

Activated Furans for Colorimetric Sensing

Subjects: Chemistry, Analytical

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Bioactive amines are highly relevant for clinical and industrial application to ensure the metabolic status of a biological process. Apart from this, generally, amine identification is a key step in various bioorganic processes ranging from protein chemistry to biomaterial fabrication. However, many amines have a negative impact on the environment and the excess intake of amines can have tremendous adverse health effects. Thus, easy, fast, sensitive, and reliable sensing methods for amine identification are strongly searched for. A newly emerging activated furan, Meldrum's acid furfural conjugate (MAFC), or otherwise called MAF, can be used as a colorimetric detecting agent for primary and secondary amines, which can be easily synthesized via the Knoevenagel condensation of simple and inexpensive precursors, 2-furfural and Meldrum's acid.

Keywords: amine identification ; furan ; colorimetric sensing ; detection agent ; activated furan ; Meldrum's acid furfural conjugate ; donor acceptor Stenhouse adduct

1. Introduction

After carbon and oxygen, nitrogen is a dominating heteroatom that has a significant role in molecular science. The presence of nitrogen can be witnessed in various biomolecules like DNA, RNA, protein, and even polysaccharides. In simple terms, the nature of chemical bonds could be amide or amine depending upon the neighboring atoms or group of atoms. When it comes to the reactivity, amines are for sure more reactive than amides, and therefore, are abundantly used functional groups that find its application in medicine, fertilizer, and pesticide production, protein quantification, in the petroleum and electrical industries, as well as in environmental protection ^[1]. In the food industry, amine sensing is further employed for the detection of food spoilage, which is characterized by the release of volatile or biogenic amines, e.g., ammonia, dimethylamine, trimethylamine, histamine, putrescine, cadaverine, spermidine, and spermine ^[2]. Such volatile amines can cause severe health issues due to their extreme toxicity when consumed by humans ^{[2][3]}, and thus, the identification of amines in a sample is highly relevant. Various excellent review articles have summarized the use of molecular probes and sensors for the efficient detection of biogenic and organic amines ^{[2][4][5][6]}.

One of the oldest detection agents for amines is ninhydrin, which was already discovered in 1910 by Siegfried Ruhemann. He found that ninhydrin reacts with primary amines to form a deep blue compound named Ruhemann's purple ^[7]. Today ninhydrin-based reagents are used in numerous laboratories for forensic fingerprint detection ^{[8][9]}, food chemistry ^[10], clinical chemistry ^[11], microbiology ^[12], pharmacology ^[13], or toxicology ^[14]. However, its use poses some disadvantages due to pH dependency, non-stoichiometric color formation, or low selectivity in more complex analytic solutions ^[15]. Moreover, the chromophore is not chemically bound to the substrate and remains stable even when the substrate is removed, which could lead to false positive results ^[15]. Therefore, excessive sample manipulation and/or purification, e.g., ion exchange chromatography is needed prior to ninhydrin application, when specific amine-containing substances are to be detected. Other approaches of ninhydrin amine sensing include expensive instrumental setups like liquid chromatography/tandem mass spectrometry (LS/MS/MS), which further requires trained staff for the operation and analysis ^[16]. Various techniques have been developed based on different detection agents and sensing methods. But often, these techniques involve not only expensive equipment but also difficult on-site analysis due to poor portability, tedious analysis procedures, or low selectivity and specificity ^{[17][18]}. Thus, new inexpensive methods providing facile operation, rapid analyte quantification, and high sensing capacity are always searched for.

Today, most abundant sensors for amine detection are based on optical sensing methods; which offer easy operation, rapid reaction times, and good sensitivity and selectivity. However, most often, analytes miss the typical structural features, e.g., conjugated π -systems, which are needed for optical detection. Therefore, optical sensing systems in general include molecules that react with the analyte solution to optically active derivatives that provide the possibility of optical measurements ^[3]. The analysis can be performed by measuring various parameters depending on the chosen type of detecting agent, e.g., absorbance, fluorescence, (chemi-)luminescence, energy transfer, reflectance, light scattering,

refractive index, diffraction, or polarization [2][3]. Especially for the development of device-based amine sensors, an enhancement of fluorescence intensity, the so-called “turn-on”, is desirable. Kumpf et al. has demonstrated the use of extended distyrylbenzenes as a strip-based “turn on” assay [19]. Mani et al. developed a zinc-based coordination polymer for the selective “turn on” detection of aliphatic amines [20]. Synthetically simple di-catechol (dicat) have shown to reach the detection limit down to the sub ppm level [21]. Similarly, 1,4-diazine-based dyes have shown a selective chemosensing ability towards aliphatic amines [22]. Enzymes, antibodies, molecularly imprinted polymers (MIPs), and aptamer-based biogenic amine sensors are dominating the literature [23]; however, single molecule-based sensors are much more simple to synthesize. It is supposed that the development of a chemosensor with the best performance has to consider a delicate balance between selectivity, the limit of detection, and simple analytics, and it should also be economical. There, colorimetric sensing is rather advantageous because of the naked eye detection feature, where basically no expensive instrumentation is required.

Chemosensing using small organic molecules are traditional as well as efficient. Therefore, various new motifs are screened for their sensing applications. Among many, activated furans appear to be good possible candidates for such a venture. Generally, furan offers various applications in synthesis, drug discovery, and photolithography, and its derivatives have been extensively explored in sensor application due to its elite chemistry [24].

2. Furan-Containing Sensors

As depicted in **Figure 1**, furan-containing sensors mainly work via the complexation of analytes through either the furan/furfural moiety or other functional sites in the detection agent. In the latter case, furan substitutions were shown to enhance the selectivity of the sensor molecule [25]. The sensing of specific amines was not demonstrated via these approaches. However, in the particular case of activated furans, which means the conjugation of the furan ring to an electron-deficient molecular species, the furan ring-opening reaction in response to the interaction with donor amines is known to result in a high colored reminiscent of the triene-2-ol fragment. Being surrounded by an electron rich amine and electron deficient activator, the triene-2-ol fragment could photoisomerize to cyclopentenone, which is extensively explored as a photoswitching molecule (see **Figure 2A**). However, from a chemosensing point of view, the intensely colored triene-2-ol formation upon reaction with amine is a unique feature of this molecule for being explored as a colorimetric sensor of amines.

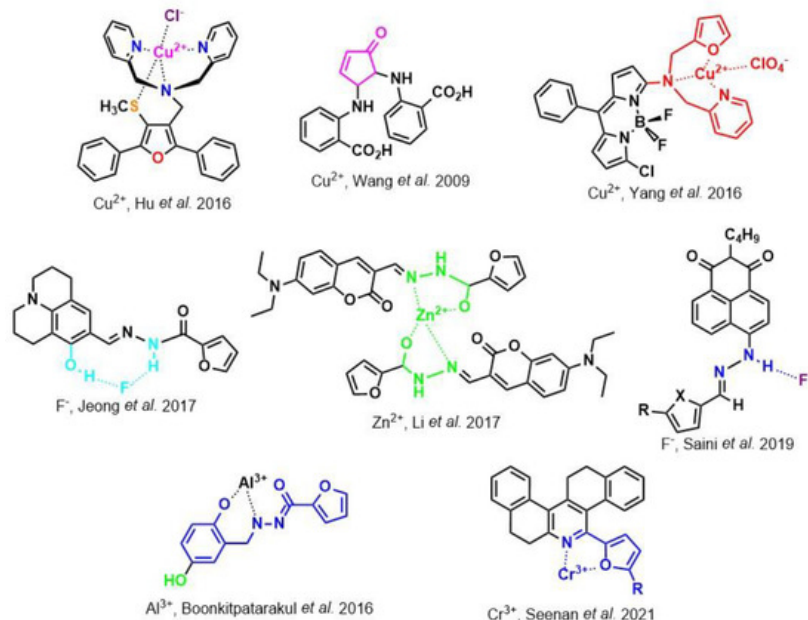


Figure 1. Molecular structure of furan derivative molecular sensors for optical ionic sensing [25][26][27][28][29][30][31][32]. Colored motifs depict the molecular scaffold of the sensor, which is actively participating in the sensing process.

The ring opening reaction of furan itself was first reported by John Stenhouse in 1850 via the reaction of aniline with a furfural-containing crude oil to the colorful Stenhouse salt (see **Figure 2B**) [33]. Acidic treatment of the Stenhouse salt leads to a conformation change of triene-2-ol to its colorless 4,5-diamino-2-cyclopentenone via a conrotatory 4π -electrocyclization, which then rearranges to its thermally more stable 2,4-isomer. The reaction did not find high interest at that time due to its low selectivity, and the chemistry community tried to find different ways for a more selective generation of Stenhouse salts via either varying reaction conditions or reactants. In 1976, the famous Piancatelli rearrangement was first demonstrated via the acid-catalyzed reaction of 2-furylcarbinols to 4-hydroxy-cyclopentenone. However, for this

reaction to be possible, 2-furylcarbinol first needed to be generated from furfural via the Grignard reaction and the reaction conditions were highly dependent on educt reactivity. From this point forward, numerous groups investigated methods based on the Piancatelli rearrangement which could provide a way to synthesize the functional five-membered rings with less harsh conditions compared to early studies [24][34][35]. Such protocols were, e.g., used for the synthesis of natural products like heptemerone G from 2-furylcarbinols [24][36]. In 2007, Batey and Li also showed the successful synthesis of the natural product Agelastatin A directly from furfural with an excellent yield via dysprosium(III)-trifluoromethanesulfonate catalysis [37]. In 2014, the portfolio of activated furans was again expanded via the synthesis of the novel so-called donor–acceptor Stenhouse adducts (DASA) by the Read de Alaniz group [38]. Hereby, activated furans were generated via the Knoevenagel condensation of furfural and Meldrum's acid or 1,3-dimethylbarbituric acid, respectively, which were classified as first-generation DASA. Colorful Stenhouse salt like DASA were then formed via the reaction of activated furans with primary or secondary amines. Both the synthesis of activated furan as well as the formation of DASA can be performed efficiently at mild conditions without the need for catalysis or harsh chemicals. Conformation change via linear to cyclic isomerization from colored triene-2-ol to colorless cyclopentenone conformation can, in general, easily be performed via visible light exposure and is usually reversible via moderate heat influence in the solution (see **Figure 2A**) [24]. Until today, three different generations of DASA have been defined which differ in their electron-donating and -accepting moieties. Every generation has its own advantages and disadvantages regarding solubility, reaction kinetics, and reversible photoswitching behavior (see **Figure 2C**) [39]. Since their first demonstration, DASA have been extensively used in various applications, ranging from drug delivery, optical sensing, phase transfer catalyst recovery, liquid crystal polymer materials, and wavelength-selective photoelectric switches to material surface modification [40]. Additionally, both triene-2-ol and cyclopentenone derivatives were explored for sensing purposes, e.g., for the detection of nerve agents [41], neurotransmitters [42], and metal ions [18][43][44], as shown in **Figure 2D**. In general, all activated furan which are conjugated to an electron deficient motif are capable of giving a rapid reaction with primary and secondary amines, which makes them ideal candidates for amine-sensing applications. However, among them, MAFC succeeds well in amine identification, due to its facile synthesis, robust shelf life, and ease of solubility.

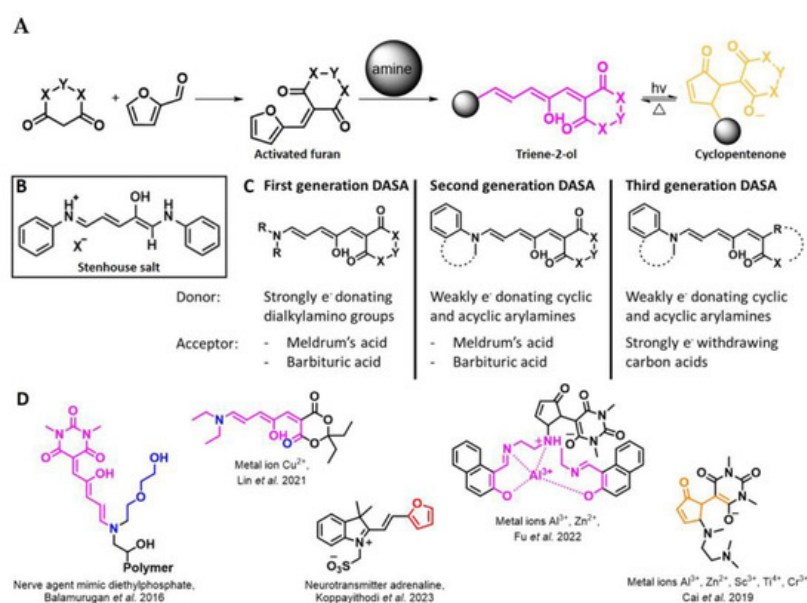


Figure 2. (A) Schematic drawing of activated furan synthesis, generation of colored linear DASA via reaction of activated furan with secondary amine and light-induced reversible linear to cyclic isomerization to colorless cyclopentenone conformation. (B) Molecular structure of Stenhouse salt. (C) Schematic comparison of molecular structure of the three DASA generations developed so far. (D) Molecular sensors based on activated furan and DASA derivatives [18][41][42][43][44]. Colored motifs depict the molecular scaffold of the sensor, which is actively participating in the sensing process.

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