Kinetic Study of the Base-catalysed Reactions of Benzaldehyde and Thiophene-2-carbaldehyde with Acetonitriles

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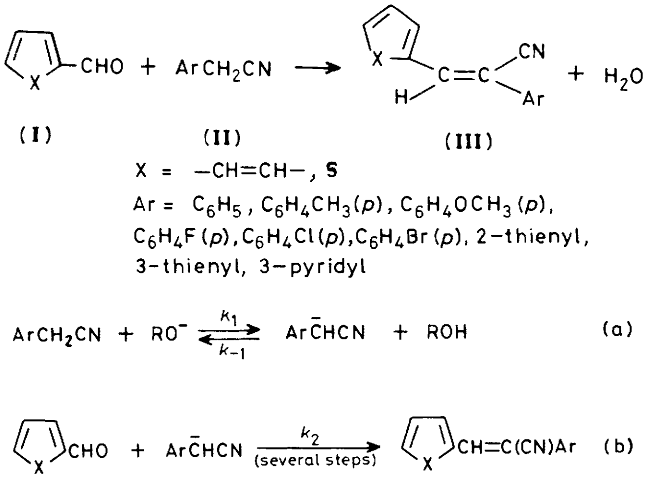
The reaction rates of the sodium methoxide-catalysed condensation of benzaldehyde and thiophene-2-carbaldehyde with heteroaromatic acetonitriles [$ArCH_2CN$; Ar = C_6H_5, $C_6H_4CH_3(p)$, $C_6H_4OCH_3(p)$, $C_6H_4F(p)$, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, 2-thienyl, 3-thienyl, 3-pyridyl] are measured in methanol. The reaction is third-order overall, first-order respect to each reactant. The reaction rates of thiophene-2-carbaldehyde with acetonitriles are lower than those of benzaldehyde indicating that the thienyl group behaves as an electron-donating substituent. The reactivity order with respect to acetonitriles is: 3-pyridylacetonitrile > thiophen-2-ylacetonitrile > phenylacetonitrile > thiophen-3-ylacetonitrile. From the Hammett treatment of the data of the reaction between benzaldehyde and acetonitriles the σ constants for the heteroatoms are obtained: $\sigma_{\alpha\text{-S}}$ 0.30, $\sigma_{\beta\text{-S}}$ −0.08, and $\sigma_{\beta\text{-N}}$ 0.49.

The Perkin condensation gives both *E* and *Z* isomers of α-carboxy-α,β-diaryl compounds,[1,2] while the base-catalysed condensation of aromatic aldehydes with arylacetonitriles formed α-cyano-α,β-diaryl compounds of *Z* configuration.[3] In the last few years we have prepared some *E* and *Z* derivatives of α,β-diarylethylenes each containing a carboxy or cyano group in the α position of the ethylenic bond. We have carried out conformational analysis of α,β-diarylacrylic acids[1,2,4] and we studied the isomerization kinetics of *cis*-αβ-diarylacrylonitriles,[3] the acid- and base-catalysed isomerization of *cis*-α-aryl-β-phenylacrylonitriles,[5] ^1H n.m.r.,[6] ^{13}C n.m.r.,[7] mass,[8] and i.r. and u.v. spectra [9] of *cis*- and *trans*-α,β-diarylacrylonitriles.

Here we report a kinetic study of the sodium methoxide-catalysed reactions of benzaldehyde and thiophene-2-carbaldehyde (I) with heteroaromatic acetonitriles (II) in methanol in order to study the mechanism of formation of (*Z*)-α,β-diarylacrylonitriles (III) and with the aim of analysing the influence of the heteroatomic nucleus on the reactivity.



Scheme.

Results and Discussion

The base-catalysed reaction of aldehydes with acetonitriles forms α-cyano-compounds only of *Z*-configuration.[3-10]

The observed reaction rate constants of the sodium methoxide-catalysed reaction of benzaldehyde and thiophene-2-carbaldehyde with phenylacetonitrile in methanol at 30 °C show that the order of the reaction is first-order with respect to each reactant and third-order overall (Table 1). The order of the reaction between benzaldehyde and thiophene-2-carbaldehyde and acetonitriles has been verified for all the compounds and in all cases it is first-order in each reactant.

The velocity of the reaction of aldehydes with acetonitriles is therefore represented by the expression $v = k[\text{aldehyde}][\text{acetonitrile}][CH_3O^-]$. Following Bruylants *et al.*[11] the mechanism of the reaction of aldehydes with acetonitriles in methanol–sodium methoxide is shown in the Scheme where the rate-determining step is the attack of the nucleophile (N^-) to the carbonyl carbon atom of the aldehyde.

The measured velocity is given by equation (1). From

$$v = k_2[N^-][E] \qquad (1)$$

reaction (a) we have equation (2). From equations (1) and (2) we have (3). If $k_2K' = k_3$, then equation (4) holds. The reaction is first-order with respect to each reactant and third-order overall,

$$K = [N^-][ROH]/[N][RO^-];$$

$$K/[ROH] = K' = [N^-]/[N][RO^-] \qquad (2)$$

$$v = k_2K'[RO^-][N][E] \qquad (3)$$

$$v = k_3[RO^-][N][E] \qquad (4)$$

as found experimentally. In pseudo-first-order conditions, in excess of acetonitrile and base we have equation (5), and from

$$v = k_{1ps}[E] \qquad (5)$$

equations (4) and (5), we have equation (6). The kinetics of the

$$k_{1ps} = k_3[N][RO^-] \qquad (6)$$

reaction here studied is thus as expected from reactions (a) and (b), and from equations (1) and (4).

Table 1. Pseudo-first-order rate constants for the reaction of benzaldehyde and thiophene-2-carbaldehyde with phenylacetonitrile at 30 °C

Run	10^2[Phenylacetonitrile]/ mol l^{-1}	[CH_3ONa]/mol l^{-1}	10^5[Benzaldehyde]/ mol l^{-1}	$10^5k_{1ps}/s^{-1}$
1	3.16	0.405	2.11	12.5
2	6.3	0.405	2.11	25.0
3	12.6	0.405	2.11	50.2
4	15.8	0.405	2.11	62.5
5	6.3	0.202	2.11	12.4
6	6.3	0.810	2.11	49.5
7	6.3	1.050	2.11	63.5
8	6.3	0.405	1.05	24.8
9	6.3	0.405	4.22	24.7
10	6.3	0.405	8.44	25.1
			10^5[Thiophene-2-carbaldehyde]/mol l^{-1}	
1	3.16	0.405	2.35	11.9
2	6.3	0.405	2.35	22.3
3	12.6	0.405	2.35	44.6
4	15.8	0.405	2.35	55.2
5	6.3	0.202	2.35	11.0
6	6.3	0.810	2.35	44.2
7	6.3	1.050	2.35	55.7
8	6.3	0.405	1.17	21.7
9	6.3	0.405	4.71	21.8
10	6.3	0.405	9.42	22.7

Table 2. Third-order rate constants and activation parameters for the reaction of benzaldehyde with $ArCH_2CN$

		$10^3k_3/s^{-1}$ mol^{-2} l^2						
No.	Ar	20 °C	30 °C	40 °C	50 °C	E_A/kcal mol^{-1}	$-\Delta S^*$/cal mol^{-1} K^{-1}	log *A*
1	C_6H_5	5.20	9.81	19.6	38.2	12.54	28.3	7.05
2	$C_6H_4CH_3(p)$	2.13	3.98	11.7	17.4	13.90	25.4	7.68
3	$C_6H_4OCH_3(p)$	1.16	2.28	5.04	10.7	14.00	26.3	7.49
4	$C_6H_4F(p)$	5.41	9.92	24.3	39.3	12.87	27.1	7.32
5	$C_6H_4Cl(p)$	30.3	49.3	107	157	10.73	30.9	6.47
6	$C_6H_4Br(p)$	23.1	55.7	92.8	156	11.76	27.7	7.17
7	2-Thienyl	35.7	62.6	133	285	13.09	22.6	8.28
8	3-Thienyl	2.91	6.05	15.2	31.2	15.11	20.7	8.71
9	3-Pyridyl	152	205	460	695	10.08	30.1	6.66

Table 3. Third-order rate constants and activation parameters for the reaction of thiophene-2-carbaldehyde with $ArCH_2CN$

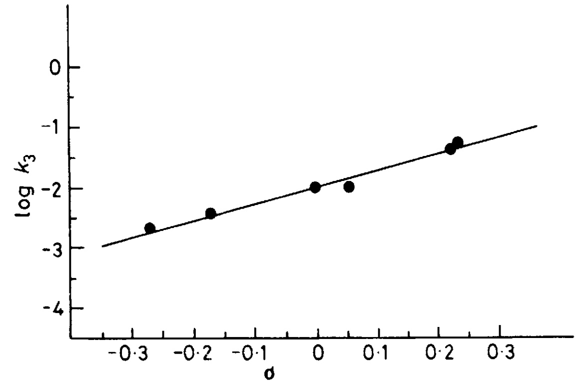
		$10^3k_3/s^{-1}$ mol^{-2} l^2						
No.	Ar	20 °C	30 °C	40 °C	50 °C	E_A/kcal mol^{-1}	$-\Delta S^*$/cal mol^{-1} K^{-1}	log *A*
1	C_6H_5	3.98	8.75	14.0	32.9	12.78	27.9	7.13
2	$C_6H_4CH_3(p)$	1.80	3.92	7.90	16.2	13.69	26.4	7.47
3	$C_6H_4OCH_3(p)$	1.08	2.17	3.92	7.53	12.06	33.0	6.02
4	$C_6H_4F(p)$	3.58	9.12	14.2	40.5	14.48	22.3	8.36
5	$C_6H_4Cl(p)$	11.3	26.1	53.9	144	15.68	16.0	9.73
6	$C_6H_4Br(p)$	12.2	26.1	57.6	109	13.86	22.0	8.42
7	2-Thienyl	22.1	46.3	98.6	184	13.38	22.5	8.32
8	3-Thienyl	2.49	5.43	11.1	21.6	13.53	26.3	7.49
9	3-Pyridyl	97.1	164	319	455	10.11	30.7	6.63

We measured the pseudo-first-order rate constant, obtained with excess of acetonitrile and base, and by dividing it by the concentration of acetonitrile and base, we obtained the third-order rate constant, reported in Tables 2 and 3.

The substituent effect on the rate constants shows that the reaction rate depends on the electron density on the carbon atom of acetonitrile: electron-donating substituents decrease the rate, electron-withdrawing groups increase the rate.

The values of the activation energy show regular variation with substituents in acetonitrile derivatives. The negative entropies of activation are as expected for reactions with a polar transition state.[12]

The plots of log k_3 *versus* σ at 30 °C for the reactions of benzaldehyde and thiophene-2-carbaldehyde with *p*-substituted phenylacetonitriles against Hammett's σ constants are linear with slopes of 2.72 (*r* 0.983) and 2.11 (*r* 0.994), respectively. The Figure reports as an example a plot of log k_3 *versus* σ at 30 °C for the reaction of benzaldehyde with phenylacetonitriles. The reaction rates of benzaldehyde with thiophen-2-ylacetonitrile (k') and 3-pyridylacetonitrile (k'') are greater than that of



Plot of log k_3 *versus* σ at 30 °C for the reaction of benzaldehyde with *p*-substituted phenylacetonitriles

phenylacetonitrile (k) whereas the reactivity of thiophen-3-ylacetonitrile (k''') is lower, the ratios at 30 °C being k'/k = 6.87, k''/k = 29.1, and k'''/k = 0.56, respectively. Hence the reactivity sequence is 3-pyridylacetonitrile > thiophen-2-ylacetonitrile > phenylacetonitrile > thiophen-3-ylacetonitrile, indicating that, in comparison with the benzene nucleus, the 3-pyridyl and 2-thienyl groups are electron-withdrawing and 3-thienyl is electron-donating.

The Hammett equation has been applied to five-membered heteroaromatic rings.[13–15] By considering the heteroatom as a substituent which replaces –CH=CH– in the benzene ring the substituent constant for the heteroatom has been calculated from equation (7)[15] where log k is the reaction rate at 30 °C of

$$\sigma_{het} = (\log k - \log k_0)/\rho \qquad (7)$$

the heteroaromatic compound, log k_0 is the reaction rate of the unsubstituted benzene derivative at the same temperature, and ρ is the reaction constant of the benzene derivative. The Hammett treatment has been applied to nucleophilic substitution at the carbonyl group and the results have shown the variability of σ_{het} values.[16]

The evaluated σ constants for the heteroatoms are: $\alpha_{\alpha\text{-S}}$ 0.30, $\sigma_{\beta\text{-S}}$ −0.08, and $\sigma_{\beta\text{-N}}$ 0.49.

The positive $\sigma_{\alpha\text{-S}}$ value indicates a net electron-withdrawal effect of the heteroatom at the α-position in the thiophene nucleus and it is similar to that found in the ionization of carboxylic acids,[17] in the basic hydrolysis of thenanilides,[18] in the acid dissociation of thiophenesulphonamides,[19] and in the protonation of thiophenecarboxamides.[20,21]

The value of $\sigma_{\beta\text{-S}}$ indicates that the heteroatom at the β-position in the thiophene nucleus behaves as an electron-donating substituent as found in the acid hydrolysis of thenanilides,[22] in the solvolysis of 1-arylethyl acetates,[23] in the pyrolysis of 1-arylethyl acetates,[24] in protiodesilylation,[25] in the solvolysis of alkyl chlorides,[26] in the reaction of arenesulphonyl chlorides with aniline,[27] in the protonation of thiophenecarboxamides,[20] in the reaction of 3-thenoyl chloride with aniline,[28] and in the reaction of sodium borohydride with ketones.[26]

The high positive value of $\sigma_{\beta\text{-N}}$ indicates that a nitrogen atom in the β-position in the pyridine ring behaves as an electron-withdrawing substituent, as found in many other reactions.[14]

The results show that thiophene-2-carbaldehyde reacts with acetonitriles by the same mechanism as that of benzaldehyde.

The reaction rates of thiophene-2-carbaldehyde with thiophen-2-ylacetonitrile (k') and 3-pyridylacetonitrile (k'') are greater than that of phenylacetonitrile (k), whereas the reactivity of thiophen-3-ylacetonitrile (k''') is lower, the ratios being k'/k = 5.3, k''/k = 18.7, and k'''/k = 0.620. Hence the reaction of thiophene-2-carbaldehyde with acetonitriles shows the same reactivity sequence as found in the reaction of benzaldehyde: 3-pyridylacetonitrile > thiophen-2-ylacetonitrile > phenylacetonitrile > thiophen-3-ylacetonitrile.

The reaction rates of thiophene-2-carbaldehyde with acetonitriles (Table 3) are lower than those of benzaldehyde, indicating that, in comparison with the benzene nucleus, the thienyl group is electron-donating, as found in other side-chain reactions.[22–28]

Several studies have been carried out for the purpose of comparing the side-chain reactivity in the five-membered heterocyclic nuclei with that of the benzene series. These groups may be expected to exert two opposing electronic effects. There will be an electron-withdrawing inductive effect caused by the electronegativities of the heteroatoms and an electron-donating mesomeric effect due to the ability of the heteroatoms to share their unshared electron pairs. It was pointed out that the heterocyclic rings, depending on the pattern of substitution and the reaction considered, can act as both electron donors and acceptors.[13,14,21,29,30]

In the reactions here studied between aldehydes with acetonitriles catalysed by sodium methoxide, the 2-thienyl group behaves as both electron donor and acceptor: electron donor when it is in the aldehyde and electron acceptor when it is in the acetonitrilic derivative.

Experimental

Materials.—Benzaldehyde, thiophene-2-carbaldehyde, and acetonitriles were Aldrich commercial products, purified by crystallization or distillation. Methanol was purified by distillation from $Mg(OMe)_2$[31] and a stock solution of sodium methoxide in methanol was obtained by dissolution of AnalaR grade sodium. Methoxide concentrations were established by titration with standard acid.

Kinetic Procedure.—Kinetic measurements were performed in methanol–sodium methoxide. Stock solutions of the reactants in methanol were prepared at the temperature at which the runs were made. An amount of solution was transferred to a u.v. cell and at appropriate intervals the absorbance of the (*Z*)-α,β-diarylacrylonitriles (**III**) was measured with a Hitachi–Perkin-Elmer EPS-3T spectrophotometer at a suitable wavelength in the range 310—341 nm. The pseudo-first-order rate constants were calculated from the slope of the line obtained by plotting log $OD_\infty/(OD_\infty - OD_t)$ against t, where OD_t was the optical density of the solution at time t. The optical density at infinite time (OD_∞) was determined for *ca.* 8—10 half-lives.

All kinetic runs were carried out in duplicate to at least 85—90% completion with <5% deviation between the two rate constants.

The activation parameters were calculated from a least-squares treatment of log k against T^{-1}. The estimated precision is *ca.* 0.7 kcal mol⁻¹ in E_A and ±2.5 cal mol⁻¹ in ΔS^*.

Product Analysis.—Standard solutions of reactants in methanol were placed in a glass stoppered bottle and maintained at the kinetic temperature until completion. The (*Z*)-α,β-diarylacrylonitriles precipitated were recrystallized from ethanol. In all cases the amount of the compounds were 95% of that expected.

(*Z*)-α-Phenyl-β-(X)acrylonitriles (X, m.p.): C_6H_5, 88;[32] $C_6H_4CH_3(p)$, 78;[33] $C_6H_4OCH_3(p)$, 112;[34] $C_6H_4F(p)$, 105;[35] $C_6H_4Cl(p)$, 114;[36] $C_6H_4Br(p)$, 112;[37] 2-thienyl, 92;[7] 3-thienyl, 69;[38] 3-pyridyl, 109.[10]

(*Z*)-α-(2-Thienyl)-β-(X)acrylonitriles (X, m.p.): C_6H_5, 92;[7] $C_6H_4CH_3(p)$, 119;[7] $C_6H_4OCH_3(p)$, 78;[7] $C_6H_4F(p)$, 94;[39] $C_6H_4Cl(p)$, 128;[7] $C_6H_4Br(p)$, 118;[39] 2-thienyl, 131;[40] 3-thienyl, 99;[38] 3-pyridyl, 152 (Found: C, 67.8; H, 3.8; N, 13.1; S, 15.0. $C_{12}H_8N_2S$ requires C, 67.9; H, 3.8; N, 13.2; S, 15.1%).

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Received 5th *March* 1984; *Paper* 4/364