COMPARATIVE STUDY OF THE KINETICS OF CYCLISATION OF N-BENZOYL-α-AMINO ACIDS AND A RELATED COMPOUND: AN APPLICATION OF THE TAFT EQUATIONS

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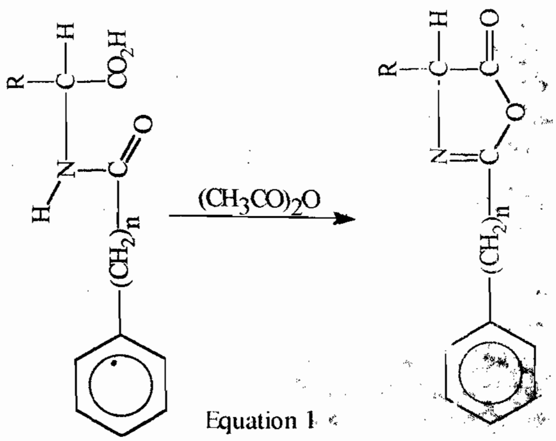
ABSTRACT

The rate constants for the cyclisation of N-benzoyl derivatives of glycine, L- and DL-α-amino acids and N-phenylethanoylglycine have been determined and compared. The values were correlated with the appropriate substituent constants and the differences attributed to the polar effects.

INTRODUCTION

We reported[1] recently the linearization of the substituent effects on rates of cyclisation of the N-benzoyl derivatives of glycine and three optically active amino acids using the Taft linear free energy relationships.

In continuation of our interest in the quantitative aspects of the rates of formation of oxazolin-5-ones, we now report the rate constants for the cyclisation of L- and DL N-benzoyl-α-amino acids ($n = 0$) and that of N-phenylethanoylglycine ($n = 1$, R= H, Equation 1) and the correlations of these values with Taft's polar and steric substituent constants.



Equation 1

EXPERIMENTAL

The starting compounds were prepared[2-6] by Schotten - Bauman type reaction and were characterised by standard methods[2].

The cyclisation reactions were carried out at 298 K on a Unicam SP 8 - 100 ultraviolet spectrophotometer at $\lambda_{max} = 284$ nm using redistilled ethanoic anhydride.

The rate constants were calculated by the least square analysis of plots of time against $\log (A_\infty - A_0)/(A_\infty - A_t)$. The rate constants were the averages of 4 - 7 determinations

RESULTS AND DISCUSSION

Preparation

The α-amino acids gave the expected N-benzoyl-α-amino acids on treatment with redistilled benzoyl chloride in high yields. Before use, their melting points were checked and found to compare favourably well with those previously prepared in our laboratory[2] or reported in the literature[3-8]. The relevant physical data are shown in Table 1.

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Table 1: Physical data of N-benzoyl-α-amino acids

No	N-benzoyl-α-amino acids of	R	Yield %	mp °C	λ_{max} nm	$\log_{10}\varepsilon$ (in water)
(a)	glycine	-H (n=0)	78.6	187-188	229	3.90
(b)	DL-alanine	$-CH_3$	80.5	164-166	229	3.98
(c)	L-alanine	$-CH_3$	79.4	150-151	229	3.98
(d)	DL-norvaline	$-CH_2CH_2CH_3$	81.2	155-157	228	3.88
(e)	L-valine	$-CH(CH_3)_2$	81.8	130-132	228	3.90
(f)	DL-leucine	$-CH_2CH(CH_3)_2$	83.9	136-138	228	4.05
(g)	DL-isoleucine	$-CH(CH_3)CH_2CH_3$	81.7	120-121	228	4.08
(h)	DL-phenylalanine	$-CH_2C_6H_5$	87.1	186-188	228	4.00
(i)	L-phenylalanine	$-CH_2C_6H_5$	89.2	140-141	228	4.05
(j)	L-threonine	$-CH(OH)CH_3$	77.2	146-148	229	3.95
(k)	Dl-methionine	$-CH_2CH_2SCH_3$	74.5	148-151	228	3.89
(l)	DL-tyrosine	$-CH_2C_6H_4-OH$	73.2	198-200	226	3.80
(m)	DL-serine	$-CH_2OH$	76.3	120-122	228	4.00
(n)	L-serine	$-CH_2OH$	75.7	138-140	228	3.88
(o)	N-phenylethanoylglycine	-H(n=1)	64.1	131-141	215	3.90

Ultraviolet - visible spectra of compounds

The λ_{max} and $\log\epsilon$ values of the compounds in distilled water are shown in Table 1. In ethanoic anhydride, they exhibited λ_{max} between 283 and 284 nm with a relatively low extinction coefficient compared with that in distilled water.

As expected, the λ_{max} value (215 nm) for N-phenylethanolglycine is comparatively lower than those of the N-benzoyl-α-amino acids (λ_{max} = 226-228 nm). This is due to the interposition of the CH_2 group between the benzene ring and the carbonyl group - leading to decrease in conjugation[8] in the N-phenylethanoyl-glycine.

Kinetic data

The rate constants for the cyclisation reactions are reported in Tables 2 & 3. All the reactions were first order in N-benzoyl-α-amino acids or N-phenylethanoylglycine.

The increase in the relative rate was found to be in the following order:

(a) L-α-amino acids and glycine (Table 2)

$-H < -CH_3 < -CH_2C_6H_5 < -CH(CH_3)_2 < -CH(OH)CH_3 < -CH_2OH$

(b) DL-α-amino acids and glycine (Table 3)

$-H < -CH_3 < -CH_2C_6H_5 < -CH_2CH_2CH_3 < -CH_2CH(CH_3)_2 < -CH(CH_3)CH_2CH_3 < -CH_2CH_2SCH_3 < -CH_2C_6H_4OH < -CH_2OH$

Table 2: Parameters used to correlate kinetic data of derivatives of L-α-amino acids and glycine at 298 K

No.	Substituent R	Rate constant k $(s^{-1}) \times 10^{-4}$	log k/k_0	σ^*	E_s
(a)	-H (n=0)	1.92	-051	+0.490	+1.24
(b)	$-CH_2C_6H_5$	7.70	0.09	+0.125	-0.38
(c)	CH_3	6.20	0	0	0
(e)	$-CH(CH_3)_2$	8.83	0.15	-0.190	-0.47
(j)	$-CH(OH)CH_3$	11.17	0.26	+0.32	
(n)	$-CH_2OH$	29.67	0.68	+0.555	

Each of the above orders of substituents[1] corresponds definitely to that of increasing steric requirements and not that of increasing electron withdrawal.

Considering the Taft polar substituent constant, σ*, two series emerge from each of the orders (a) and (b) above: one, for electron-donating group (+I) and the other for electron-withdrawing group (-I) .

(a) L-α-amino acids and glycine (Table 2)

(i) $-H < -CH_3 < -CH(CH_3)_2$ (+I)

(ii) $-CH_2Ph < -CH(OH)CH_3 < -CH_2OH$ (-I)

(b) DL-amino acids and glycine (Table 3)

(i) $-H < -CH_3 < -CH_2CH_2CH_3 < -CH_2CH(CH_3)_2 < -CH(CH_3)CH_2CH_3$ (+I)

Table 3: Parameters used to correlate kinetic data of derivatives of DL-α-amino acids and glycine at 298 K

No.	Substituent R	Rate constant k $(s^{-1}) \times 10^{-4}$	log k/k_0	σ^*	E_s
(a)	-H (n=0)	1.92	-0.43	+0.490	+1.24
(b)	$-CH_3$	5.17	0	0	0
(h)	$-CH_2C_6H_5$	6.17	0.08	+0.215	-0.38
(d)	$-CH_2CH_2CH_3$	7.03	0.13	-0.115	-0.36
(f)	$-CH_2CH(CH_3)_2$	11.10	0.33	-0.125	0.93
(g)	$-CH(CH_3)CH_2CH_3$	14.16	0.44	-0.210	-1.13
(k)	$-CH_2CH_2SCH_3$	15.73	0.48		
(l)	$-CH_2-C_6H_4-OH$	17.67	0.53		
(m)	$-CH_2OH$	21.50	0.62	+0.555	
(o)	-H (n=1)	1.32	-		

(ii) $-CH_2Ph < -CH_2CH_2SCH_3 < -CH_2C_6H_4OH$

For series (a) (i) and (b) (i) above, the increase in the rate constants parallels the order of increasing electron-donating power of the substituents. Similarly, for series (a) (ii) and (b) (ii) above, it is evident that as the electron-withdrawing power of the substituents increases, rate constant increases.

In general, the rate constant of the N-benzoyl derivative of L-α-amino acids is greater than that of the corresponding DL-α-amino acids[2] (compare nos (b) and (c), (h) and (l) and (m) and (n) in Tables 2 and 3).

This shows that the addition of the N-benzoyl derivative of a D-α-amino acid to that of the corresponding L-α-amino acid lowers the rate of cyclisation.

Similarly, the rate constant for the cyclisation of N-phenylethanoylglycine ($1.32 \times 10^{-4}\ s^{-1}$) is comparatively lower than that of N-benzoylglycine ($1.92 \times 10^{-4}\ s^{-1}$). This is expected, since the CH_2 group will attenuate the electronic effect[9] in the former.

Taft analysis

The correlation[9-13] of the Taft polar substituent constant, σ^*, with log k/k_o for each of the derivatives of L-α-amino acids gave two distinct lines with electron donating substituents (+1) on one line and the electron -withdrawing substituents (-1) on the other.

The equations of the least-square lines for the derivatives of the L-α-amino acids and DL-α-amino acids are:

(a) L-α-amino acids and glycine

(i) (+1): $\log k/k_o = -0.98\sigma^*$ (n= 3; R= 0.998)

(ii) (-1): $\log k/k_o = 1.30\sigma^*$ (n= 3; R= 0.963)

(b) DL-α-amino acids and glycine

(i) (+1): $\log k/k_o = -1.27\sigma^*$ (n= 5; R= 0.665)

(ii) (-1): $\log k/k_o = 1.16\sigma^*$ (n= 3; R= 0.962)

(where n = number of substituents, R = correlation coefficient, k_o = rate constant for the standard N-benzoyl-α-alanine and k = rate constant for each of the other derivatives).

However, correlation of the Taft steric substituent, E_s, with log k/k_o gave a single line for each of the series.

The equations of the least-square lines are:

(a) L-α-amino acids and glycine

$\log k/k_o = -0.25E_s - 0.11$ (n= 4; R= 0.884)

(b) DL-α-amino acids and glycine

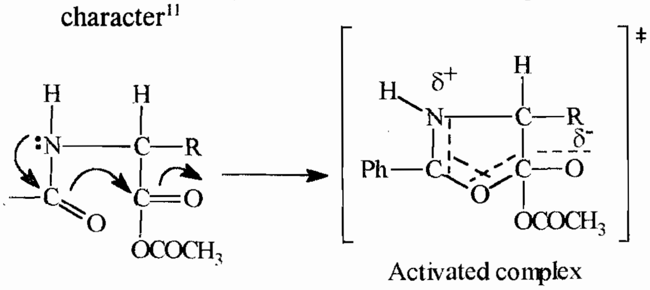
$\log k/k_o = -0.25E_s + 0.02$ (n= 6; R= 0.878)

The magnitude and sign of the reaction, ρ^*, for the +1 group in the N-benzoyl derivatives of L-α-amino acids ($\rho^* = -0.98$) and that of DL--α-amino acids ($\rho^* = -1.27$) indicate that a partial positive charge might have developed probably on nitrogen in the activated complex[9,11,12], with that of the DL-α-amino acids slightly more partially positive and hence, leading to decrease in the rate constants of the DL-α-amino acids compared with that of L-α-amino acids.

For the - I groups in each of the derivatives of L-α-amino acids ($\sigma^* = 1.30$) and DL-α-amino acids ($\sigma^* = 1.16$) very small negative charge might have developed on oxygen in the activated complex with that of the derivatives of L-α-amino acids slightly more negative.

The relatively small values of σ^* indicate that the reaction is cyclic[14,15] and that the small charges might have developed in positions relatively far away from the positions of the substituents[9].

This leads to the suggestion that the activated complex may have an ion-pair character[11]



The low negative value of the steric reaction constant, E_s, which, surprisingly, is the same for the two types of derivatives ($E_s = -0.25$) indicates that the steric effect, although small, causes rate to be accelerated to the same extent in both types of derivatives[1].

CONCLUSION

The apparent difference in the rate constants of the N-benzoyl derivatives of L- and DL-α-amino acids is due to polar effect and not steric requirements, while the low values of the polar and steric reaction constants were due to the cyclic nature of the reactions.

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