Multistep Synthesis on the Surface of Self-Assembled Thiolate Monolayers on Gold: Probing the Mechanism of the Thiazolium-Promoted Acyloin Condensation

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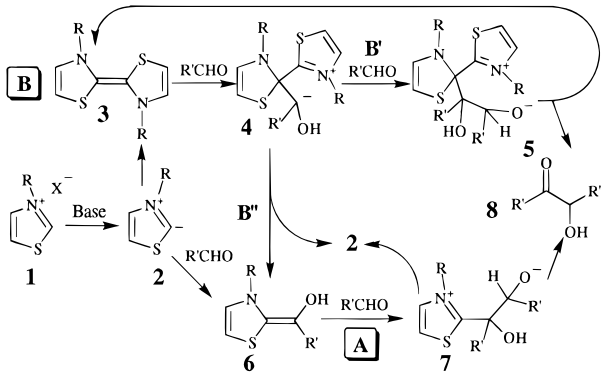
In this paper, we demonstrate the feasibility of multistep synthesis on self-assembled thiolate monolayers on gold.[1,2] We use these synthetically modified self-assembled monolayers (SAMs) to investigate the mechanism of an organic reaction: the thiazolium-promoted acyloin condensation. Kinetic studies by Breslow show that, under mildly basic conditions, the rate of condensation is first order in thiazole (Scheme 1, pathway A).[3] Addition of ylide **2** to the aldehyde, followed by proton transfer, affords the acyl anion equivalent **6** that undergoes addition to a second aldehyde. After proton transfer, elimination of thiazolium regenerates **2** and yields the acyloin product **8**. A second catalytic pathway (pathway B), involving the formation of a thiazole dimer (**3**), typically observed under strongly basic conditions, has also been suggested.[4] After proton transfer, the unlikely carbanionic intermediate **4** was proposed. Intermediate **4** can act as the acyl anion equivalent either by adding to a second aldehyde (pathway B′) or alternatively (pathway B″) by undergoing cleavage to regenerate a thiazolium ylide and acyl anion equivalent **6**, as proposed by Breslow in pathway A.

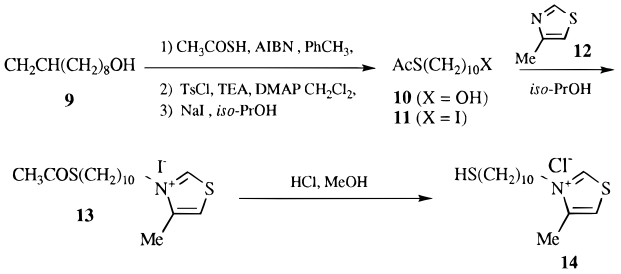
We chose to study the mechanism of the thiazolium-catalyzed acyloin condensation in the context of thiazolium-functionalized SAMs. Thiazolium-terminated thiols were synthesized via a short sequence (Scheme 2). Mixed monolayers of thiazolium-terminated thiol and octanethiol were formed by immersion of polycrystalline gold on silicon in a solution containing octanethiol (30 mM) and the thiazolium-terminated thiol (2.5 mM). We could then investigate the reaction of the surface-bound thiazoliums with fluorescently[5,6] labeled reactants from solution.

We synthesized fluorescently labeled intermediates and substrates to investigate the mechanism of the acyloin condensation. To examine the catalytic activity of monothiazolium salts (pathway A, Scheme 1), mixed monolayers of monothiazolium-

Scheme 1



Scheme 2



functionalized decanethiol and octanethiol formed on gold films (**15**) were immersed in 1.6 mM solutions of 9-anthraldehyde in ethanol, acetone, or dichloromethane to synthesize enol intermediate **17b**. Excess triethylamine was added to each reaction mixture to activate the catalyst. After the samples were warmed (*ca.* 40−50 °C) for 3−12 h[7] in ethanol, acetone, or dichloromethane, the monolayers were removed and rinsed with pure reaction solvent. Fluorescence spectroscopy was used to detect the presence of the anthracyl moiety on the surface.[8] In all three solvents, a fluorescent intermediate, bonded covalently to the surface, was detected.[9] We attribute this to the formation of the enol intermediate **17b** (Scheme 3) on monolayer surface, analogous to intermediate **6** (Scheme 1).

To examine formation of the thiazole dimer (analogous to **3**) and its role in the catalytic cycle, we synthesized an anthracene-labeled thiazolium salt by alkylating 4-methylthiazole with 9-(chloromethyl)anthracene. Mixed monolayers of monothiazolium salts **15** were immersed in 1.0 mM solutions of the anthracene labeled thiazolium salt in ethanol, acetone, or dichloromethane. Excess triethylamine was added, and the solutions were warmed for 12 h. Examination of the fluorescence of the monolayers, after removal from the reaction mixture and rinsing showed the presence of the anthracene moiety on the surface (**18b**) as evidenced by the fluorescence emission. Formation of mixed monolayers of thiazole dimer prepared in solution and octanethiol afforded SAMs that gave fluorescence emission spectra that were identical to the previously obtained

(1) (a) Ulman, A. *Ultrathin Organic Films from Langmuir Blodgett to Self-Assembly;* Academic Press: New York, 1991. (b) Bain, D. B.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 321. (c) Porter, M. D.; Bright, T. B.; Allara, D. L.; Chidsey, C. E. D. *J. Am. Chem. Soc.* **1987**, *109*, 3559. (d) Ulman, A.; Eilers, J. E.; Tillman, N. *Langmuir* **1989**, *5*, 1147. (e) Ulman, A.; Evans, S. D.; Shindman, Y.; Sharma, R.; Eilers, J. E.; Chang, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 1499. (f) Zhang, L.; Lu, T.; Gokel, G. W.; Kaifer, A. E. *Langmuir* **1993**, *9*, 786.

(2) For examples of chemical reactions on surface of SAMs, see: (a) Muller, W. T.; Klein, T. L.; Less, T.; Clarke, J.; McEuwn, P. L.; Schultz, P. G. *Science* **1995**, *268*, 272. (b) Balachander, N.; Sukenik, C. N. *Langmuir* **1990**, *6*, 1621. (c) Lander, L. M.; Brittain, W. J.; Tsukruk, V. *Polym. Prepr., Am. Chem. Soc., Div. Polym. Chem.* **1994**, *35*, 488.

(3) See (and references therein): (a) Breslow, R.; Kool, E. *Tetrahedron Lett.* **1988**, *29*, 635. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699. (c) Breslow, R.; Schmuk, C. *Tetrahedron Lett.* **1996**, *37*, 8241.

(4) (a) Castells, J.; Lopez-Calahorra, F.; Geijo, F.; Perez-Dolz, R.; Bassedas, M. *J. Heterocycl. Chem.* **1986**, *23*, 715. (b) Castells, J.; Lopez-Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433. (c) Doughty, M. B.; Risinger, G. E. *Bioorg. Chem.* **1987**, *15*, 1. (d) Lappert, M. F.; Maskell, R. K. *J. Chem. Soc., Chem. Commun.* **1982**, 580.

(5) Motesharei, K.; Myles, D. C. *J. Am. Chem. Soc.* **1994**, *116*, 7413.

(6) (a) Mathauer, K.; Frank, C. W. *Langmuir* **1993**, *9*, 3002. (b) Chen, S. H.; Frank, C. W. *Langmuir* **1991**, *7*, 1719. (c) Chen, S. H.; Frank, C. W. *Langmuir* **1989**, *5*, 978. (d) Hall, R. A.; Thistlethwaite, P. J.; Grieser, F. *Langmuir* **1993**, *9*, 2128. (e) Stine, K. J.; Uang, J. Y.-J.; Dingman, S. D. *Langmuir* **1993**, *9*, 2112. (f) Grabbe, E. S. *Langmuir* **1993**, *9*, 1574.

(7) The thermal stability of these monolayers has been examined by surface-enhanced Raman spectroscopy. By following the change in the integral of several signals, the half-life of an octanethiol monolayer in ethanol at 40 °C was estimated to be ca. 30 h (R. L. Garrell and L. Yeager, Department of Chemistry & Biochemistry, UCLA, unpublished results). The thermal stability of thiolate monolayers has also been investigated by wetting and X-ray photoelectron spectroscopy (Jennings, G. K.; Laibinis, P. E. *Langmuir*, **1996**, *12*, 6173). These experiments suggest that the half-life of thiolate monolayers in hydrocarbon solvent at 40 °C to be well in excess of 30 h.

(8) Fluorescence spectra were obtained according to the procedure described in ref 5. Monolayers were excited at 400 nm and afforded the following emission spectra reported as emission wavelength (reaction solvent): **17b** 589 (ethanol), 591 (acetone), 592 (dichloromethane); **18b** 571 (ethanol), 566 (acetone), 564 (dichloromethane); **19a**, **20a** 588 (ethanol), 591 (acetone), 595 (dichloromethane).

(9) Pure octanethiol monolayer and gold substrate showed no adsorption of aldehyde upon identical treatment.

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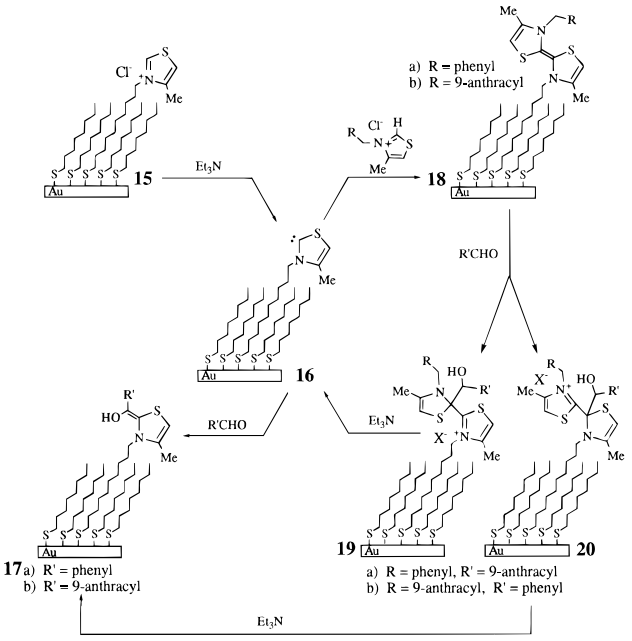
Scheme 3



dimerized thiazolium SAMs (**18b**). These experiments achieve two important goals. First, they demonstrate that dimerization of surface-bound thiazolium salts is possible. Second, they set the stage for an investigation of the fate of the dimer under conditions suitable for the acyloin condensation.

To test the viability of the thiazole dimer as a potential catalyst in the acyloin condensation reaction, the dimer monolayer **18a**, formed from **15** and the benzylthiazolium salt, was subjected to a second synthetic transformation. This thiazole dimer monolayer (**18a**) was immersed in 1.6 mM solutions of 9-anthraldehyde in ethanol, acetone, or dichloromethane and warmed to ca. 40 °C. For the first set of experiments, no triethylamine was added to the solutions. After 12 h, the monolayers were removed from the reaction mixtures and rinsed. The resulting monolayers showed fluorescence bands similar to monothiazolium/9-anthraldehyde adduct monolayer (**17b**). Lower fluorescence intensities were observed when excess triethylamine was added to the reaction mixtures. Two possible scenarios exist to account for the presence of fluorescent functionality on the monolayer surfaces. First, dimer **18** might add to the aldehyde to form regioisomeric adduct SAMs **19a** and **20a**[10] without undergoing further reaction. Alternatively, cleavage of the adducts would afford **17b** directly from **20a** and also regenerate the ylide/carbene **16** from **19a**, which would then be free to react with additional 9-anthraldehyde to generate the fluorescently labeled SAM **17b**.

(10) Due to the unsymmetrical nature of the dimer on the surface, two regioisomeric addition products on the surface are possible. Examination of molecular models of these SAMs suggests that the plane of the thiazolium dimer is roughly parallel to the plane of the surface of the monolayer. Thus, the steric environments of the two nucleophilic carbon atoms of the dimer are similar.

To distinguish between these two possibilities, a second set of experiments was conducted using fluorescently labeled thiazole dimer monolayers (**18b**). These SAMs were treated with benzaldehyde in the absence of triethylamine. The resulting SAMs showed fluorescence emissions, *albeit* at somewhat diminished intensities, corresponding to the presence of anthracyl on the surface. Thus, dimer adducts **19b** and **20b** appear to be stable under these conditions. Interestingly, treatment of **18b** with excess benzaldehyde in the presence of triethylamine resulted in almost complete loss of fluorescence presumably due to the cleavage of dimer and loss of the fluorescent anthracyl group to afford **17a**. It should be noted that the thiazole dimer monolayer **18b** was inert to exposure to triethylamine in the absence of benzaldehyde. Taken together, these results suggest that a stable intermediate adduct (*i.e.*, **19**/**20**) between the thiazole dimer and the aldehyde is formed in the absence of base and that base and excess aldehyde result in cleavage of the dimer.

The synthetic transformations **15** → **16** → **18** → **19**/**20** → **17** model pathway B″ in Scheme 1 and confirm the role of the dimer as a competent intermediate on a pathway for the acyloin condensation. The apparent stability of dimer/aldehyde adducts **19** and **20** in the absence of triethylamine reinforces the importance of the base in the overall reaction. We believe that the loss of fluorescence of **19** and **20** is due to base-promoted cleavage of the aldehyde dimer on the surface.

In conclusion, we have used multistep synthetic modification of self-assembled monolayers to probe the mechanism of the thiazolium-promoted acyloin condensation by isolating intermediates of the mechanistic pathway on the surface of the monolayer. This work shows the potential of SAMs to serve as models in which to study reaction mechanism and has provided insights into the thiazolium-catalyzed acyloin reaction. We have shown that surface-bound thiazole dimers will add to aldehydes. Cleavage of the dimer is the major pathway through which these materials promote the condensation. Thus, we conclude that thiazole dimers participate in catalysis of the acyloin condensation reaction via pathway B″ rather than pathway B′ and that carbanionic intermediate **4** is not part of the catalytic cycle (Scheme 1). We are currently pursuing the use of functionalized SAMs both as mechanistic probes and as chemoselective catalysts.

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Supporting Information Available: Experimental procedures for the preparation of compounds **10**−**14** and monolayers **15**−**20** including ^{1}H NMR and ^{13}C spectra; procedures for preparation of monolayers; procedures for fluorescence experiments; contact angle data (7 pages). See any current masthead page for ordering and Internet access instructions.

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