 ± 0·1
(8)	20	0·011—0·018	14·2 ± 0·3	6·0 ± 0·1
(9)	20	0·11—0·37	6·2 ± 0·4	9·4 ± 0·4
(10)	20	0·11—0·18	4·9 ± 0·2	35 ± 1
(11)	20	0·11—0·18	4·0 ± 0·1	46 ± 2
(12)	20	0·11—0·18	1·7 ± 0·1	63
(13)	20	0·11—0·37	0·52 ± 0·02	
(14)	20	0·11—0·18	6·4 ± 0·1	17·3 ± 0·5
(15)	20	0·11—0·18	3·9 ± 0·1	68 ± 1
(16)	20	0·037—0·11	2·4 ± 0·1	
(17)	20	0·11—0·26	0·89 ± 0·09	
(4)	20	0·037—0·11	14·6 ± 0·5	1·6 ± 0·1

[a] Equilibrium constant for the addition of the thiol. [b] Apparent second-order rate constant based on $[PrSH]_0$; ± denotes the probable errors.

TABLE 2

Deuterium solvent isotope effect for the addition of propanethiol to substituted N-benzylideneanilines at 25° [a]

Compound	K^H/ l mol^{-1}	$10^2k_f^H$/ l mol^{-1} s^{-1}	K^D/ l mol^{-1}	$10^2k_f^D$/ l mol^{-1} s^{-1}	K^H/K^D	k_f^H/k_f^D
(2)	66	2·82	127	2·22	0·52	1·4
(6)	1·65		3·5		0·47	
(8)	0·94	0·62	29	0·62	0·50	1·5

[a] Data are obtained from experiments at a single thiol concentration.

Solvent Isotope Effect.—The deuterium solvent isotope effects on equilibrium and rate constants are shown in Table 2. The data are based on a single run and hence they do not agree with the average values given in Table 1. The solvent isotope effect on the equilibrium constants for thiol addition (K^{MeOH}/K^{MeOD}) is *ca.* 0·5, which is in contrast to that for the addition of methanol (K^{MeOH}/K^{MeOD} 0·98).[5] A value of *ca.* 0·45 has been reported for the addition of thiol to carbonyl compounds.[7] The solvent isotope effects (k_f^{MeOH}/k_f^{MeOD}) on the rate of addition of the thiol to N-benzylidene- and N-p-nitrobenzylidene-m-chloroanilines are small (*ca.* 1·5).

Solvent Effect.—Since acetonitrile and methanol have similar dielectric constants (*i.e.*, 37 and 33, respectively) a mixture was used as solvent to observe the effect of protic and aprotic solvents. Though there is practically no effect on the equilibrium constant, the rate constant increased markedly with an increase in methanol content, and is expressed as $k_f = k_f'[MeOH]^n$. Here, the value of n was determined, by plotting log k_f against log[MeOH], to be 3·0 for (1), 2·6 for (2), and 2·4 for (4), while $n = 1$ for addition of hydrogen cyanide to (11).[4] These data can be used only for comparisons of rates with variation of the solvent composition.

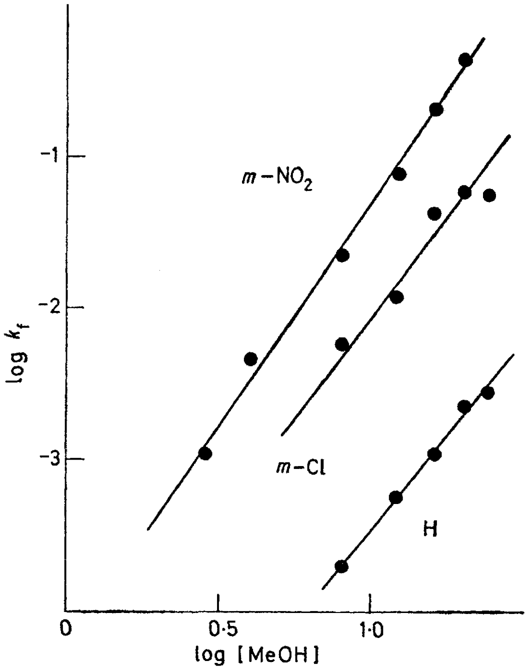


FIGURE 1 Solvent effect on the rate of addition of propanethiol to N-nitrobenzylidene(substituted anilines) in methanol–acetonitrile at *ca.* 30°

Acid and Base Catalysis.—The rate of reaction with (2) was decreased remarkably on addition of *ca.* 3×10^{-4}M-acetic acid, which implies that base catalysis is operating for N-p-nitrobenzylidene(substituted anilines) (1)—(4) where a positive ρ value was obtained.

Catalysis by acetate buffers in methanol–acetonitrile (90 : 10 v/v) was examined. The reactions for (6) and (11) are also subject to general acid catalysis. The data in Table 3 indicate that the catalytic constants for acid catalysis by oxonium ion (k_H) and acetic acid (k_{HOAc}) are larger for (11) than for (6) and that the reverse is true for base catalysis by acetate ion. Although the addition of

---

[7] G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 1966, **88**, 3982.

the thiol to (1) and (4) was catalysed by acetate ion, the catalytic constants for (1)—(4) were not determined, since the reaction was accompanied by acetate ion-catalysed addition of solvent methanol.

Table 3

Acid and base catalyses in methanolic acetate buffers at 25°

Compound	Catalytic constant (l^2 mol^{-2} s^{-1}) k_{H^+}	k_{HOAc}	k^a_{HOMe}	k_{OAc^-}	k_{OH^-}
(11)	1×10^8	8×10^{-1}	9×10^{-4}	0	
(6)	3×10^6	7×10^{-2}	1×10^{-5}	6×10^{-2}	10

[a] $k_{HOMe} = k_0/[MeOH]$.

Effect of Temperature.—From the equilibrium constants K and the forward second-order constants k_f at 15, 25, and 35° in methanol–acetonitrile (90 : 10 v/v) thermodynamic parameters were calculated (Table 4).

Table 4

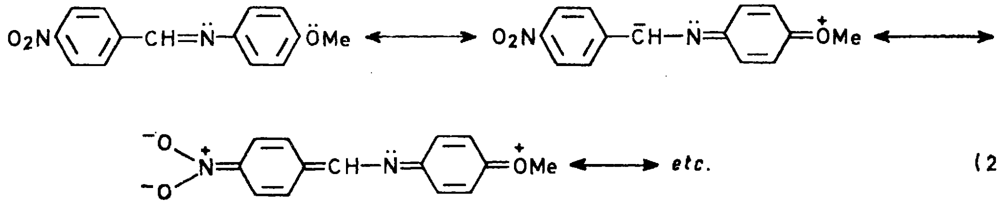
Thermodynamic parameters for the addition of propanethiol to substituted benzylideneanilines [a]

Compound	ΔF^0/ kcal mol^{-1}	ΔH^0/ kcal mol^{-1}	$\Delta S^0(25°)$/ cal mol^{-1} K^{-1}	$\Delta F^‡$/ kcal mol^{-1}	$\Delta H^‡$/ kcal mol^{-1}	$\Delta S^‡(25°)$/ cal mol^{-1} K^{-1}
(1)	−2·9	3·8 ± 0·3	−23 ± 1	18·5	14·5 ± 2·2	−14 ± 7
(2)	−2·7	9·4 ± 0·5	−42 ± 2	19·4	12·7 ± 0·4	−23 ± 1
(3)	−2·3	9·4 ± 0·7	−41 ± 2	19·9	8·7 ± 1·4	−39 ± 5
(4)	−1·85	8·2 ± 0·6	−35 ± 2	21·7	6·0 ± 1·5	−55 ± 5
(5)	−1·45	9·4 ± 0·2	−38 ± 1	21·9	7·3 ± 1·1	−51 ± 4
(6)	−0·6	7·5 ± 0·5	−28 ± 2	21·9	7·9 ± 1·1	−49 ± 3
(7)	−2·4	8·9 ± 0·1	−39 ± 1	20·0	12·3 ± 0·5	−27 ± 2
(8)	−1·9	9·7 ± 0·2	−40 ± 1			

± Denotes uncertainties due to the probable errors in the equilibrium and rate constants.

DISCUSSION

Equilibria.—The equilibrium for addition of butanethiol to the C=N bond has been established by Oakes and Stacy.[6b] In the present reaction, adducts are unstable as expected for equilibrium addition reactions. The equilibrium constants K correlate well with σ^+. This trend can be explained, as in the addition of alcohols,[5] by resonance stabilisation of the benzylideneanilines by an electron-releasing group in both the aniline and the benzylidene rings [equation (2)]. Such resonance must be important in spite of dihedral[8] or nonplanar[9] conformations with dihedral angles of 50—60°.



(2)

The observed correlation of K with σ^+, in contrast to the correlation of k_f with σ, is reasonable since the effect of substituents on reactant stability rather than on product stability may be a controlling factor on the equilibrium, while the effect of substituents on transition state stability rather than on reactant stability may be a controlling factor on the rate.

The observed solvent deuterium isotope effect (K^{MeOH}/K^{MeOD}) can be explained approximately by the zero point energy difference.[10] If any deuterium effect other than on zero point energy is negligible, and if the stretching and bending frequencies of the S–H bond of *ca.* 2600 and *ca.* 800 cm^{-1} and the N–H bond of *ca.* 3400 and *ca.* 1500 cm^{-1} are considered, the value of K^{MeOH}/K^{MeOD} is 0·35, in fair accord with the observed value of 0·5. The reaction can be regarded as a simple change, $S{-}H \rightleftarrows N{-}H$. Since $\nu_{NH} = \nu_{OH} =$ *ca.* 3400 cm^{-1}, it is reasonable that the observed value should be in accord with the isotope effect of 0·44 for the addition of ethanethiol to acetaldehyde[7] and the equilibrium constant of 0·44 for the H–D exchange between pentyl alcohol and ethane[^{2}H]thiol.[11]

The equilibrium constants (1—10^2 l mol^{-1}) for the addition of the thiol to Schiff's bases are 10^3 times larger than those (10^{-3}—10^{-1} l mol^{-1}) for the addition of methanol.[5] The difference between the energy change of S–H to S–C and that of O–H to O–C is assumed to be 6·7 kcal mol^{-1} from the bond energies,[12] which corresponds to a ratio K(PrSH)/K(MeOH) of 10^4. Therefore, the stability of the S–C bond of the adduct relative to the S–H bond of the reactant is higher than that of the O–C bond relative to the O–H bond. The observed enthalpy differences between ΔH^0_S for thiol addition and ΔH^0_O for methanol addition[5] are *ca.* 6 kcal mol^{-1}. This difference is analogous to that in the additions to the carbonyl group,[1] where the equilibrium constants for additions to form-

---

[8] V. I. Minkin, Y. A. Zhdanov, E. A. Medyantseva, and Yu. A. Ostroumov, *Tetrahedron*, 1967, **23**, 3651.

[9] H. B. Bürgi and J. D. Dunitz, *Chem. Comm.*, 1969, 472.

[10] K. B. Wiberg, 'Physical Organic Chemistry,' Wiley, New York, 1963, pp. 273, 400.

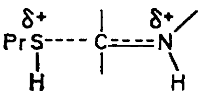
[11] F. W. Hobden, E. F. Johnstone, L. H. P. Welden, and C. L. Wilson, *J. Chem. Soc.*, 1939, 61.

[12] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1959, p. 24.

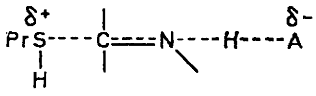
aldehyde are $1{\cdot}3 \times 10^3$ l mol^{-1} for methanol and $1{\cdot}4 \times 10^6$ l mol^{-1} for β-mercaptoethanol. Sander and Jencks [1] have proposed γ values, as a measure of affinity toward the carbonyl group, of $-2{\cdot}22$ for methanol and $+0{\cdot}35$ for β-mercaptoethanol. Although the γ value of propanethiol is unavailable, it would be slightly larger than that for β-mercaptoethanol. Hence, the difference ($\Delta \log K$ *ca.* 3) in equilibrium constant for methanol and thiol addition to Schiff's bases can virtually be accounted for by γ values ($\Delta\gamma$ *ca.* 3).

Mechanism of Addition.—In contrast to the addition of methanol, which requires a basic catalyst,[5] thiol adds readily to Schiff's bases without a basic catalyst. This is due to the higher ionization constant of thiol and the higher nucleophilicity of the thiolate ion as discussed later. In view of the observed effect of substituents on rate and the occurrence of acid and base catalysis, benzylideneanilines can be classified into three categories differing in the type of addition mechanism. (i) The Schiff's bases (7)—(11) and (14)—(17) which do not bear a *p*-nitro-group are characterised by negative Hammett ρ values (−1·91 and −1·61), a solvent isotope effect of 1·5 for (8), and acid catalysis for (11). (ii) *N*-*p*-Nitrobenzylidene(substituted anilines) (1)—(4) substituted by electron-withdrawing groups in the aniline ring (1)—(4) are characterised by a positive ρ (+2·81), base catalysis and a solvent deuterium isotope effect of 1·4 for (2). (iii) *N*-*p*-Nitrobenzylidene(substituted anilines) (4)—(6) substituted by electron-releasing groups in the aniline ring (4)—(6) are characterised by a small substituent effect and acid–base catalysis.

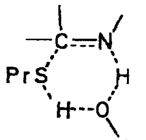
These observations suggest some probable mechanisms. (a) By analogy to the addition of HCN [4] or water [2,3] the observed negative ρ values and acid catalysis suggest that the proton transfer to the nitrogen atom of the Schiff's base is involved [category (i)]. In methanol, oxonium ion catalysis (I) and general acid catalysis (II) are possible in view of the observed catalytic constants given in Table 3. Mechanism (II) may be replaced by a cyclic one (III) as in the addition of HCN to Schiff's bases.[4] From the catalytic constants $k_0 = 2 \times 10^{-2}$ l mol^{-1} s^{-1} for solvent catalysis and $k_{H^+} = 10^8$ l^2 mol^{-2} s^{-1} for oxonium ion catalysis together with the assumption of pK_a values of 18·1 for methanol [13] and 15 for propanethiol,* oxonium ion catalysis (I) and solvent catalysis (II) in methanol of [H^+] *ca.* 10^{-9}M have comparable rates. In acetate buffer of [H^+] *ca.* 10^{-10}M, oxonium ion, acetic acid, and solvent catalysed reactions have comparable rates. As a solvent catalysed or uncatalysed reaction corresponding to the k_{HOMe}[MeOH] $= k_0$ term given in Table 3, attack by the thiolate ion on the protonated Schiff's base is impossible, since it would require a second-order rate constant greater than the diffusion-controlled value (k *ca.* 10^{11} l mol^{-1} s^{-1}) because of the extremely low concentrations of the protonated Schiff's base and the thiolate ion since $k_0[PrSH][C{=}N] = k(K_a^{PrSH}/K_a^{C=NH^+})[PrS^-][C{=}NH^+]$.† As $k_f = k_{H^+}[H^+] + k_{HOMe}$ [MeOH] in neutral methanol, the observed solvent isotope effect of 1·5 may reflect a preference for general acid catalysis (II) over oxonium ion catalysis (I), based on the criteria that the solvent isotope effect is larger than unity for general acid catalysis and less than unity for specific oxonium ion catalysis.[10] (b) The reaction of Schiff's bases bearing strongly electron-withdrawing substituents such as (1)—(4) may involve an attack of the thiolate ion resulting from spontaneous ionisation of the thiol on the unprotonated Schiff's bases even in neutral methanol solutions [category (ii)]. Positive ρ values and retardation by acid are understandable in terms of mechanism (IV). Moreover, this is consistent



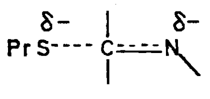
(I)



(II; A = OMe or OAc)



(III)



(IV)

with the fact that the rate constants tend to decrease with increasing initial concentration of the thiol as the extent of ionisation of the thiol is lowered. An attack by undissociated thiol on unprotonated Schiff's bases is excluded because of retardation by acetic acid. The

---

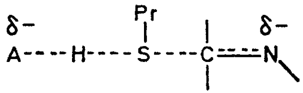
* The pK_a of propanethiol in aqueous solution is 10·3.[7] The pK_a value in methanol is higher by 4–5 pK units than in aqueous solution because of the difference in anion solvation; for example, pK_a is 4·8 for acetic acid and 4·4 for thiophenol.[14]

† The value of the pK_a of the conjugate acid of *N*-benzylideneaniline in aqueous solvent is *ca.* 2 (I. R. Bellobono and G. Favini, *Tetrahedron,* 1969, **25**, 57). The value in methanol may be analogous to or slightly higher than that in water. For example, the ionization constant for NH_3 in water is $1{\cdot}8 \times 10^{-5}$ at 25°, while in methanol it is *ca.* 10^{-6} (R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1568 and ref. 12 therein); the values of pK_a of anilinium ion and *N*-methylanilinium ion in methanol are 0·5—1·0 pK unit higher than those in water and that of *NN*-dimethylanilinium ion is similar to the value in water (Y. Kondo and N. Tokura, *Bull. Chem. Soc. Japan*, 1972, **45**, 818). Assuming the pK_a values of 18·1 for methanol, 15 for propanethiol, and 2 for *N*-benzylideneanilinium ion in methanol, the ratios $[PhCH{=}NH^+Ph]/[PhCH{=}NPh]$ and $[PrS^-]/[PrSH]$ in neutral methanol solution can be calculated as *ca.* 10^{-7} and *ca.* 10^{-8}, respectively. Since the observed rate constant k_f is 10^{-2} l mol^{-1} s^{-1}, the calculated rate constant for the reaction of thiolate ion with protonated Schiff's base is 10^{11} l mol^{-1} s^{-1}, which is over the diffusion-controlled rate constant. If the pK_a of the protonated Schiff's base in methanol is >2, the calculated value will be higher than 10^{11} l mol^{-1} s^{-1}.

[13] The autoprotolysis constant of MeOH is 2×10^{-17}, S. Bruckenstein and I. M. Kolthoff, ' Treatise on Analytical Chemistry,' Interscience, New York, 1959, Part I, vol. 1, p. 475.

[14] B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, 1966, **88**, 1911.

solvent isotope effect (k_f^{MeOH}/k_f^{MeOD}) of 1·4 is explicable in terms of combined effects on the ionisation of the thiol (K_a) and on the rate of the thiolate ion attack ($k_f^{PrS^-}$) rather than by acid catalysis. The equilibrium solvent isotope effect ($K_a^{H_2O}/K_a^{D_2O}$) on the ionisation of propanethiol (pK_a 10·3 in H_2O) is estimated by means of an empirical equation[15] to be 2·5 and the kinetic solvent isotope effect (k_f^{MeOH}/k_f^{MeOD}) for an attack of methoxide ion on the Schiff's base was observed to be 0·60.[6] Allowing that $K_a^{MeOH}/K_a^{MeOD} = 2{\cdot}5$ for propanethiol and $k_f^{MeOH}/k_f^{MeOD} = 0{\cdot}6$ for an attack of the conjugate base and neglecting any other factors, the solvent isotope effect (k^{MeOH}/k^{MeOD}) for the present reaction is estimated as *ca.* 1·5, which is in reasonable agreement with the observed value of 1·4. (c) For the reaction of Schiff's bases with two substituents such as (4)—(6), the addition of the thiol is subject to general acid and general base catalysis (II) and (V) [category (iii)]. In neutral methanol, the reaction consists of oxonium ion catalysis (I) and uncatalysed or solvent catalysed reaction (II) in view of the observed values of k_{H^+} and k_{MeOH} in Table 3. The rate constants are the minimum for the Schiff's bases used and this category of compounds corresponds to borderline cases of the Hammett plots ($\rho \lesssim 0$), because an acid catalysed reaction has a negative ρ value and a base-catalysed reaction a positive ρ value as reported for the addition of water,[2,3] hydrogen cyanide,[4] and methanol.[5]



(V)

As shown in Table 4, both $\Delta H^‡$ and $\Delta S^‡$ change in the order (1) > (2) > (3) > (4) < (5) < (6) with increasing nucleophilicity of the nitrogen atom. This order is compatible with the change in mechanism from (b) to (c). If a single mechanism were operating, plots of $\Delta H^‡$ against $\Delta S^‡$ should give a single line.[16] Unfortunately, whether the plots give a single line or two lines is not clear because of uncertainties in the activation parameters.

Solvent Effect.—The rate of addition to (1), (2), and (4) in methanol–acetonitrile is proportional to $[MeOH]^{2{\cdot}4-3{\cdot}0}$, where the reaction involves an attack by the thiolate ion on the Schiff's base. Since the dielectric constant is virtually unchanged with change in solvent composition, the protic solvent is more effective in promoting the reaction. Acid catalysis by methanol, however, cannot explain the results since first-order dependence on methanol was observed in the addition of HCN.[4] A second possibility is solvation of the thiolate ion and proton [(equation (3)] which affects the degree of ionization of thiol in the absence of added base. Since anion solvation by protic methanol is much greater than by aprotic acetonitrile, and since solvation of a proton by methanol is much stronger

$$PrSH + (n + m)\ MeOH \rightleftharpoons PrS^-(HOMe)_n + H^+(MeOH)_m \quad (3)$$

than by the less basic acetonitrile,[17] the equilibrium concentration of thiolate ion should be much higher in methanol than in acetonitrile. On the other hand, the nucleophilic reactivity of thiolate ion should be higher in dipolar aprotic acetonitrile than in methanol.[18] Hence the rate increase is due to the increase in concentration of thiolate ion.

Nucleophilicities of Thiolate and Alkoxide Ions.—The rate constant for attack of thiolate ion ($k_f^{PrS^-}$) was estimated by assuming the pK_a values in methanol of propanethiol and methanol to be 15 and 18·1, respectively[13,14] (Table 5). The value of $k_f^{PrS^-}$ for some benzylideneanilines (1)—(4) was compared with the observed value of $k_f^{MeO^-}$.[5] The ratio of nucleophilicities ($k_f^{PrS^-}/k_f^{MeO^-}$) is *ca.* 10^5 and the ratio of their equilibrium constants (K_S/K_O) is 10^3. The higher nucleophilicity of the less basic thiolate ion can be explained as follows. (a) Polarisability can explain the higher reactivity of thiolate ions[6] but since Swain's nucleophilicity parameters for an attack on a saturated carbon atom[19] are 4·2 for n_{OH^-} and 5·1 for n_{SH^-}, the observed differences seem to be too large. (b) Product stability (K_S/K_O *ca.* 10^3) may contribute to the nucleophilicity, assuming that adduct stabilities are reflected in the energy of the transition state. A large ρ value implies considerable C–S bonding in the transition state. It is true that ($\Delta F_O^\circ - \Delta F_S^\circ$) is parallel to ($\Delta F_O^‡ - \Delta F_S^‡$), but ($\Delta H_O^\circ - \Delta H_S^\circ$) is not parallel to ($\Delta H_O^‡ - \Delta H_S^‡$). Therefore, the product stability alone is not a satisfactory explanation for the nucleophilic reactivity. Solvation of the transition state also contributes. (c) *d* Orbital resonance[20] or back bonding is a possibility. This involves the stabilisation of transition state (VI) by resonance between the antibonding π orbital of the nitrogen formed by an attack of thiolate ion on the C=N bond and the vacant *d* orbital of the attacking sulphur, which is postulated for attack of thiolate ions on C=C[20] and C=O bonds.[7] Thus, thiolate

TABLE 5

Relative nucleophilicities of methoxide and propanethiolate ions

Compound	$k_f^{MeO^-}$/ l mol^{-1} s^{-1} [a]	$k_f^{PrS^-}$/ l mol^{-1} s^{-1}	$k_f^{PrS^-}/k_f^{MeO^-}$	$K(PrSH)/K(MeOH)$
(1)	6·6	4×10^5	2×10^5	$1{\cdot}8 \times 10^3$
(2)	0·88	1×10^5	1×10^5	$1{\cdot}8 \times 10^3$
(3)	0·36	4×10^4	1×10^5	$1{\cdot}8 \times 10^3$
(4)	0·060	1×10^4	2×10^5	$1{\cdot}9 \times 10^3$

[a] Second-order rate constants for attack of methoxide ion on Schiff's bases (ref. 5).

---

[15] W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, 1971, **93**, 4433.

[16] J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 315.

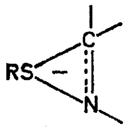
[17] M. K. Chantooni and I. M. Kolthoff, *J. Amer. Chem. Soc.*, 1967, **89**, 1582; R. Alexander, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *ibid.*, p. 3707.

[18] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.

[19] C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.

[20] M. Friedman, J. F. Cavins, and J. S. Wall, *J. Amer. Chem. Soc.*, 1965, **87**, 3672.

ions are *ca.* 300-fold more reactive than amines of similar basicity.[20] Solvation of ions, basicity and steric effect cannot explain the results, and factors (a)—(c) may be important, though the relative weights of these contributions are unknown.



(VI)

Since the C=N bond is less polarisable than C=O and azomethines (pK_a 1—8) [21,22] are more basic than carbonyl compounds (pK_a −5 to −7),[23] the reactions of azomethines are more subject to acid catalysis than those of carbonyl compounds. However, the reaction of benzylideneanilines bearing strongly electron-withdrawing groups proceeds easily by a mechanism involving attack of alkoxide [5] or thiolate ion on the unprotonated Schiff's bases.

The equilibrium constant K for the addition of propanethiol to (3) at 25° in methanol–acetonitrile (90 : 10 v/v) is 30 l mol^{-1} and the rate constant $k_f^{\mathrm{PrS}^-}$ is estimated roughly to be 4×10^4 l mol^{-1} s^{-1} (Table 5). It has been reported that K and $k_f^{\mathrm{EtS}^-}$ for the addition of ethanethiol to acetaldehyde at 25° in aqueous solution are 36 l mol^{-1} and 5×10^5 l mol^{-1} s^{-1}, respectively.[7] Hence there is no parallel relationship for rates and equilibria between carbonyl and azomethine compounds.

EXPERIMENTAL

N.m.r. spectra were recorded on a JEOL spectrometer, model C-60 HL, and u.v. spectra on a Hitachi double beam spectrophotometer, model 124. For the equilibrium and rate study a Hitachi spectrophotometer, model EPU-2A with a thermostatted cell compartment was used.

Materials.—Benzylideneanilines were prepared as described previously.[3-5] Methanol (dried over Mg) and acetonitrile were purified by distillation. Propanethiol, b.p. 67—68°, was of commercial guaranteed grade and had no appreciable impurity by g.l.c. analysis.

Adducts and Equilibria.—In general, the products of addition of propanethiol to substituted *N*-benzylideneanilines are not stable enough to be isolated. For example, a crude product was obtained from the reaction of *N*-*p*-nitrobenzylidene-*m*-nitroaniline (1·85 mmol) with propanethiol (3·7 mmol), and had m.p. 142—145° (sealed capillary). On heating in an open capillary it decomposed to the parent Schiff's base with liberation of the thiol. This product is expected from the Hammett relationship to be the most stable of those studied. Equilibrium addition was also confirmed by n.m.r. spectra and the constancy of the equilibrium constants calculated from extinction changes.

Measurements of Rate and Equilibrium Constants.—The reaction was carried out in a thermostatted, glass-stoppered spectrophotometer cell.[4] The consumption of benzylideneaniline was followed by the spectral changes at 320—340 nm where the extinction of adducts is negligible.[4] Since a large excess of thiol was used, the reaction was treated as pseudo-first order and reversible. Equilibrium constants K and pseudo first-order rate constants for a reversible reaction, k_{obs}, were calculated by means of the equations (4)—(6) where subscript 0 refers to the initial concentration, E denotes extinction, and subscripts f, r, 0, t, and ∞ denote forward, reverse, time 0, time t, and equilibrium state, respectively.

$$K = k_f/k_r = E_0 - E_\infty/E_\infty[\mathrm{PrSH}]_0 \qquad (4)$$

$$k_{\mathrm{obs}} = \frac{2\cdot303}{t}\log\frac{E_0 - E_\infty}{E_t - E_\infty} = k_f[\mathrm{PrSH}]_0 + k_r \qquad (5)$$

$$k_f = k_{\mathrm{obs}}/([\mathrm{PrSH}]_0 + 1/K) \qquad (6)$$

Plots of log $(E_t - E_\infty)$ against t gave a straight line in each run and the value of k_{obs} was obtained from the slope. Forward, second-order rate constants for the reaction of Schiff's base with thiol, k_f, were calculated from the values of K, $[\mathrm{PrSH}]_0$, and k_{obs}.

The rate constant k_f can be expressed by equation (7)

$$k_f = (k_0 + k_{\mathrm{H^+}}[\mathrm{H^+}] + k_{\mathrm{OMe^-}}[\mathrm{MeO^-}]) + k_{\mathrm{HOAc}}\left(1 + \frac{k_{\mathrm{OAc^-}}[\mathrm{Ac^-}]}{k_{\mathrm{HOAc}}[\mathrm{AcOH}]}\right)[\mathrm{AcOH}] \qquad (7)$$

where k_0, $k_{\mathrm{H^+}}$, $k_{\mathrm{OMe^-}}$, k_{HOAc}, and $k_{\mathrm{OAc^-}}$ are catalytic constants for solvent methanol, oxonium ion, methoxide ion, acetic acid, and acetate ion, respectively. Catalytic constants were calculated as follows: (i) $(k_0 + k_{\mathrm{H^+}}[\mathrm{H^+}] + k_{\mathrm{OMe^-}}[\mathrm{MeO^-}])$ from the intercept and k_{HOAc} $(1 + k_{\mathrm{OAc^-}}$ − $[\mathrm{AcO^-}]/k_{\mathrm{HOAc}}[\mathrm{AcOH}])$ from the slope of a plot of k_f against acetate buffer concentration [AcOH], respectively; (ii) $k_{\mathrm{H^+}}$ and k_0 from a plot of the intercept against $[\mathrm{H^+}]$ calculated from the pK_a of methanol and buffer composition $[\mathrm{AcO^-}]/[\mathrm{AcOH}]$; and (iii) k_{HOAc} and $k_{\mathrm{OAc^-}}$ from a plot of the slope against buffer composition. The values of $k_{\mathrm{OMe^-}}$ are negligible for the reaction in neutral methanol.

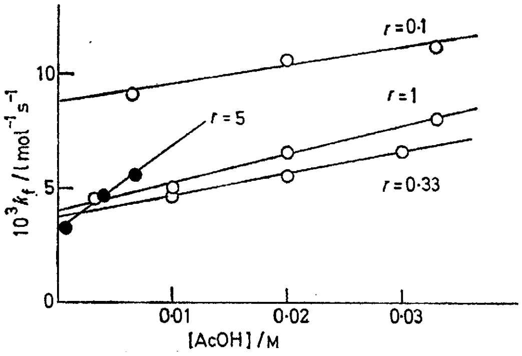


FIGURE 2 General acid and general base catalysis of the addition of propanethiol to *N*-p-nitrobenzylidene-*p*-anisidine in methanolic acetate buffer at 25° and ionic strength 0·33 (NaBr). r = [AcONa]/[AcOH]

[4/1258 *Received, 25th June,* 1974]

---

[21] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1963, **85**, 2843.

[22] I. R. Bellobono and G. Favini, *Tetrahedron*, 1969, **25**, 57.

[23] V. A. Palm, U. L. Haldna, and A. J. Talvik, 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, London, 1966, p. 421.