Kinetics and Mechanism of the Pyrylium to Pyridinium Cation Transformation in Dichloromethane

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Kinetic rates for cyclisation of divinylogous amides (derived from pyrylium cations and primary amines) into pyridinium cations are measured for CH_2Cl_2 solutions and compared with previous results in water and other solvents. The ring-closure is catalysed by carboxylic acids; a postulated mechanism involves the free acid in catalysis of electrocyclic ring closure.

The mechanism of the pyrylium into pyridinium conversion is believed [1] to be as given in Scheme 1 (R^2 = H).

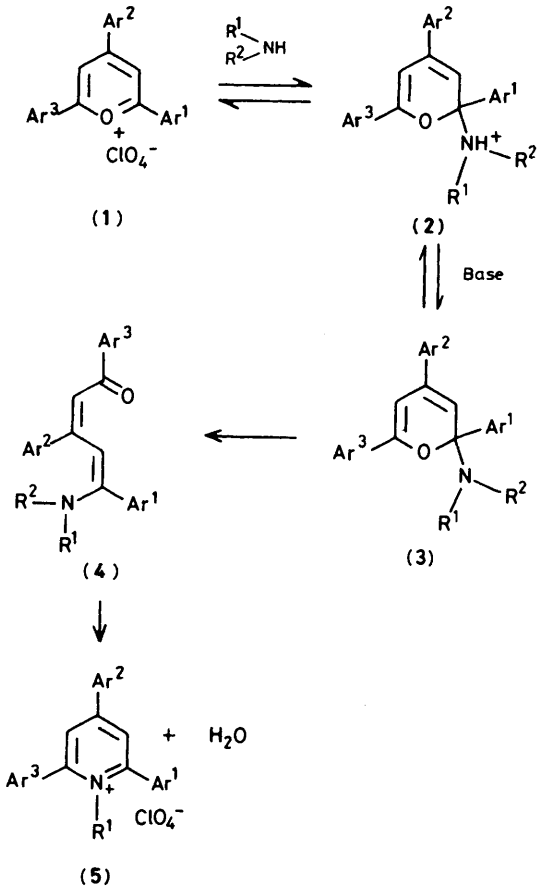
Exceptionally, the 2*H*-pyran intermediate (**3**) can be detected by ^{13}C n.m.r. spectroscopy [*e.g.* (**3a**), R^1 = Bu^t, R^2 = H] or even isolated [*e.g.* (**3b**), R^1 = Bu^s, R^2 = H],[2] but normally all steps up to the formation of (**4**) are fast and the ring-opened intermediate (**4**) is the only one that can be detected by spectroscopic methods. However, stopped-flow studies[3] of the ring-opening in MeOH are able to detect the pyran (**3**), measure its rate of formation from (**1**), and show specific base catalysis [indicating fast (**2**) → (**3**) conversion; rate-determining (**3**) → (**4**) conversion] for secondary [($R^2 \neq$ H) in Scheme 1], but not for primary amines. ^{13}C N.m.r. studies[1,4] confirmed the structure of the divinylogous amide (**4**).

Ring-closure rates for the (**4**) → (**5**) conversion, measured in CH_2Cl_2,[5] are independent of amine concentration when [R^1NH_2] ≫ [pyrylium], approximately first-order in pyrylium cation, and acid catalysed.

Kinetic studies[2,6] of the pyrylium→pyridinium conversion in water, where pH can be measured and controlled, are complicated by concomitant hydrolysis of the pyrylium cation. First-order ring-closure rate constants *k* for divinylogous amides derived from arylamines are faster by *ca.* 10^2 than for those from alkylamines.[2] Pyrylium salts with fused α-phenyl groups give divinylogous amides that cyclise $> 10^3$ times faster than those with free α-phenyl groups.[6] This evidence suggested that the step (**4**) → (**5**) proceeded by an electrocyclic ring-closure of the all-*cis* conformation (**7**) [more favoured sterically for (**4**) derived from pyrylium salts with fused α-phenyl groups] of the iminodienol tautomer (**6**) ⇌ (**7**) (more favoured for R^1 = aryl than for R^1 = alkyl).

Because of the preparative importance of these reactions[7] we have now studied the nature of the acid catalysis of ring-closure and compare our results with those in water[2,6] and other solvents.[5] Reactions studied kinetically were first carried out preparatively, using known procedures (Table 1).

Spectra for the divinylogous amides were obtained by diluting the kinetic solution (kinetic method A), without addition of acid catalyst, into dimethylformamide (DMF) within two minutes of mixing. Spectra of isolated pyridinium salt samples in DMF were compared with the spectra at infinite time of the kinetic reactions and gave fair agreement (Table 2).



a; $Ar^1 = Ar^2 = Ar^3$ = Ph
b; $Ar^1 = Ar^3$ = 4-$HO_3SC_6H_4$, Ar^2 = 4-MeO,3-$HO_3SC_6H_3$

Scheme 1.

Rate Measurements.—Earlier,[5] ring-closure rates for the (**4a**) → (**5a**) conversion were increased by factors of up to 50 on addition of AcOH. However, we have now found that under the conditions previously used, and in particular when the molar ratio of AcOH to the ([amine] − [pyrylium]) concentration is above 0.12, the rate plots can show considerable initial curvature.

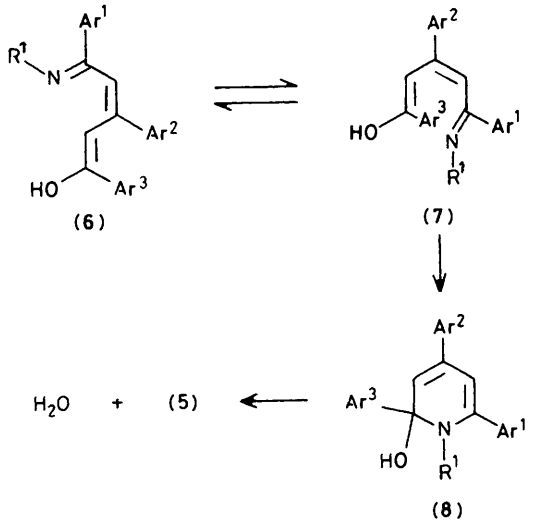
These experiments[5] were conducted with a pyrylium to amine ratio of 1:2. Conversion of the pyrylium (**1**) into (**4**) involves conversion of the second mole of amine into its protonated form. As (**4**) ring closes to (**5**), the protonated amine provides the H^+ and the free amine is reformed. Hence the amount of free amine increases as the reaction proceeds. The amount of available AcOH will depend inversely on the amount of free amine. Hence, as the reaction proceeds, [AcOH] falls and the rate decreases. Increasing [AcOH] increases the rate of ring closure and the proportion of the reaction occurring in the non-first-order phase.

We have now studied the effect of acid catalysts on rates under conditions where there is sufficient excess of amine

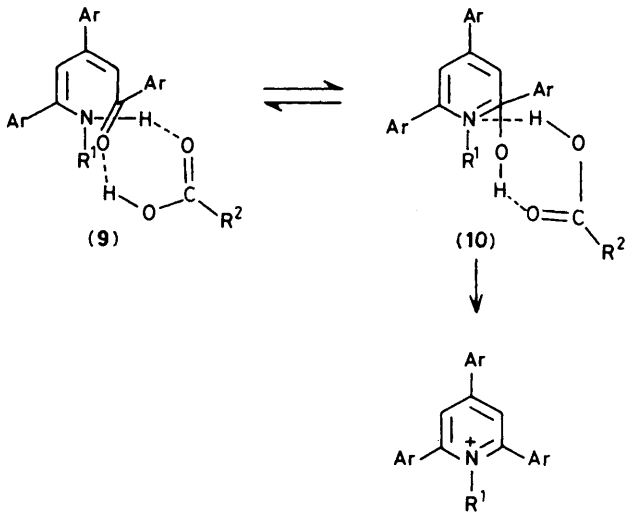
Table 1. Preparation of *N*-(substituted aryl)-2,4,6-triphenylpyridinium perchlorates (preparative method A)

Amine			Crystal	M.p. (*t*/°C)		k_{obs} [a]
Type	Substituent	Yield (%)	form	Lit.	Found	$\times 10^3/s^{-1}$
Aniline ($R^1 = XC_6H_4$)	*m*-Br	50	Needles	*b*	274—275	0.71
Aniline	*p*-Br	71	Needles	*c*	165—167	1.7
Aniline	*p*-Cl	46	Needles	212—213 [d]	215—216	1.6
Aniline	*p*-MeO	47	Needles	245 [d]	251—252	14
Aniline	*p*-Me	57	Needles	247—248 [d]	249—251	9.0
Aniline	H	51	Needles	278—280 [e]	276—277	4.1
Aniline	*m*-NO_2	62 [f]	Plates	244—246 [e]	244—246	0.34
Benzylamine ($R^1 = XC_6H_4CH_2$)	H	62	Needles	196—198 [g]	180—182	—
Benzylamine	*p*-Cl	95 [e]	Needles	143 [h]	145—147	—

[a] Approximate pseudo-first-order ring-closure rate constants $k_{obs.}$ for (**4a**) → (**5a**) in CH_2Cl_2, [(**1a**)] = 6.11 mM, [amine] = 6.11 mM, [Et_3N] = 12.2 mM, [AcOH] = 24.4 mM. [b] Found: C, 61.9; H, 3.7; N, 2.4. $C_{29}H_{21}BrClNO_4$ (M_r 562) requires C, 61.9; H, 3.8; N, 2.5%. [c] Found: C, 60.4; H, 3.9; N, 2.3. $C_{29}H_{23}BrClNO_5$ (M_r 580) requires C, 60.4; H, 3.9; N, 2.3%. [d] K. Dimroth and C. Reichardt, *Liebigs Ann. Chem.*, 1969, **727**, 93. [e] Ref. 1. [f] Preparative Method B. [g] A. R. Katritzky, J. B. Bapat, R. J. Blade, B. P. Leddy, P. -L. Nie, C. A. Ramsden, and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1979, 418. [h] A. R. Katritzky, A. M. El-Mowafy, G. Musumarra, K. Sakizadeh, C. Sana-Ullah, S. M. M. El-Shafie, and S. S. Thind, *J. Org. Chem.*, 1981, **46**, 3831.



Scheme 2.



Scheme 3.

(kinetic methods A and B) for the [AcOH] to be buffered. Under these conditions the ring closure (**4a**) → (**5a**) is accurately first order in (**4a**). U.v. spectra show (Table 2) that, in the ring-opening to the divinylogous amide, benzylamine reacts with (**1a**) to give complete conversion into (**4a**) under the conditions used (kinetic methods A and B). Reaction of (**1a**) with anilines (kinetic method A) also gives complete conversion into (**4a**) except with *meta*- and *para*-nitroanilines where u.v. spectra showed unchanged (**1a**) (Table 2).

Ring-closure Rates.—The ring-closure rates of (**4a**) (R^1 = CH_2Ph, R^2 = H), prepared in CH_2Cl_2 from (**1a**) (4.85×10^{-5}M) and $PhCH_2NH_2$ (over the range 0.04—0.10M), are approximately first order in (**4a**) and independent of amine concentration with a first-order rate constant k of $8 \pm 1 \times 10^{-5}$ s^{-1}.

The dependence of the ring-closure rate for (**4a**) [prepared from (**1a**) (4.85×10^{-5}M) and $PhCH_2NH_2$ (0.1M)] on the concentration of added AcOH was studied. Up to [AcOH] = 0.012M accurate first-order plots were obtained. The ring-closure rate increased markedly with increasing [AcOH] (Table 3).

The rate-enhancement effect of various acids on ring-closure rate have been measured (Table 4). Only the carboxylic acids showed rate enhancement.

Semi-quantitative studies of the ring-closure rates for the divinylogous amides derived from a series of *para*- and *meta*-substituted anilines (Table 1) showed that electron-donor substituents increased and electron-withdrawing substituents decreased the rate: Hammett ρ^0 value -1.7 ± 0.2.

Comparison of Ring-closure in CH_2Cl_2 *and* H_2O.—The ring-closure rate constant k for the divinylogous amide (**4a**) (R^1 = CH_2Ph, R^2 = H) measured in CH_2Cl_2 (large excess of amine, but absence of any acid catalyst) is 8.0×10^{-5} s^{-1}, *i.e.* 25 times slower than that for the comparable divinylogous amide (**4b**) measured in H_2O at pH 10.1.[2]

For (**4a**) (R^1 = Bu^n, R^2 = H) in CH_2Cl_2, *k decreased*[5] with increased solvent dielectric constant for aprotic solvents from 5×10^{-4} s^{-1} in PhCl (dielectric constant 5.6) to 5×10^{-6} s^{-1} in DMF (dielectric constant 37.6).

We rationalise these results in the following way: low solvent polarity should cause a shift (*i*) to the less polar iminodienol

Table 2. U.v. spectral data for divinylogous amides and pyridinium cations derived from 2,4,6-triphenylpyrylium perchlorate in DMF

Amine		Divinylogous amide Extrapolation				Pyridinium Extrapolation [c]		Pyridinium Isolated [d]	
Type	Substituent	λ/nm	$10^{-3}\ \varepsilon$[a]/l cm^{-1} mol^{-1}	λ/nm	$10^{-3}\ \varepsilon$[b]/l cm^{-1} mol^{-1}	λ/nm	$10^{-3}\ \varepsilon$/l cm^{-1} mol^{-1}	λ/nm	$10^{-3}\ \varepsilon$/l cm^{-1} mol^{-1}
Aniline (R^1 = XC_6H_4)	*p*-MeO	475	9.5	475	7.2	312	32.3	312	29.8
Aniline	*p*-Me	466	6.9	466	7.2	312	23.0	312	31.5
Aniline	H	452	9.2[e]	458	5.4[f]	312	25.3	312	30.4
Aniline	*p*-Cl	452	7.5	452	4.3	312	26.7	312	28.2
Aniline	*p*-Br	452	7.0	452	4.8	312	25.1	312	28.2
Aniline	*m*-Br	452	5.1	452	4.3	312	24.8	312	30.8
Aniline	*m*-NO_2	452	3.3	452	2.5	*g*	*g*	317	17.4
Benzylamine (R^1 = $PhCH_2$)	H	452	15	452	18	312	25.5	312	26.3

[a] Prepared from pyrylium, amine, and Et_3N in CH_2Cl_2 and diluted into DMF. [b] Extrapolated rate plots. [c] Infinite time of rate plots. [d] Authentic sample. [e] Average of two measurements. [f] Average of three measurements. [g] Pyridinium cation formation not observed.

Table 3. Effect of acetic acid on rate of ring-closure of the divinylogous amide[a] (**4a**) (R^1 = CH_2Ph, R^2 = H) (kinetic method **B**)

$[AcOH]_s/[Py^+]$[b]	$10^3\ k_{obs.}$[c]/s^{-1}	$10^{-3}\ \varepsilon_0$[d]/l cm^{-1} mol^{-1}
0	0.080 ± 0.002	16.6
10	0.80 ± 0.01	19.7
50	4.3 ± 0.02	19.2
100	7.6 ± 0.05	20.4
150	10 ± 0.2	14.5
200 (i)	14 ± 0.5	20.4
(ii)	12 ± 0.2	15.8
250	15 ± 0.4	20.4

[a] [pyrylium] = 4.85 × 10^{-5}M, [b] Ratio [AcOH]:[pyrylium]. [c] Observed pseudo-first-order ring-closure rate constant. [d] Extinction coefficient of [(**4a**), R = CH_2Ph] extrapolated to zero time.

Table 4. Effect of different acids on the observed pseudo-first-order ring-closure rate constant $k_{obs.}$ of the divinylogous amide (**4a**) (R^1 = CH_2Ph, R^2 = H) (kinetic method **A**)

Acid	pK_a[a]	$10^5 k_{obs.}$/s^{-1}	Relative rate
None	—	3.3 ± 0.4	1.0
CH_3CO_2H	4.8	60 ± 3	18
CF_3CO_2H	0.2	2.8 ± 0.5	0.85
PTSA[b]	−1.3[c]	*d*	1.0
$PhCO_2H$	4.2	39 ± 2	12
HCO_2H	3.8	14 ± 1	4.2
$ClCH_2CO_2H$	2.9	8.7 ± 0.6	2.6
2-Pyridone	11.65[e]	5.7 ± 0.2	1.7
Salicylic acid	3.0	4.4 ± 0.3	1.3
PhOH	10.0	3.5 ± 0.4	1.1
p-$MeOC_6H_4OH$	10.2	3.6 ± 0.9	1.1
Et_3NHCl	10.8	3.4 ± 0.4	1.1

[a] In H_2O, taken from 'Dissociation Constants of Organic Acids,' eds G. Kortum, W. Vogel, and K. Andrussow, Butterworths, London, 1961. [b] Toluene-*p*-sulphonic acid. [c] In H_2O, taken from 'Dissociation Constants of Organic Acids,' eds E. P. Sergeant and B. Dempsey, Pergamon, Oxford, 1979. [d] *k* Measured by kinetic method **B** showing no rate enhancement. [e] 'Dissociation Constants of Organic Bases,' ed. D. D. Perrin, Butterworths, London, 1965.

tautomer (**6**) ⇌ (**7**) from the divinylogous amide (**4**) and (*ii*), on electrostatic grounds, to the all-*cis* conformation (**7**) from the *cis–trans* form (**6**) of this tautomer.[8]

Effects of Amine Structure and Nature of Acid Catalyst on Ring-closure Rate.—In H_2O,[2] the divinylogous amide (**4b**) (R^1 = Ph, R^2 = H) with an *N*-phenyl group cyclises at 50 times the rate of its *N*-benzyl analogue (**4b**) (R^1 = CH_2Ph, R^2 = H). In CH_2Cl_2, the order is the same, but the difference is less: (**4a**) (R^1 = Ph, R^2 = H) 3.3 times the rate of (**4a**) (R^1 = CH_2Ph, R^2 = H).

Of the acids tested as catalysts, acetic acid was the most effective. The catalytic activity falls (Table 4) as the acidity of the carboxylic acid increases: $MeCO_2H$ > $PhCO_2H$ > HCO_2H > $ClCH_2CO_2H$ > CF_3CO_2H with the last having no catalytic activity. HCl (added as NEt_3HCl) also had no catalytic effect. These results suggest that the active catalyst is the free carboxylic acid molecule; perhaps a 'push–pull', simultaneous proton donation and acceptance is involved. Phenols showed no catalytic activity, and 2-pyridone only little.

The carboxylic acid is possibly involved as depicted in (**9**) → (**10**): proton transfer forms (**7**) the correct alignment of which for subsequent electrocyclic ring-closure to (**10**) is assisted by hydrogen bonding with the carboxylic acid. Thus the carboxylic acid can promote fast equilibration (**9**) ⇌ (**10**) which is then followed by rate-determining dehydration (**10**) → (**11**). Carboxylic acids increase $k_{obs.}$ by increasing the proportion of the reactive intermediate (**10**) in the equilibrium. The adverse effect of electron-withdrawing substituents in R on the ring-closure rate could then be due to slow-down of step (**10**) → (**11**).

Experimental

U.v. spectra were recorded with Pye–Unicam SP8-200 or PU8800 spectrophotometers. M.p.s were determined on a Reichert hot-stage apparatus. CH_2Cl_2 was dried over anhydrous K_2CO_3 and stored on 4 Å molecular sieves. Amines were distilled from, and stored over, KOH before use or recrystallised from EtOH until observed as single spots on t.l.c. (silica; EtOH). CH_2Cl_2 was stored over potassium carbonate, filtered, and dried over molecular sieves before use.

Kinetic Method A.—To the pyrylium salt (25 mg, 0.0611 mmol) dissolved in CH_2Cl_2 (5 ml) at 20 °C was added the amine (0.0611 mmol) in CH_2Cl_2 (*ca.* 1 ml), Et_3N (0.122 mmol) in CH_2Cl_2 (*ca.* 1 ml), and the acid (0.006 11 mmol) in CH_2Cl_2 (*ca.* 0.05 ml). The whole was made up to 10 ml with CH_2Cl_2 and equilibrated at 20 °C. Aliquots (*ca.* 0.2 g) were removed at known time intervals, and added to weighed flasks containing DMF (*ca.* 15 ml) which were reweighed and then made up to 25 ml with more DMF. The u.v. spectrum was then recorded. Plots of $-\ln(A_{452}/S)$ *versus* time were used to estimate the pseudo-first-order rate constant, $k_{obs.}$, where A_{452} is the absorbance at 452 nm and *S* is the aliquot weight in grams.

Kinetic Method B.—A solution of the pyrylium salt (**1a**) (25 mg, 0.0611 mmol) in CH_2Cl_2 (10 ml) was prepared. Solutions of $PhCH_2NH_2$ were prepared (0.04—0.1M) in CH_2Cl_2 (25 ml). The amine solution (2.5 ml) was transferred to a cuvette and equilibrated at 25 ± 0.1 °C. Reaction was initiated by injecting 20 μl of pyrylium cation solution into the cuvette to give a pyrylium cation concentration of 4.85×10^{-5}M by inverting the cuvette. The reaction was followed by monitoring the disappearance of the divinylogous amide band (452 nm).

Reactions with acid catalyst were carried out similarly except the amine solution (0.1M) was prepared containing the appropriate concentration of acid.

Preparation of Pyridinium Salts from Pyrylium Salts.—*Preparative method A.* In a typical experiment, 2,4,6-triphenylpyrylium perchlorate (0.5 g, 1.2 mmol), aniline (0.11 g, 1.2 mmol), and Et_3N (0.12 g, 1.2 mmol) were mixed together in CH_2Cl_2 (*ca.* 10 ml) forming a deep-red solution. AcOH (0.30 g, 0.29 ml, 5 mmol) was added and the mixture was stirred for 3 h. The mixture was then added dropwise to rapidly stirred, ice-cooled ether (*ca.* 250 ml) whereupon the pyridinium perchlorate precipitated. The solution was filtered and the precipitate was washed with cold ether and recrystallised from EtOH (Table 1).

Preparative method B. This was as for method A, except before addition of AcOH, Ac_2O (0.2 g, 0.18 ml, 2.0 mol) was also added to scavenge water (Table 1). MeOH (0.2 ml, 5.0 mmol) was added before work-up to quench any excess of Ac_2O.

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