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Aromaticity in azlactone anions and its significance for the Erlenmeyer synthesis

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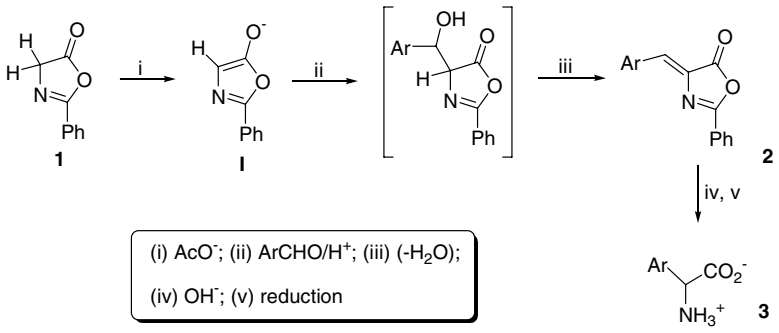
Abstract—Azlactone anions—the key intermediates in the classical Erlenmeyer synthesis of amino acids—apparently possess aromatic stabilization, as indicated by the relative rate of base catalyzed deuterium exchange in the following analogs: 1-methyl-2-phenyl-5(4*H*)-imidazolone > 2-phenyl-5(4*H*)-oxazolone (azlactone) > 3,3-dimethyl-2-phenyl-4(3*H*)-pyrrolone. This is paralleled by the relative rate of condensation of these compounds with hexadeuteroacetone. Reported pK_a data also suggest that the azlactone products of the Erlenmeyer synthesis are analogs of the fulvenes.

The classical Erlenmeyer azlactone synthesis (1893) is an important method for preparing aromatic α-amino acids,[1] and azlactones continue to find diverse applications in synthesis as revealed by several recent reports.[2–4] These include asymmetric syntheses of various natural and unnatural amino acids[2,3] and peptide synthesis.[4] The general revival of azlactone chemistry is exemplified by a report on the asymmetric alkoxyallylation of azlactones with a chiral Pd(II) catalyst.[5]

The key steps of the Erlenmeyer synthesis are the base-catalyzed deprotonation of azlactone **1**, and the addition of the resulting anion **I** to an aromatic aldehyde; the initially formed arylidene derivative **2** is subsequently transformed into the amino acid **3** (Scheme 1). It is interesting to note that deprotonation of **1** is effected by the rather weakly basic acetate ion (p$K_a \sim 5$):[6] it is possible that the acidity of **1** is derived from the aromatic stabilization of its anion **I**, which possesses six electrons in cyclic conjugation (with the lone pair of the ring oxygen atom included).[7] We have addressed this possibility as follows.

We have studied the relative rate of base-catalyzed deprotonation in azlactone **1** and its analogs



Scheme 1. The key steps in the Erlenmeyer azlactone synthesis of amino acids.

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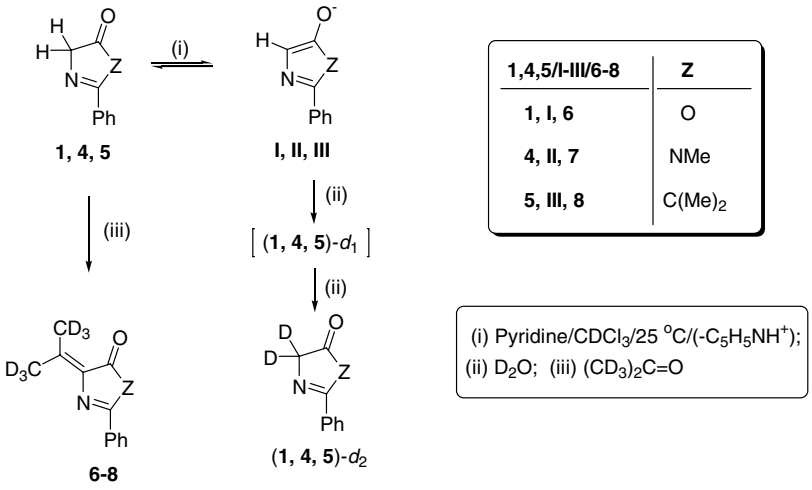


Scheme 2. Reactions of azlactone **1** and its analogs **4** and **5**: (i) and (ii) base catalyzed H-D exchange to form (**1**,**4**,**5**)-d_2, via the corresponding monodeutero derivatives (**1**,**4**,**5**)-d_1; (iii) condensation with acetone-d_6 to form the isopropylidenes **6**–**8**.

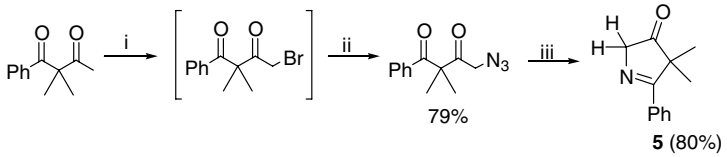
imidazolone **4** and pyrrolidone **5** (Scheme 2), in two processes, using ^{1}H NMR spectroscopy: deuterium exchange and condensation with hexadeuteroacetone. As both these processes would be mediated by the anions of **1**, **4** and **5**, their relative rates would reflect the relative stabilities of these anions. (This follows from Hammond's postulate, as discussed under 'Mechanistic aspects' below). Compounds **1**, **4** and **5** are expected to exist in the 'oxo' forms shown, rather than as the enol tautomers;[8] compounds **1**[9] and **4**[10] were prepared as previously reported and pyrrolidone **5** via an intramolecular aza-Wittig reaction (Scheme 3).[10–12]

Deuterium exchange. Generally, the rate of deuterium exchange would follow (inversely) the order of pK_as: ketone < ester (lactone) < amide (lactam).[6] On this basis, the rate of deuterium exchange would be pyrrolidone **5** > azlactone **1** > imidazolone **4**; however, the order would be **4** > **1** > **5** were aromatic stabilization to be included (vide infra). The deuterium exchange in **1**, **4** and **5** was studied by ^{1}H NMR spectroscopy in CDCl$_3$, by monitoring the disappearance of the resonance of the proton α to the carbonyl group upon the addition of D$_2$O and a catalytic amount of pyridine. These resonances occurred at δ 4.42 (**1**), 4.36 (**5**) and 4.29 (**4**), as sharp singlets that gradually broadened and diminished as the deuterium exchange progressed. The three analogs could thus be studied together as the chemical shifts of the protons undergoing exchange were well separated (by > δ 0.06). The NMR spectra were recorded at five time periods as indicated. The results obtained are shown in Table 1 (first row).

These results clearly show that the rate of the base-catalyzed deuterium exchange is in the order imidazolone **4** > azlactone **1** > pyrrolidone **5**. (Thus, 90 min after the start of the reaction, **4** had all but disappeared and **1** had nearly half disappeared; at 24 h both **1** and **4** had totally disappeared, whereas **5** had barely reacted.) This reactivity order is explicable on the basis of the stabilization of the derived anions **I** and **II** (Scheme 2) by aromaticity, which is absent in **III**. The higher reactivity of **4** versus **1** would arise from the greater aromaticity of the imidazole nucleus (cf. **II**) relative to the oxazole (cf. **I**).[13,14] Note also that the least deshielded α proton exchanges the fastest, ruling out a simple inductive effect.

Condensation with acetone-d_6. The above trend is paralleled by the relative rate of condensation of **1**, **4** and **5** with acetone-d_6 (hexadeuteroacetone: 'HDA'), to form the corresponding isopropylidene derivatives **6**–**8** (Scheme 2). Although far slower than deuterium exchange, this reaction occurred without added base upon addition of HDA to a solution of **1**, **4** and **5** in CDCl$_3$, the reaction being followed by ^{1}H NMR analysis at 400 MHz.

This reaction is analogous to the penultimate step in the Erlenmeyer synthesis (cf. Scheme 1), in which the azlactone condenses with an aldehyde. In the absence of base,



Scheme 3. Synthesis of pyrrolidone **5** via an aza-Wittig reaction.

Table 1. Relative reactivity of azlactone **1**, imidazolone **4** and pyrrolidone **5** with deuterium oxide (D_2O) and with hexadeuteroacetone (HDA)[a,b]

Reactants	Ratio **1**:**4**:**5** at time				
	T_1	T_2	T_3	T_4	T_5
1 + **4** + **5** + D_2O	1.00:1.00:1.00 (0 min)	0.93:0.72:1.00 (5 min)	0.74:0.35:1.00 (60 min)	0.54:0.10:1.00 (90 min)	0.00:0.00:0.95 (24 h)
1 + **4** + **5** + HDA	1.20:1.05:1.00 (0 h)	1.07:0.77:1.00 (18 h)	0.98:0.60:1.00 (25 h)	0.96:0.45:1.00 (36 h)	0.73:0.16:1.00 (48 h)

[a] As measured by the changes in the reactant ratios by ^{1}H NMR spectroscopy [300 MHz (D_2O reaction)/400 MHz (HDA reaction)] at 25 °C: the intensities of the resonances of the protons α to the carbonyl group were recorded at the indicated time intervals, and are shown above relative to **5**. The exchange reaction was performed in 0.1 M $CDCl_3$ solution (0.5 ml) in an NMR tube, with pyridine (2 μl) and D_2O (5 μl). The condensation with HDA was similarly performed in 0.12 M $CDCl_3$ solution (0.4 ml) with added HDA (0.1 ml).
The initial rates approximation[17] can be employed to arrive at a rough measure of the relative reactivity: in the D_2O reaction the ratio of the percent reaction at 5 min (T_2) is **1**:**4** = 7:28 (relative rate = 1:4); in the HDA reaction at 18 h the percent ratio is **1**:**4** = 13:28, which upon correction for the ratio of the starting concentrations (1.20:1.05) becomes 10.8:26.7 (relative rate = 2.47).

[b] *Preparative methods*. 2-Phenyl-5(4*H*)-oxazolone (azlactone **1**[9]) and 1-methyl-2-phenyl-5(4*H*)-imidazolone (imidazolone **4**[10]) were prepared as previously reported, and characterized from melting point and spectral data (IR, 300 MHz ^{1}H NMR). 3,3-Dimethyl-2-phenyl-4(3*H*)-pyrrolone (pyrrolidone **5**) was prepared by the intramolecular aza-Wittig reaction employed by Japanese workers for the synthesis of **4**, but starting from 1,1-dimethylbenzoylacetone (Scheme 3):[10–12] this was first converted, with Br_2/AcOH, to the 3-bromo derivative (not purified), which upon treatment with NaN_3/DMSO at 25 °C furnished the corresponding azide in 79% yield; this was treated with Ph_3P/benzene at 25 °C to effect the aza-Wittig reaction to form **5** in 80% yield (Scheme 3). Pyrrolidone **5** was thoroughly characterized by IR, ^{1}H and ^{13}C NMR, LRMS and HRMS.
The condensation products **6** and **7** were isolated via evaporation of the solvent from the reaction mixture, and characterized by IR, ^{1}H and ^{13}C NMR, LRMS and HRMS (**8** was formed in minuscule amounts and was not isolated); **6** and **7** were identified by their IR spectra, which showed carbonyl bands at 1781 cm^{-1} and 1699 cm^{-1}, respectively, being much lower than the carbonyl bands in the corresponding parent compounds **1** (1814 cm^{-1}) and **4** (1741 cm^{-1}).

it possibly occurs via the corresponding enols (not shown, but cf. their conjugate bases **I**–**III**, Scheme 2), the relative stabilities of these also being governed by the above aromaticity criteria. The relative reactivity was again imidazolone **4** > azlactone **1** > pyrrolidone **5**, as measured by the rate of disappearance of the resonances of the methylene protons α to the carbonyl group (Table 1, second row).

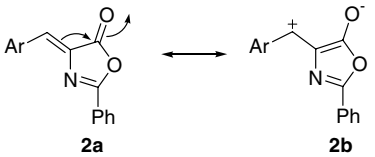
The isopropylidene derivatives **6**–**8** were clearly distinguished from the corresponding starting materials **1**, **4** and **5** by having a lower wavenumber (by ~35 cm^{-1}) carbonyl stretch. The *N*-Me signal in the imidazolone derivative **7** showed a discernible downfield shift of 0.1 ppm relative to the parent **4**. This deshielding seems to indicate the presence of a ring current in **7**, most likely a consequence of its aromaticity (vide infra).[7,15]

Mechanistic aspects. Both the exchange and condensation involve a sequence of two steps—deprotonation-deuteration (exchange) and deprotonation-addition (condensation). By the Hammond postulate,[16] the transition states for all these processes would resemble the reactive intermediate in each case, that is, **I**–**III**, and the relative stabilities of these would determine the relative reactivity. These arguments would apply equally to both the above mentioned steps, regardless of which is rate determining. (We note that in all the cases, the concentrations of the deprotonating base and the electrophilic acceptor remain the same for the three competing substrates: the relative reactivity in each case would then depend solely on the relative free energy of activation for the overall process.)

In fact, the data in Table 1 lead to a rough measure of the relative reactivities based on the initial rates approximation,[17] particularly in the case of the deuterium exchange: the ratio at 5 min (T_2) indicates that imidazolone **4** is around four times as reactive as azlactone **1**, as explained briefly in the experimental note. (The corresponding relative reactivity in the HDA reaction is **4**:**1** = 2.5:1.)

The above results also explain the easy racemization of 4-substituted azlactones (which are unwanted by-products and intermediates in certain peptide syntheses).[18] Interestingly also, the initial Erlenmeyer products **2** may well be stabilized by conjugation that enhances the aromaticity of the oxazole moiety (cf. Scheme 4), a charge transfer process rather reminiscent of fulvenes.[19] Intriguingly, the pK_a of ~12 reported[20] for compounds **2** indicates that they are more basic than trialkylamines (pK_a ~ 11),[6] and suggests that canonical form **2b** (Scheme 4) is an important contributor. Therefore, although it is generally believed that oxazoles are only marginally aromatic,[13,14] the present results suggest that this may have to be reconsidered—at least vis-à-vis the azlactone anions.

Such is the ease of the Erlenmeyer synthesis that the azlactones are generated, deprotonated and reacted in situ, typically in a mixture of *N*-benzoylglycine, acetic anhydride, sodium acetate and aromatic aldehyde.[1] Also, as azlactones are apparently isoelectronic analogs of acetic anhydride, the Erlenmeyer synthesis has often been considered to be an extension of the Perkin condensation.[1,21] However, this ignores the critical importance of the cyclic conjugation that is present in the azlactone anion **I**, as demonstrated in the present study.



2a **2b**

Scheme 4. Possibility of fulvenoid aromaticity in Erlenmeyer products **2**.

Thus, this study fills a puzzling lacuna in the mechanistic understanding of this fascinating reaction, which continues to be an important method for the synthesis of amino acids. Apart from the renewal of azlactone chemistry mentioned above,[2–5] the theoretical extension of the aromaticity concept[7] to heterocyclic and other systems is of much contemporary interest.[8,14,22]

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