The Influence of *para* Substituents on the Rate of Cyclization of 5-Anilino-N-phenyl-2,4-pentadienylidenimine[1]

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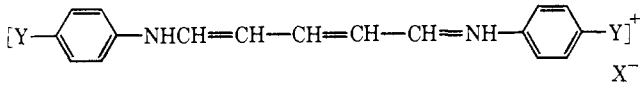
Abstract: The series of substituted salts **1a–f** was prepared and shown to undergo ring closure to an arylpyridinium ion and an arylamine in methanol in the presence of excess triethylamine. First-order rates were observed for all compounds under these conditions, and the rate constants differ by less than fivefold from the slowest (**1a**) to the fastest (**1f**). The data do not fit the Hammett equation. The results are interpreted in terms of a mechanism with an electrocyclization as the rate-determining step.

Zincke[2] discovered that the colored salts obtained by reaction of 2,4-dinitrophenylpyridinium chloride with primary aromatic amines decompose readily in the presence of acids or bases to form N-arylpyridinium chloride and arylamines. In earlier work[3] we showed that in the presence of sufficient triethylamine to convert all 5-anilino-N-phenyl-2,4-pentadienylideniminium ion to the imine, ring closure proceeds by an electrocyclic reaction of the imine. In view of the scarcity of information on structure–reactivity relations in electrocyclic reactions, and in view of the ready availability of iminium salts with equivalent substituents in both aryl rings,[2,4,5] we have studied the kinetics of the reactions of a series of these salts.

Results

Compounds **1a–e** (X = Cl) were prepared by Zincke's method,[2] and compound **1f** (X = Br) was prepared by König's procedure.[6] All except **1d** are known and



1a, Y = NMe_2; X = Cl
b, Y = OMe; X = Cl
c, Y = CH_3; X = Cl
d, Y = F; X = Cl
e, Y = Cl; X = Cl
f, Y = NO_2; X = Br

were identified by their melting points and spectral properties. Each exhibits the expected pair of peaks in the visible spectrum with the longer wavelength absorption assigned to the iminium salt and the shorter wavelength peak to the imine.[3-5] Preparative scale studies showed that all but **1a** reacted cleanly under the experimental conditions to form the relevant arylpyridinium halide and arylamine. Compound **1a** was an exception since the products decomposed during isolation. The nature of its reaction is assumed by analogy and is supported by a report that the expected products are formed in aqueous media.[7] The kinetic behavior of **1a** showed no abnormalities which might suggest that it was reacting in a manner different from the others.

Rate studies for **1a–f** were carried out in methanol solution in the presence of excess triethylamine. The visible spectra showed that the substrate in each case was converted completely to the imine. The kinetics were followed spectrophotometrically and the reaction was carried out directly in a thermostated cell compartment. For all six compounds the rate was shown to be cleanly first order in substrate (Figures 1 and 2) and independent of the triethylamine concentration. Kinetic runs were made at three temperatures and the activation parameters were calculated in the usual manner.[8] These data are given in Table I.

Table I. First-Order Rate Constants and Activation Parameters for **1a–f**

Compd	$k_1 \times 10^4$ sec^{-1}, at 40°	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1a	2.53	22.6	−1
1b	3.65	22.0	−1
1c	3.11	22.8	0
1d	5.23	22.3	0
1e	6.22	22.7	+1
1f	12.0	22.7	0

Discussion

All of the compounds investigated exhibited the characteristic kinetic behavior, *i.e.*, clean first order in substrate and a rate independent of the concentration of the added base, which was shown earlier[3] to be diagnostic of a rate-determining ring closure of the imine (Scheme I). The present data show that this rate-determining step is remarkably insensitive to polar effects. An attempt to fit the data to the Hammett equation[9] showed that no satisfactory fit can be obtained either with σ or σ^+ values, but the best fit ($N = 0.93$) is obtained using σ values and the ρ value ($\rho = 0.35$) indicates the weak response to the polarity of *para* substituents.

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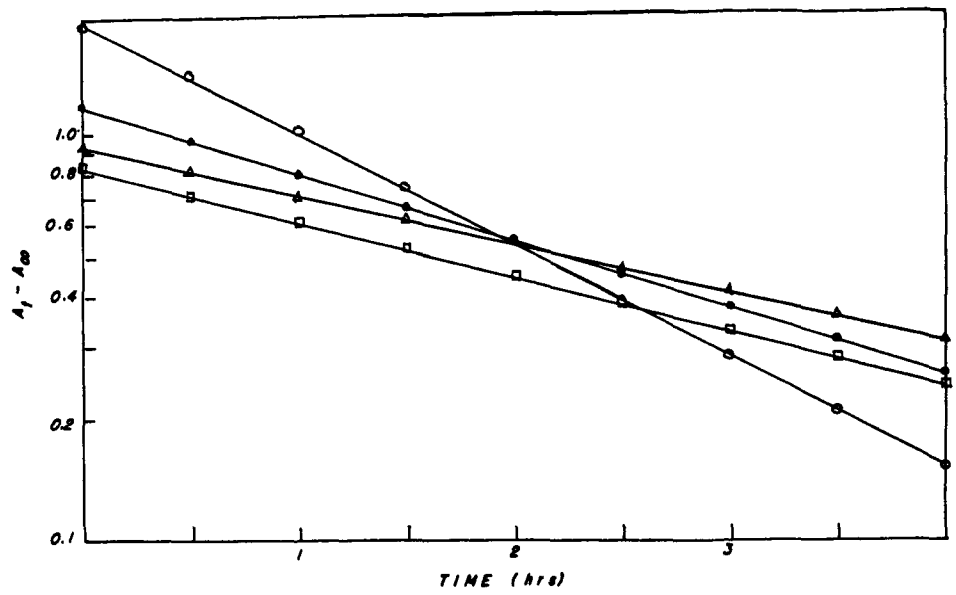
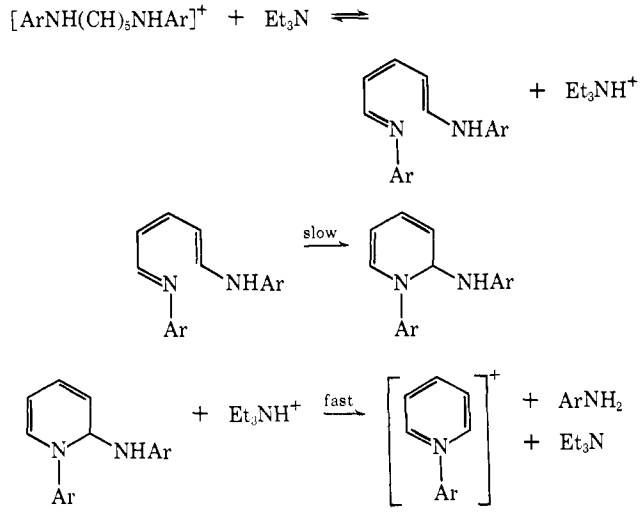


Figure 1. First-order plots for **1a**, △; **1b**, ●; **1c**, □; and **1e**, ○.

For the mechanism represented by Scheme I, the aryl grouping attached to the imino nitrogen is expected to exert a major influence since it is directly conjugated to the reactive moiety. The aryl group on the amino nitrogen should be less effective owing to its isolation from that reaction grouping. Relative to the unsubstituted imine (**1**, Y = H) the rates for the substituted cases are NMe_2 0.83, OMe 1.2, Me 1.0, F 1.7, Cl 2.0, and

Scheme I



NO_2 4.0. For electron-releasing substituents the rate is very nearly independent of the substituent and effectively equal to that of the unsubstituted imine. Electron-attracting substituents appear to cause a small increase in rate. At present it is not clear what might be expected regarding polar substituent effects on the rate since the polarity of the imino nitrogen in the ground state as compared to its polarity in the transition state is not known and cannot be unambiguously predicted. The present results suggest that the imino nitrogen is more negative in the transition state, but the change must be small. The point we wish to emphasize is not the direction of the polarity effect but its small magnitude.

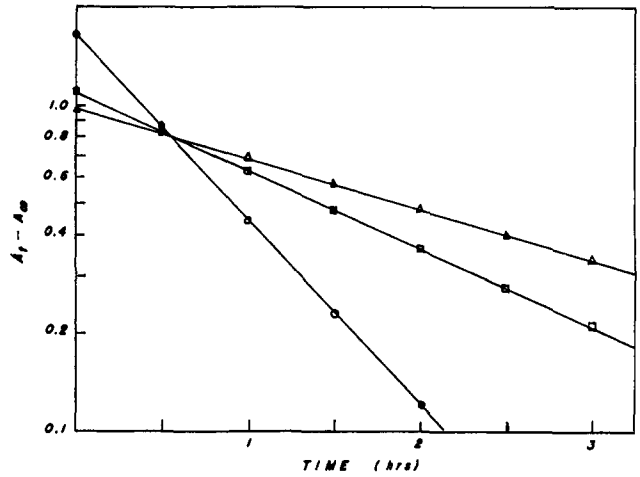


Figure 2. First-order plots for **1d**, □; **1f**, ○; and **1** (Y = H), △.

This result is in excellent agreement with the relatively meager results now available as to the influence of substituents at the terminal atams of a triene on the rate of its electrocyclization. Thus relative rates based on *cis*-hexatriene as 1.0[10] are *trans*-2,*cis*-4,*trans*-6-octatriene (1.1),[11] 1-phenyl-*trans*-1,*cis*-3,5-hexatriene (1.2),[12] and 1-(*p*-chlorophenyl)-*trans*-1,*cis*-3,5-hexatriene (1.2).[12] In the series with one terminal *cis* double bond, *cis*-2,-*cis*-4,*trans*-6-octatriene (0.01) and 1,8-diphenyl-*trans*-1,*cis*-5-*trans*-7-octatetraene (undergoing cyclization to *trans*-5-styryl-6-phenyl-1,3-cyclohexadiene)[13] differ in rate by less than threefold.

As the comparison between the present reaction and the electrocyclic reactions of hexatrienes shows, the interpretation of the rate-determining ring closure as an electrocyclic process permits a consistent rationalization

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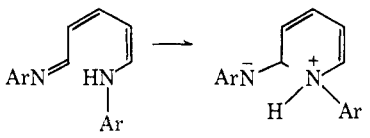
of all the experimental findings. There are however enough similarities between the present results and the data for hydrolysis of imines[14] to warrant consideration



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of the nucleophilic addition interpretation of the rate-determining step (eq 1). Cordes and Jencks[14] found that the rates of hydrolysis of a series of aryl-substituted benzylidene-1,1-dimethylethylamines in the basic region (rate independent of pH) were not particularly responsive to the nature of the substituent. Their data are "correlated moderately well by the σ^+ substituent constants with a ρ^+ value of -0.21." The sign of the ρ value may be variable since for a different imine Koehler, Sandstrom, and Cordes[15] found that electron-attracting substituents increased the rate and withdrawing groups decreased the rate, *i.e.*, a positive ρ. Clearly the results are quite similar to the present substituent effects.

Further consideration suggests that the similarities may be coincidental. Thus, for the imines the substituent alteration was in a ring attached to the *carbon* of the imine, while ours are for a ring attached to the *nitrogen*. For the imine hydrolysis the nucleophile was hydroxyl in all cases, whereas if our reaction is considered analogous the nucleophile was varied in each example. Finally in the present case the imine and the nucleophile are not electronically independent, but are attached *via* a chain of conjugated double bonds. It is difficult to predict the combined influence of substituent changes in both rings. However since the imino nitrogen (eq 1) is in the process of becoming negatively charged and disconnected from the conjugated system, while the amino nitrogen is becoming positive but remaining a part of the conjugate chain, we had expected the groups on the imino nitrogen ring to dominate. Since a reaction which places a negative charge on nitrogen (ionization of diphenylamines, $\rho = 4.07$)[16] is more responsive to substituents than is one which places a positive charge on nitrogen (dissociation of anilinium ions, $\rho = 2.89$),[17] we suspect that the nucleophilic addition mechanism would show a rather substantial positive ρ value.

Experimental Section

5-(Arylamino)-N-aryl-2,4-pentadienylideniminium Halides. The halides **1a–c** were prepared by the procedure of Zincke.[2]

General Procedure. A solution of the appropriate arylamine (1.2 mol per mol of 2,4-dinitrophenylpyridinium chloride) in 80% aqueous ethanol (*ca.* 0.8 *M* in arylamine) was slowly added to a 0.4 *M* solution of 2,4-dinitrophenylpyridinium chloride in the same solvent. Crystals of product form rapidly and were removed by filtration at 10–15-min intervals. As soon as the characteristic crystals of 2,4-dinitroaniline were observed, the reaction solution was discarded. The product salts were recrystallized from anhydrous methanol, washed thoroughly with ether, and dried *in vacuo* to constant weight.

5-(*p*-Dimethylaminoanilino)-N-(*p*-dimethylaminophenyl)-2,4-pentadienylideniminium chloride (1a) exhibited the following: purple needles; mp 142° (lit.[7] mp 147°); λ_{max} (MeOH) 548 nm (82,000) (lit.[7] λ_{max} (EtOH) 550 nm (93,000)). A solution of **1a** in methanol containing excess triethylamine has λ_{max} 440 nm (62,000) (lit.[4] 440 (39,000)).

5-(*p*-Anisidino)-N-(*p*-anisyl)-2,4-pentadienylideniminium chloride (1b) showed the following characteristics: dark red needles; mp 150–151° (lit.[5] mp 127–129°, crystallized from acetone–ethanol, mp 168–170); λ_{max} (MeOH) 498 (94,000) (lit.[18] λ_{max} (EtOH) 500 (82,000)). The imine form, λ_{max} 414 (63,000), was present in methanol solutions containing excess triethylamine (lit.[4] λ_{max} 415 (39,000)).

5-(*p*-Toluidino)-N-(*p*-tolyl)-2,4-pentadienylideniminium chloride (1c) appeared as violet needles: mp 150–152° (lit.[2] mp 142–143°); λ_{max} (MeOH) 489 (100,000) (lit.[18] λ_{max} (EtOH) 495 (99,000)). The related imine, λ_{max} (MeOH–Et_3N) 400 (35,000) (lit.[4] λ_{max} 402 (35,000)).

5-(*p*-Fluoroanilino)-N-(*p*-fluorophenyl)-2,4-pentadienylideniminium chloride (1) appeared as brilliant red crystals: mp 128–129°; λ_{max} (MeOH) 478 nm (100,000).

Anal. Calcd for $C_{17}H_{15}ClF_2N_2$: C, 63.66; H, 4.2. Found: C, 63.45; H, 4.86.

A solution of the imine form of **1d** in methanol containing excess triethylamine has λ_{max} 403 nm (60,000).

5-(*p*-Chloroanilino)-N-(*p*-chlorophenyl)-2,4-pentadienylideniminium chloride (1c) appeared as deep red needles: mp 139° (lit.[2] mp 143°); λ_{max} (MeOH) 492 nm (112,000) (lit.[5] λ_{max} 494 nm). The imine form has λ_{max} (MeOH–Et_3N) 410 nm (67,000).

5-(*p*-Nitroanilino)-N-(*p*-nitrophenyl)-2,4-pentadienylideniminium Bromide (1f). This iminium salt was prepared according to the method of König.[6] Solid cyanogen bromide (5.3 g, 50 mmol) was added cautiously to a solution of 4.0 g (51 mmol) of pyridine in 50 ml of 95% ethanol. This solution was added slowly to a solution of 14.0 g (0.1 mol) of *p*-nitroaniline in 200 ml of 95% ethanol at 50°. The product crystallizes slowly from the reaction and the crystals were isolated by filtration at *ca.* 10-min intervals. After the fourth crop was isolated, the solution was discarded, and the combined solids were washed repeatedly with anhydrous ether and dried *in vacuo* to constant weight: mp 171–172; λ_{max} (MeOH) 522 nm (lit.[5] λ_{max} 524 nm). The imine form shows λ_{max} (MeOH–Et_3N) 450 nm (54,000) (lit.[4] λ_{max} (EtOH) 445 nm).

Product Isolation Studies. The products from the reactions of **1b–f** in methanol solution containing sufficient excess triethylamine to ensure that the substrate in all cases was the imine, were isolated and identified as indicated below.

From 1b. A solution of 1.04 g (3.00 mmol) of **1b** and 1.56 g (15.5 mmol) of triethylamine in 200 ml of methanol was heated at 65° for 24 hr. The solvent was removed by evaporation at reduced pressure and the residue was triturated with anhydrous ether. The ether insoluble residue was recrystallized from ethanol–ethyl acetate giving 0.71 g (105%), mp 134° (lit.[2] mp 137°), of *p*-anisylpyridinium ion. Evaporation of the ether gave 0.33 g (88%) of *p*-anisidine, mp 56–58°.

From 1c. A solution of 1.0 g (3.2 mmol) and 1.62 g (16 mmol) of triethylamine in 300 ml of methanol was heated at 50° for 8 hr. Isolation according to the procedure under **1b** gave 0.31 g (90%) of *p*-toluidine, mp 42–43°, and 0.685 g (104%) of N-(*p*-tolyl) pyridinium chloride, mp 206°. This salt was converted to the ferric chloride complex according to the procedure of König,[6] mp 156–157°.

Anal. Calcd for $C_{12}H_{12}Cl_4FeN$: C, 39.18; H, 3.29. Found: C, 39.04; H, 3.31.

From 1d. A solution of 2.00 g (6.2 mmol) of **1d** and 3.01 g (30 mmol) of triethylamine in 300 ml of methanol was heated at 60° for 12 hr. Isolation as described under **1b** gave 0.65 g (93%) of *p*-fluoroaniline, infrared spectrum identical with that of an authentic sample, and 1.35 g (103%) of N-(*p*-fluorophenyl) pyridinium chloride. The salt was converted to a ferric chloride complex by König's procedure,[6] mp 168°.

Anal. Calcd for $C_{11}H_9Cl_4FFeN$: C, 35.53; H, 2.44. Found: C, 35.36; H, 2.33.

From 1e. A solution of 1.0 g (2.8 mmol) of **1e** and 1.97 g (19 mmol) of triethylamine in 300 ml of methanol was heated for 24 hr at 55°. The products, isolated as under **1b,** were 0.22 g (60%) of *p*-chloroaniline, mp 69–70°, and 0.76 g (17%) of N-(*p*-chlorophenyl)-pyridinium chloride, mp 127–128° (lit.[2] mp 123–124°).

From 1f. A solution of 0.20 g (0.48 mmol) of **1f** and 5.0 g (49 mmol) of triethylamine in 3 l. of methanol was heated at 30° for 16 hr. The products, isolated as described under **1b,** were 59 mg

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(91%) of *p*-nitroaniline, mp 145–147°, and N-(*p*-nitrophenyl)-pyridinium bromide, 144 mg (106%). The salt was identified as its ferric chloride derivative, mp 146–147° (lit.[19] mp 149°).

Kinetic Studies. Rates of reaction of **1a–f** were determined in methanol solution at three different temperatures for each substrate. The methanol was dried by the method of Lund and Bjerrum[20] and was then distilled through an efficient fractionating column. In all cases rate studies were made on solutions containing sufficient triethylamine to convert all the iminium salt to free imine as indicated by uv spectral test. Rates were followed spectrophotometrically for disappearance of the imine using the appropriate wavelength for each substrate. Studies were made in a thermostated cell holder capable of maintaining the temperature at ±0.1° with a Cary Model 15 spectrophotometer. With each substrate studies at one temperature were made at several triethylamine concentrations to show the lack of dependence on base concentration. The rates were followed generally for *ca.* three half-lives and no deviation from first order was observed. The results are given in Table I, and typical runs for each substrate are illustrated in Figures 1 and 2.

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A General Approach to Cycloalkanone Synthesis.[1] Intramolecular Alkylation of 2-Chloro-1-olefins

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Abstract: Various cyclic ketones can be synthesized by incorporating allylic–vinylic dichlorides, *e.g.*, 2,3-dichloropropene, into reaction sequences originating with nucleophilic displacement at the allyl carbon. The relative inertness of vinyl chlorides allows various intervening chemical transformations of the adducts to be carried out, and minimizes the problem of haloalkene isomerization. Cycloalkanone formation is completed by intramolecular, electrophilic attack upon the "2-chloro-1-ene" side chain to produce a cyclic α-chlorocarbonium ion, which is then solvolyzed. Monocyclic C_5- to C_7-ketones, as well as *cis*-hydrindan-2-one and *trans*-2-decalone derivatives, have been synthesized in fair to good overall yield.

The construction of suitably functionalized cyclohexane units (*e.g.*, cyclohexenones and cyclohexanones) in polycyclic molecules has occupied a central position in the synthesis of natural products such as steroids,[3] terpenes,[4] and tetracyclines.[5] Most commonly, the key step in cyclohexanoid genesis is one of the following: (1) dissolving metal reduction of an aromatic ether[6] or pyridine[7] to produce ultimately a Δ^2-cyclohexenone; (2) Michael addition of an enolate ion[8] or enamine[9] to electrophilic olefins such as vinyl ketones or their equivalents (*e.g.*, 1,3-dichloro-2-butene or Mannich bases) followed by intramolecular aldol condensation or a second Michael reaction;[9d] (3) Diels–Alder cycloadditions;[3b] and (4) biogenetic-like 1,5-polyene cyclizations[10] which can produce even tetracyclic steroid-like molecules of "natural" stereochemistry from acyclic substrates in a single step.[11]

By comparison, cyclopentanoid rings are less readily produced directly, although the aldol condensation of 1,4-dicarbonyl compounds to Δ^2-cyclopentenones has some generality.[12] Quite often five-membered rings are obtained by ring contraction of a cyclohexanone derivative[13a] as in the synthesis of A-nor steroids[13b] and the normal D ring.[3b] Seven-membered rings are likewise often obtained indirectly by ring expansion of cyclohexanones with diazoalkanes.[14] The synthetic approach discussed in this paper allows for the creation of various monocyclic C_5–C_7 cyclanones, as well as fused and bridged analogs. Moreover, a variety of heteroatoms (*e.g.*, N, S) can be introduced into the ring.

The key step envisioned for producing a cyclanone involves intramolecular electrophilic attack upon a vinylic chloride;[15] in eq 1 and elsewhere, L signifies a

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