Polymer site–site interactions: mechanistic implication in the solid-phase Zincke reaction

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Mechanistic aspects of the solid-phase Zincke reaction have been investigated using Wang resins; a proton transfer mechanism is proposed which obviates the need for covalent bond site–site interactions.

In 1903, Zincke reported the ring opening-reaction of 2,4-dinitrophenylpyridinium chloride (**1**) with aniline to give 5-anilino-*N*-phenyl-2,4-pentadienylideniminium chloride (**3**, R = Ph; Scheme 1)[1] which underwent ring reclosure to give *N*-phenylpyridinium chloride (**4**, R = Ph).[1] This process, known as the Zincke reaction, is now the standard route to *N*-arylpyridinium salts which cannot be formed by direct reaction of electrophiles with pyridine.[2] The Zincke mechanism had previously been divided into ring-opening[3] (**1** → **3**) and ring-closing[4] (**3** → **4**) stages until Ise and co-workers determined the complete process for **1** → **4** as shown in Scheme 1.[5] In this mechanism, excess amine (RNH$_2$) assists in proton transfer and reacts twice with **1** to deliver intermediate **3**.
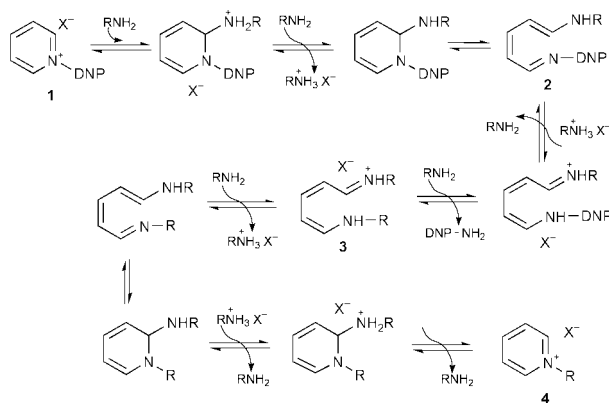
Scheme 1

We recently reported[6] a solid-phase (SP) variant of the Zincke reaction, which according to Ise's mechanism, would require two kinds of resin-bound amine interactions — 'proton transfer site–site interactions' and 'covalent bond site–site interactions' (Scheme 2). However, an intriguing question arises as to whether the SP Zincke reaction proceeds *via* **3** as formation of this intermediate requires covalent bond site–site interactions between two resin-bound amines. Since the amine moiety (RNH$_2$) is attached to resin in the SP system, formation of the SP aminopentadienylideniminium (**3′**; Scheme 3) and subsequent re-closure to the SP Zincke product (**4′**) would seem to be inefficient because each covalent bond site–site interaction generates a new crosslink which would reduce resin mobility[7] and hinder formation of SP intermediate **3′**. Moreover, most SP
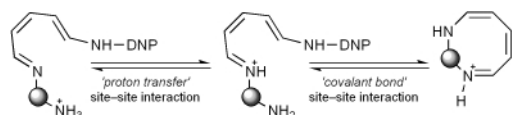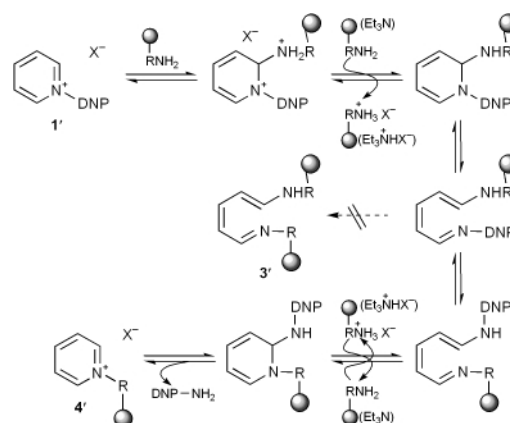
aminopentadienylideniminiums (**3′**) would not be able to negotiate the six membered transition-state required for electrocyclic ring closing.
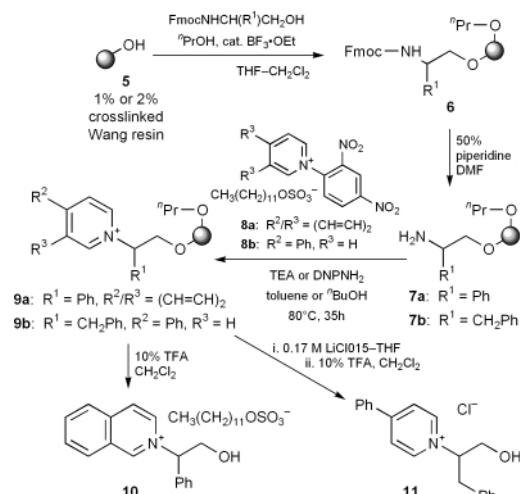
We reasoned that conversion of Zincke salt to Zincke product (**1′** → **4′**; Scheme 3) by a process which avoids the intermediacy of aminopentadienylideniminiums would be more likely in the SP reaction. To probe this, we have carried out more detailed studies of the SP Zincke reaction and report our findings here.

Three crucial factors mediate site–site interactions in SP reactions: (i) crosslinking density, (ii) functional group loading, and (iii) solvent properties.[8] Therefore, we have compared Zincke reactions using Wang resins (both 1%- and 2%-crosslinked; Novabiochem) at a variety of amine loading levels.[9] Wang resin (**5**) was loaded[10] with a mixture of Fmoc–amino alcohol and a suitable amount of *n*-propanol to provide resin **6** (Scheme 4). The actual amino loading of **7** was determined by UV spectrophotometric analysis of the Fmoc decomposition product.

Reaction of amino resin **7a** (100 mg) with Zincke salt **8a**[11] (5 eq. relative to **7a**'s amine loading) both with and without TEA (10 μL) or 2,4-dinitroaniline (DNP–NH$_2$, 13 mg) in solvent (toluene or *n*-butanol, 2 mL) at 80 °C for 35 h gave SP Zincke product **9a**. Cleavage of the Wang tether in **9a** using 10% TFA in CH$_2$Cl$_2$ solution gave Zincke product **10**. The overall yield of **7a** → **10** was determined by HPLC analysis [Symmetry® C$_{18}$, 4.6 × 150 mm, linear gradient elution of 10–100% MeOH–phosphoric acid buffer solution (pH 7.0) for 20 min; flow rate 1 mL min^{-1}; detection, 220 nm, **10**: t_R = 9.32 min]. Fig. 1 shows the relationship between resin **7a**'s amine loading and the yield of Zincke product **10**. Running SP reactions with TEA increases product yield at all loading levels for either degree of crosslinked resin. Addition of DNP–NH$_2$ causes no yield improvement (*i.e.* product yield with and without DNP–NH$_2$ were similar) suggesting that DNP–NH$_2$ (formed *in situ*) does not assist proton transfer in **7a** → **9a**. In contrast, TEA does play an important role in assisting proton transfer so that **7a** → **9a** proceeds primarily *via* the process outlined in Scheme 4.

Scheme 2

Scheme 3

Scheme 4

Fig. 2 Plotted yield of **11** *versus* the amine loading of **7b**: 1% crosslinked (●), 2% crosslinked (○), 1% crosslinked + TEA (■), and 2% crosslinked + TEA (□) in toluene.

Relative to *n*-butanol (effective solution-phase solvent),[11] toluene is the solvent of choice for SP Zincke reactions due to its ability to swell the resin.[12] Unfortunately, these distinct solvent requirements make meaningful rate comparisons between solution (24 h, 118 °C)[2b,11] and SP (35 h, 80 °C) unworkable.
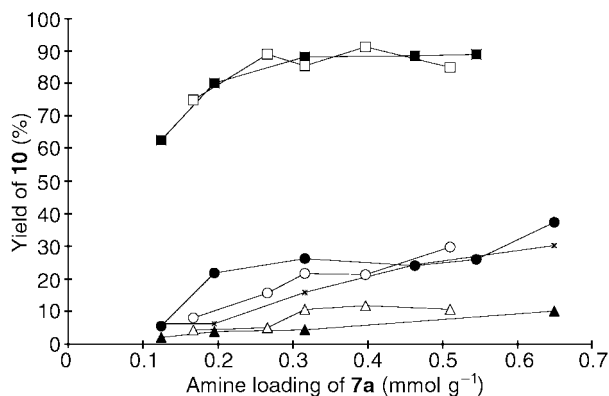

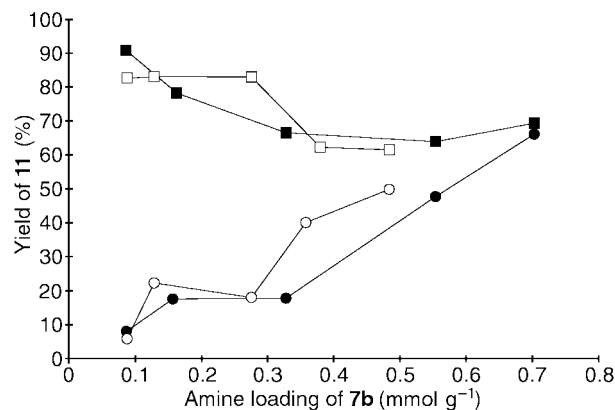**Fig. 1** Plotted yield of **10** *versus* the amine loading of **7a**: 1% crosslinked (●), 2% crosslinked (○), 1% crosslinked + TEA (■), and 2% crosslinked + TEA (□) in toluene, and 1% crosslinked (▲) and 2% crosslinked (△) in *n*-butanol; 1% crosslinked + DNP–NH$_2$ (✳) in toluene.

We also studied the more reactive combination of SP amine **7b** condensing with Zincke salt **8b**[6] to give SP Zincke product **9b**. Subsequent treatment of **9b** with LiCl, followed by cleavage, liberated **11** as the chloride salt. The relationship between amine loading in starting resin **7b** and yield of **11** is shown in Fig. 2. Again, reactions in the presence of TEA resulted in good product yields. In reactions without TEA, yield improvement was observed with resin loadings for **7b** of > 0.3 mmol g^{-1}. This result—namely, that effective site–site interactions occur at loadings > 0.3 mmol g^{-1}—is in agreement with Patchornik's report that 0.1–0.3 mmol g^{-1} loadings can be employed successfully in syntheses requiring effective site-isolation.[13] The fact that SP Zincke reactions proceed in good yield at resin loadings of ≤0.3 mmol g^{-1}—even at lower loading such as 0.09 mmol g^{-1}—in the presence of TEA indicates that this reaction can progress from Zincke salt **1′** to SP Zincke product **4′** without the formation of intermediate **3′**. No amine site–site interactions are required if TEA is present to negotiate proton transfer and direct conversion of **1′** to **4′**. However, reactions run without added TEA on resin with loadings of > 0.3 mmol g^{-1} experience significant proton transfer site–site interaction as evidenced by the increased yield.

The yields of Zincke product from 1%- and 2%-crosslinked Wang resin are generally equivalent (see Fig. 1). Indeed, solvent swelling ratios (*s*) for 1%- and 2%-DVB–styrene beads are quite similar (*s* = 5.13 and 4.52 in toluene, respectively)[14] which suggests that these crosslink densities are not sufficiently disparate to cause differential site–site interactions.

In summary, we have analyzed the SP Zincke mechanism under a variety of resin loadings and reaction conditions. We conclude that while **3′** may be involved to some limited extent in this SP Zincke transformation, a proton transfer mechanism provides the more likely reaction path for conversion of polymer-supported amine (●–RNH$_2$) to polymer-supported Zincke product (**4′**; Scheme 3). Addition of TEA greatly facilitates the SP Zincke reaction by involvement of Et$_3$N–Et$_3$N·HX in several key SP proton transfer steps.

Notes and references

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