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Anion-assisted amidinium exchange and metathesis†

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Dynamic covalent chemistry has become an invaluable tool for the design and preparation of adaptable yet robust molecular systems. Herein we explore the scope of a largely overlooked dynamic covalent reaction – amidinium exchange – and report on conditions that allow formal amidinium metathesis reactions.

Development of new dynamic covalent chemistries (DCvC) benefits a wide range of research areas such as materials science,[1–4] bioconjugation,[5,6] stereoselective synthesis,[7] (bio)molecular sensing,[8,9] and the construction of mechanically interlocked architectures (MIAs).[10] Dynamic covalent reactions (DCRs) involving primary amines are especially important due to the ubiquity of this class of organic compounds. The reversible formation and exchange reactions of imines, aminals, and amides are classical examples of amine-based DCRs.[11] While these reactions are being constantly studied and advanced,[12,13] there is a number of new (rediscovered) DCRs, which utilize primary amines; these new chemistries involve imides,[14] carbamates,[15] ureas,[16] guanidines,[17] and sulfonamides.[18] A remarkable example of an amine-based DCR was reported in 2011 by Petitjean and coworkers who recognized the dynamic covalent nature of amidines.[19] In this first report, the authors focused on the exchange of aryl amines with N,N'-diarylformamidines and demonstrated that this DCR could be used for the carboxylate-templated assembly of macrocycles.[19] It occurred to us that amidines and their amidinium salts are widely used in coordination chemistry,[20] biomedical science,[21,22] advanced materials,[23,24] and supramolecular chemistry,[25,26] and therefore deserve a wider exploration from the perspective of DCvC.

Recently, we showed that amidinium exchange can be exploited for the synthesis of MIAs (*i.e.*, [2]rotaxanes) and unique dynamic combinatorial libraries with kinetically trapped constituents.[27] We realized, however, that the basic principles that govern amidinium exchange remain largely obscure thus precluding the realization of

the full potential of this DCR. In particular, we felt that the substrate scope, solvent effects and most importantly, the ability of different anions to affect the rate of exchange could be better understood.

Herein we report on two notable features of amidinium exchange that render this DCR a promising tool in biomedical research and studies of chemical networks. First, we found that besides a wide range of organic solvents amidinium exchange can take place in aqueous media, at least under certain conditions. Second, we discovered the extraordinary ability of anions to modulate the kinetics of amidinium exchange and formal metathesis‡ (Fig. 1B). In recent years, kinetic effects in dynamic covalent systems have been receiving increased attention due to a shift of interest towards out-of-equilibrium networks.[30–35] The anion-specific modulation of the kinetics of (amidinium-based) dynamic covalent reactions may therefore become a tool for controlling the behavior of complex networks.

To obtain further insights into amidinium exchange,[19] we set out to study a model reaction between the simplest unsubstituted formamidinium ion (**FA**) and benzylamine (**BnNH₂**). The tetraphenylborate salt of **FA** already played the central role in our previous preparation of MIAs.[27] **BnNH₂** is a cheap, water-soluble moderately basic aliphatic amine that is convenient to monitor by HPLC. The reaction between **FA** and **BnNH₂** yielded an equilibrium mixture of two compounds – the product of single exchange (**1a**) and the product of double exchange (**1aa**) (Fig. 1C). First, we performed this reaction in a range of solvents of different polarity and hydrogen bond donating/ accepting ability (Section 3.2, ESI†). Typical equilibration times at room temperature were between 40 and 70 minutes and did not depend on the solvent polarity. The fastest equilibration (40 min) was observed in acetonitrile (MeCN) or ethyl acetate as a solvent. Interestingly, protic solvents (*e.g.*, methanol or aqueous THF with 20% v/v H_2O) significantly decreased the exchange rate, possibly due to hydrogen bonding between solvent and **BnNH₂**, which decreased the nucleophilicity of the amine.

Next, we wanted to compare the performance of different starting materials and essentially replace **FA**-BPh₄ with amidinium

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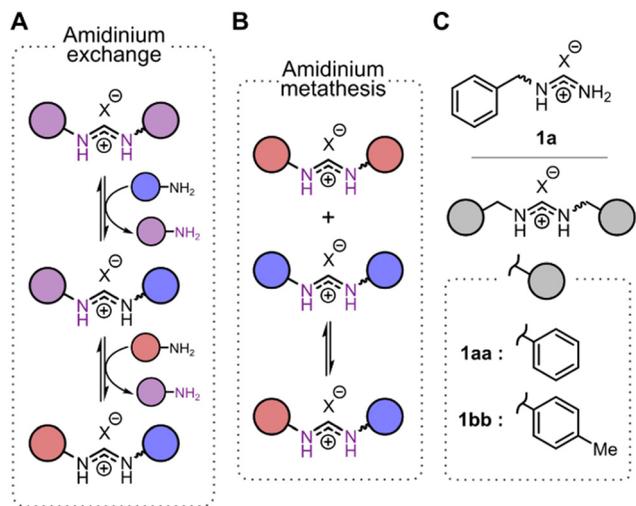
Fig. 1 (A) General scheme of the amidinium exchange. (B) General scheme of the amidinium metathesis. (C) Key amidinium species studied in this work.

ions featuring amines of different basicities and reactivities, *i.e.*, benzylic (**1bb**), aliphatic (**1dd**), and aromatic (**1cc**) amines (Fig. 2A). At this stage of the study, we used formamidinium salts with weakly coordinating anions, in order to exclude the influence of anion-binding on the kinetics and thermodynamics of the exchange reactions. In MeCN, the simplest amidinium ion (**FA**)
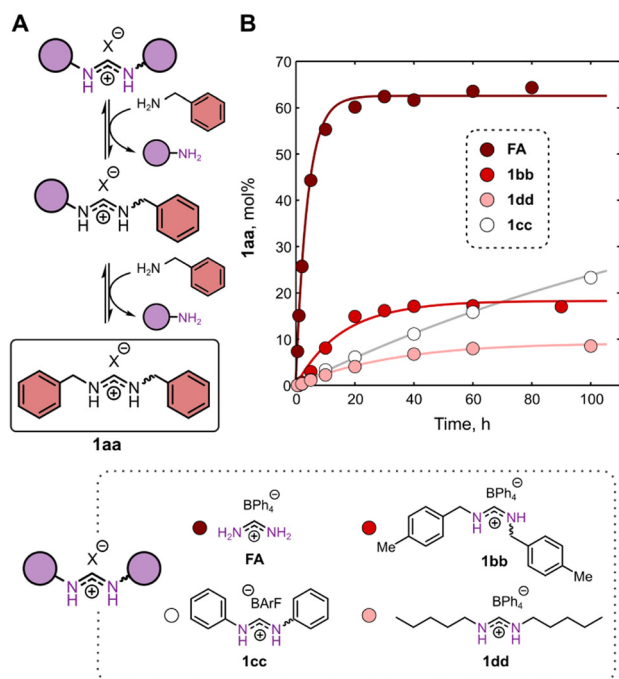

Fig. 2 Effect of the amidinium substrate on the exchange rate and the product distribution. (A) Reaction scheme. (B) Monitoring the formation of the two-fold exchange product (**1aa**) from four different amidinium salts. The lines are shown to guide the eye. Reaction conditions: 50 mM amidinium salt (**FA/1bb/1cc/1dd**), 100 mM **BnNH₂**, solvent: MeCN; room temperature. Details of the experimental procedures can be found in ESI,† Section 3.1.

exhibited the fastest exchange kinetics and afforded the most complete conversion (*ca.* 60%) towards the product of double exchange **1aa** (Fig. 2B). Amidinium substrates **1bb** and **1dd** showed slower exchange rates compared to **FA** and afforded only 10–20% conversion to **1aa**. The outlier kinetics observed for the formation of **1aa** from **1cc** are likely a consequence of the outlier acidity of **1cc** and **1ac**.[19] The increasing equilibrium concentration of **1aa** in the row **1dd–1bb–1cc** is reciprocally proportional to the basicities of the corresponding amine leaving groups (the less basic amine being the better leaving group). The exceptionally large amount of **1aa** formed from **FA** represents a clear outlier that is due to the ability of NH_3 to escape the reaction mixture[27] and therefore is more of a kinetic rather than a thermodynamic effect.

Having identified the simplest unsubstituted formamidinium ion as the most reactive starting material and knowing that some of its commercially available salts are well-soluble in water, we wondered if amidinium exchange could be carried out in aqueous media, despite the risk of competing and irreversible hydrolysis. Indeed, a reaction between formamidinium acetate (**FA-OAc**) and **BnNH₂** in pure water at room temperature afforded a mixture of **1a** and **1aa**, where the former was the major product (Fig. S9, ESI†). Similar outcomes were observed in aqueous buffers in the pH range from 5.5 to 9.5 (Fig. S10, ESI†). With respect to competing hydrolysis to formamides, this dynamic covalent system exhibited unusual behavior: while **1aa** reached equilibrium and its amount remained constant (yet low), **1a** was metastable and slowly hydrolysed over time. The hydrolysis was especially pronounced at pH 11.5 (Fig. S10, ESI†). The water solubility and transient nature of **1a** and similar mono-*N*-substituted formamidinium ions make these molecules interesting candidates for the use in drug delivery and out-of-equilibrium systems.

To test whether the counterion had any influence on amidinium exchange, we performed the exchange reaction with **FA-OAc** in those solvents that were previously used for the amidinium salt **FA**-BPh₄ (wherever the solubility of **FA-OAc** allowed) (Table S2 and Fig. S11, S12; ESI†). Besides slight variations in the composition of the equilibrium mixture, we observed a moderately increased exchange rate. This finding indicates that acetate as a weakly basic anion affects the kinetics of amidinium exchange. Our observation is corroborated by computational studies by Petitjean and coworkers who showed that a carboxylate ion served as a proton shuttle in the mechanism proposed for the exchange of *N,N'*-diarylsubstituted formamidinium ions.[19]

One of the key features of compounds with dynamic covalent bonds is their ability to undergo metathesis reactions.[34,36–39] This type of DCR has been widely used in numerous fields including the synthesis of polymers as well as advanced molecular architectures and the exploration of complex chemical systems.[1,40–44] Therefore, we decided to test if *N,N'*-disubstituted formamidinium ions were able to undergo formal metathesis.‡ To our delight, the reaction between **1aa** and **1bb** did take place and afforded the metathesis product **1ab** (Fig. 3). The hydrolysis of the amidinium salts at room temperature did not produce sufficient amounts of **BnNH₂** to initiate the
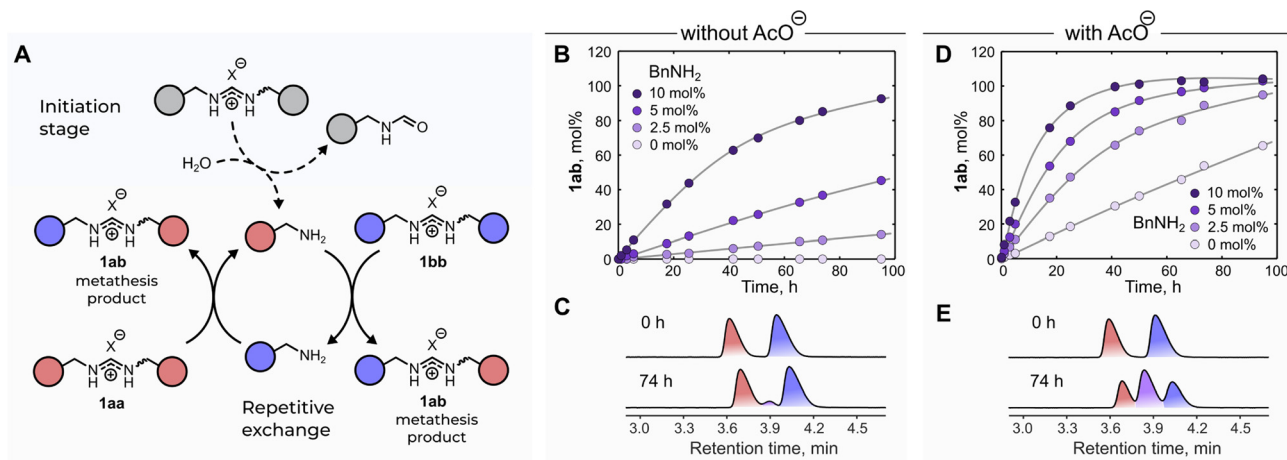
Fig. 3 (A) Reaction cycle of the formal amidinium metathesis‡ studied in the present work. In the absence of acetate, hydrolysis of the amidinium salts under standard reaction conditions did not afford sufficient amounts of the amines to initiate the exchange cycle. (B and D) Kinetic plots: formation of metathesis product **1ab** in the absence (B) or presence (D) of AcO^- (**1aa** and **1bb** were used in the form of BPh_4-salts). Relative amounts of **BnNH$_2$** are indicated with respect to the total amount of the amidinium species. Relative amount of **1ab** (mol%) was calculated with respect to the initial amount of either **1aa** or **1bb** (which were used as an equimolar mixture). The lines are shown to guide the eye. (C and E) HPLC traces at 0 h and 74 h of the amidinium metathesis (with 2.5 mol% **BnNH$_2$**). The purple peak denotes metathesis product **1ab**. Reaction conditions: 25 mM **1aa**, 25 mM **1bb**, 50 mM NBu_4OAc, 0–5 mM **BnNH$_2$**, solvent: MeCN; room temperature. Details of the experimental procedures can be found in ESI,† Section 4.1.

reaction§ (although this scenario is common for some other metathesis reactions, *e.g.*, (trithio)orthoester[37,39] or imine[29,34] metathesis) (Fig. 3A). Therefore, we used externally added **BnNH$_2$** and found that the reaction was substantially accelerated upon increasing the catalytic amount of **BnNH$_2$** (Fig. 3B, C and Fig. S13, ESI†).

Having in mind that anions affect the amidinium exchange rate, we were curious about anion effects in the metathesis reaction. By adding one equivalent of NBu_4OAc to a mixture of **1aa** and **1bb**, we observed a dramatic increase in the metathesis rate (Fig. 3D, E and Fig. S14, Table S3, ESI†). To our surprise, even in the absence of **BnNH$_2$** the reaction took place at a reasonable rate. We attributed the latter observation to the ability of the carboxylate to accelerate the hydrolysis of **1aa**/**1bb** thus leading to generation of **BnNH$_2$** (for supporting experimental evidence, see Fig. S15, ESI†). Intrigued by this finding, we decided to test if carboxylate ions can be used to ramp up the metathesis rate on demand. We launched the reaction between **1aa** and **1bb** in the presence of 4 mol% **BnNH$_2$** and observed its very slow progression over one day. Next, we added different substoichiometric amounts of acetate and continued the reaction monitoring. As expected, the reaction significantly accelerated and, more importantly, its equilibration rate depended on the acetate amount (Fig. 4A and Fig. S16, ESI†). This finding showcases the potential of anionic stimuli for fine-tuning the kinetic parameters of complex dynamic chemical systems approaching equilibrium.

Finally, we tested other simple anions as potential modulators of the metathesis kinetics. The chloride ion and especially the dihydrogen phosphate ion did increase the reaction rate, even in a solvent (MeCN) containing 10–20% (v/v) MeOH and despite poor solubility of the amidinium-phosphate complexes (Fig. 4B and Fig. S17, Table S3, ESI†). Other anions such as I^-,

NO_3^-, and PF_6^- did not significantly alter the metathesis kinetics, possibly due to their lower basicity preventing them to act as efficient proton shuttle during amidinium exchange. Interestingly, hydrogen sulfate fully suppressed the metathesis reaction, which we attribute to the relatively strong acidity of HSO_4^- ($pK_a = 1.99$).[45] This anion can thus fully protonate benzylic amines – key metathesis intermediates – and thereby renders them unreactive. Although dihydrogen phosphate ($pK_a = 7.20$)[45] also protonates the amines, the equilibrium concentration of the unprotonated amine was still sufficient to drive the amidinium metathesis.

In conclusion, we identified the simplest unsubstituted formamidinium ion as the most reactive substrate for amidinium exchange and explored the solvent scope of the reaction. Amidinium exchange can be carried out with substrate **FA-OAc** in aqueous medium (either in pure water or a buffer in the pH range of 5.5–9.5), indicating potential uses of this underexplored DCR in biomedical studies. Furthermore, we showed a rare case of control over the kinetics of a dynamic covalent reaction by addition of certain anions (as NBu_4^+ salts). Our results establish amidinium exchange as a platform for anion sensing and kinetically gated chemical networks.
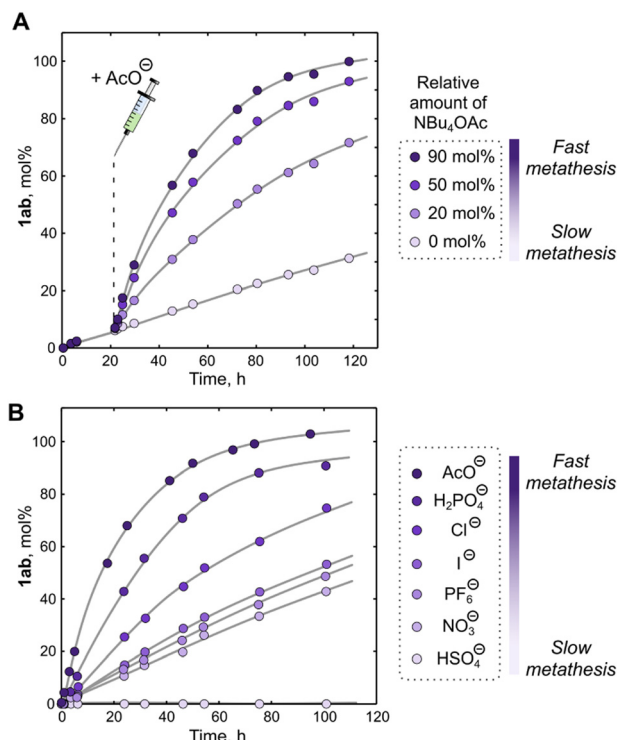
Conflicts of interest

There are no conflicts to declare.

Fig. 4 Kinetic plots of the formal amidinium metathesis‡ in an equimolar mixture of **1aa** and **1ab** controlled by anions (solvent – MeCN, room temperature, total concentration of the amidinium species – 50 mM). All experiments were carried out in the presence of catalytic amounts of **BnNH₂** (4–5 mol%). Relative amount of metathesis product **1ab** (mol%) was calculated with respect to the initial amount of either **1aa** or **1bb** (which were used as an equimolar mixture). (A) Kinetic plots showing dramatic increase of the metathesis rate upon addition of different amounts of the acetate. (B) Kinetic plots comparing formation of the metathesis product in the presence of 5 mol% **BnNH₂** and different anions (as NBu₄⁺ salts, 100 mol%). All relative amounts (besides the amount of **1ab**) are with respect to the total amount of the amidinium species. The lines are shown to guide the eye. Details of the experimental procedures and full kinetic plots can be found in ESI,† Sections 4.1 and 4.3.

Notes and references

‡ Consistent with precedence in the field of DCvC,[28,29] we use the term "metathesis" in a strictly formal way to indicate a reaction of type "AA + BB ⇌ AB" without making any claim about the reaction mechanism.

§ Hydrolysis of the starting materials – **1aa** and **1bb** – results in formation of either **BnNH₂** or 4-methylbenzylamine, respectively. However, the amidinium metathesis did not take place until at least 2.5 mol% **BnNH₂** was added to the reaction mixture. This clearly indicates that the hydrolysis of the starting amidinium salts did not generate enough benzylamines to make the metathesis happen at observable rates.

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