Molecular Catalysis 452 (2018) 192–246

Contents lists available at ScienceDirect

Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

Review

Applications of biological urea-based catalysts in chemical processes

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ARTICLE INFO

This review is dedicated to Prof. Habib Firouzabadi on the occasion of his 75th birthday.

Keywords:
Urea
Catalyst
Hydrogen-bonding catalyst
Chiral urea
Enantioselective reactions

ABSTRACT

The present critical review outlines the close relationship and mutual interplay between molecular recognition, active site considerations in enzyme catalysis involving organocatalysis via hydrogen bonding. These interconnections are generally not made although; as we demonstrated they are quite apparent as exemplified with pertinent examples in the field of urea organocatalysis. Urea organocatalysis derivatives have been used as efficient Lewis-acidic catalysts due to effective H-bonding, basic catalyst, coupling with metals as catalyst, chiral acid catalysts, urea anions catalysts, coupling with ionic liquids, urea polymer catalysts and immobilization on solid acid and magnetic nanoparticle supports. Consecutively, the discovery and mechanistic elucidation of such reactions are likely to improve the understanding of enzyme active sites.

1. Introduction

Diazo compounds participate in a variety of attractive bond-forming reactions [1]. Conventionally, the useful reactivity patterns of diazo compounds are often accessed with the aid of transition metal catalysis [2]. Recent advances in hydrogen-bond-donor catalysis [3–16] have demonstrated the potential to develop new and useful reactivity patterns that are difficult and/or inaccessible with transition metal catalysis [17]. Urea and its derivatives are examples of biological diazo compounds. Substituted ureas have found widespread use as agricultural chemicals, pharmaceuticals, resin precursors, dyes, and additives to petroleum compounds and polymers [18]. One of the uses of urea and its derivatives is their use as a fertilizer and growth regulator. Fertilizers play a vital role to guarantee enough crops to meet the increasing population food needs and the progressive energy requirements. Among the nutrients required by plants, nitrogen, phosphorus and potassium are essential and, therefore, used in large quantities. Urea is the most important nitrogenous source consumed by the agriculture sector both as a fertilizer and animal feed additive, which makes its production considerably higher than others. It has the highest nitrogen content (46 wt%) within all the other solid sources of nitrogen available in the market [19–22]. Forchlorfenuron, formaly1-(2-chloropyridin-4-yl)-3-phenyl urea (CPPU) with a urea moiety, is a growth regulator too that increases the size (and therefore the value) of such fruits as apple, cherry, and kiwi. It has been used on watermelon too; but at least once, the results were unexpected. In China in 2011, about 20 farmers applied too much CPPU on their watermelon crops too late in the growing season. The weather conditions were ideal, so much so that the watermelons grew too fast and exploded. The watermelon fragments, about 46 ha worth, were used to feed fish and pigs [23,24]. Urea has been used for synthesis of energetic materials with various forms such as urea nitrate, [25,26] nitrourea [27–32] and dinitrourea [33–40]. Also urea derivatives have been applied as reagent in various organic transformations [26,41–46]. Among the numerous methods for synthesis of *N,N*-disubstituted ureas are the reactions of primary amines with isocyanates, phosgene, or phosgene derivatives [47]. While reports describing the synthesis of disubstituted ureas are prevalent, methods for the synthesis of tetrasubstituted ureas are less common, due to the difficulty of converting secondary amines directly to tetrasubstituted ureas [48]. Urea is a widely used protein denaturant. Despite its widespread use, however, the molecular mechanism underlying urea-induced denaturation is not well understood. Two classes of interaction models are distinguished in the literature. In the first, direct interactions between urea and the protein are considered the main denaturation driving force [49–53]. In the second, urea-induced changes in the water structure are suggested as indirect interactions that drive unfolding [54–56]. While several recent studies support the direct interaction model [53,57–61], it is still unclear whether polar or apolar residues or the peptide backbone constitute the main interaction sites for urea. That the peptide backbone is an important interaction site for urea is now widely accepted [62–64]. However, some studies [52,58,59,61,65,66] stress the importance of urea-protein hydrogen bonds to polar residues. Scientists studies [60,67–75] support the importance of apolar urea protein contacts weakening the hydrophobic

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https://doi.org/10.1016/j.mcat.2018.03.009
Received 10 November 2017; Received in revised form 28 February 2018; Accepted 10 March 2018

effect. Hence, more detailed insights into the interactions of a denaturant with amino acids are imperative to understand how denaturants work. Nowadays, ureas are widely recognised as highly useful templates upon which powerful organocatalytic systems [76–81], both mono- and bifunctional, can be constructed. However, the explosion of interest in these materials as potential catalysts is a relatively recent occurrence, particularly when one considers that the parent molecule (urea) was the product of arguably mankind's first total synthesis in 1828.

It is known that urea derivatives have been used as efficient Lewis-acidic catalysts for organic transformations due to effective H-bonds that are formed with the amide hydrogens. Due to the acidic hydrogens in urea compounds that contain electron-withdrawing substituents, stable cocrystals with a variety of proton acceptors, including carbonyl compounds, are readily formed [82].

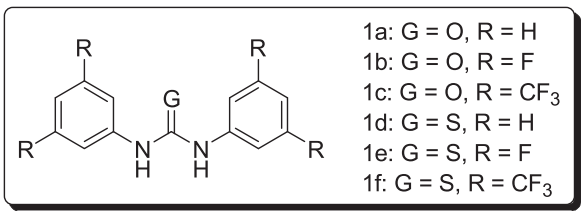
Chiral urea derivatives have proven extraordinarily useful as catalysts for the enantioselective activation of imine and carbonyl derivatives toward nucleophilic addition [83]. However, despite the extensive application of these organic catalysts in asymmetric synthesis, their use in conjunction with organometallic reagents has yet to be developed. We sought to take advantage of the modular nature of these catalysts by incorporating a Lewis basic group in proximity to the urea moiety in order to promote the addition of organometallic reagents to C═N bonds through dual activation [84].

Urea and its derivatives have been applied as catalysts for different reactions such as Claisen rearrangements and Diels-Alder reactions [85–88], respectively. Since, these materials have been shown to serve as active and versatile promoters of the addition of cyanide and silyl ketene acetals tonitrones [89], the Baylis-Hillman reaction [90], Friedel-Crafts typereactions [91], acetalisations [92], Claisen rearrangements [90,93], ring-openingreactions of oxiranes, [94,95] acyl Strecker reactions [96], tetrahydropyranylations [97] and imine reductions [98,99].

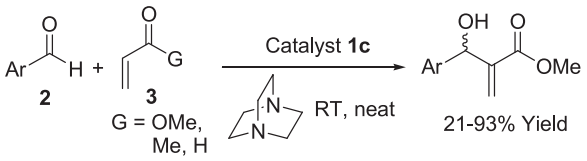
2. Urea derivatives as hydrogen-bonding lewis-acidic organocatalysts

Despite possessing a flat, readily modifiable and rotationally restricted structure with two mutually proximal N−H bonds available for hydrogen bond donation, the potential of bis-aryl ureas and thioureas to serve as Lewis-acidic organocatalysts has only recently begun to be explored [86,100]. Given the accepted reaction mechanism (vide supra) and the known strong proclivity of aryl ureas and thioureas for carbonyl group [88,101] and (in particular) anion binding, [102] it appeared that these species would hold promise as novel, stable and readily accessible co-catalysts for the tertiary amine-promoted Baylis-Hillman reaction. In all the reactions in Section 2, urea derivatives act as lewis-acidic organocatalysts which in some cases refers to its mechanism.

It has been demonstrated for the first time that bis-aryl ureas such as **1a–f** can serve as efficient, stable and recyclable 1,4-diazabicyclo [2.2.2]octane (DABCO) compatible organocatalysts (Scheme 1) for the Baylis-Hillman reaction between a range of aromatic aldehydes **2** and methyl acrylate **3** in the absence of solvent (Scheme 2), and in this capacity are considerably more powerful mole per mole promoters of the reaction than either methanol or water.



Scheme 1. Candidate Baylis-Hillman reaction catalysts **1a–f**.



Scheme 2. Baylis-Hillman reactions involving a range of substrates catalysed by **1c**.

Preliminary results implicate a mechanism involving binding to a Zwitterionic intermediate/transition state, a more definitive understanding of which is necessary before further catalyst optimisation/derivatisation can proceed [90].

Reek, Meijer and co-workers developed a homogeneous catalyst that is anchored to a soluble dendrimer support using supramolecular interactions. The catalytic system **4** is noncovalently attached to the periphery of a urea adamantyl poly-(propylene imine) dendrimer **5** by ionic interactions in combination with multiple hydrogen bonds, which positions the guest ligand at the periphery of the dendrimer in a well-defined way (Scheme 3).

The supramolecular dendrimeric system shows the same activity and selectivity in the Pd-catalyzed allylic amination as its unbound monomeric analogue, which indicates that every active site on the dendrimer acts as an independent catalyst and is easily accessible to the substrate (Scheme 4).

Moreover, the catalyst is strongly bound such that the system can be operated in a continuous setup, which results in efficient separation of the catalyst from the reaction mixture. Employing the concept of non-covalent anchoring simplifies the route toward sophisticated dendrimeric catalysts since ligand modification with the binding motive is straightforward. One of the limitations in dendrimeric catalysis is the troublesome synthesis of functionalized dendrimers, since quantitative coupling of ligands to the periphery is not always possible. With this strategy these problems are circumvented [103].

In 2005, An efficient and green procedure for the urea catalyzed Knoevenagel condensation was developed. In the presence of a catalytic ammount of urea, stoichiometric aldehyde and active methylene compound reacted under solvent-free conditions at 100 °C for 5–60 min to give nearly quantitative yield of product (Scheme 5).

The possible mechanism of urea catalyzed Knoevenagel reaction has been proposed in Scheme 6. At first, active methylene compound **8** reacts with urea **7** to form a six-membered cyclic intermediate **10**. Because the active hydrogen of **8** is pulled strongly toward the more electronegative atoms, oxygen and nitrogen in **10**, it is easier for **8** to add nucleophilically to the aldehyde. Along with the leaving of **11** intermediate **12** is obtained. There is equilibrium between **12** and **13**. The **11** reacts with the **13** to remove one mole of H_2O via ion pair **14** to afford the target product **9** and regenerate the urea [104].

Connon, Rozas and co-workers have shown for the first time that appropriately substituted *N*,*N*-diarylureas and thioureas **15a–k** are capable of the efficient catalysis of the Corey-Chaykovsky reaction (CC reaction) involving the inexpensive trimethylsulfonium iodide **16** at ambient temperature (Scheme 7). Rather unusually, urea derivatives are clearly superior catalysts to their thiourea analogues in these processes. These catalyzed reactions are of wide scope with respect to the aldehyde component **17** and clean formation of the epoxide **18** is observed under optimal conditions a property which was exploited in the development of an epoxidation-Meinwald rearrangement process which allows convenient aromatic aldehyde homologation without requiring intermediate purification steps. Organocatalysed epoxidation of **19** followed by separation of the phases and addition of $Cu(BF_4)_2$ (25 mol %, hydrate) to the organic portion resulted in the isolation of the chain-extended phenyl acetaldehyde derivative **20** in good overall yield (Scheme 8) [105].

The authors therefore posited that (thio)urea derivatives could