Sustainable synthesis of amino acid based three-component surfactants via Diels-Alder reaction

Technology
Arts Sciences
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Summary

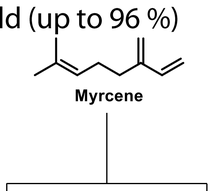
- Amino acid-based surfactants employ mild & environmentally friendly properties
  - Bio-based, renewable resources
- Three-component-design offers structural variety for surfactants to address different application profiles easily
  - Amino acid can be exchanged to apply different properties to the surfactants head, depending on the side-chain
  - Surfactant tail can be modified by variation of the diene-bearing chain, effectively altering chain-length and structure
  - Application of natural occurring terpenes as diene
  - Cyclic anhydride linker serves as potentially renewable, active species for lipid-amine-coupling without the necessity for additional activating agent (e.g. acyl-chlorides, coupling agents)
- The Three-Component-Surfactants were tested exemplarily regarding surface tension, foaming ability and emulsification behaviour
- Antimicrobial properties can be found in some surfactants with amino acid head groups

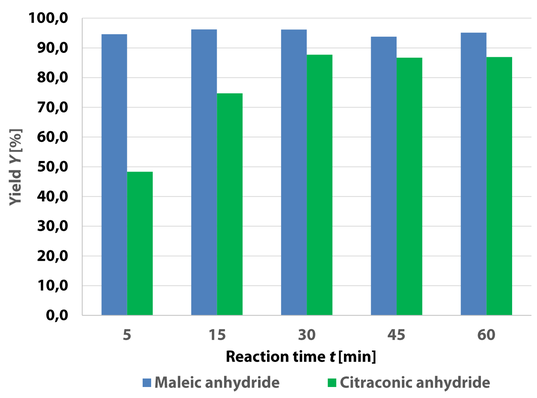
Surfactant Synthesis

Two-Step-Reaction:

1) Diels-Alder build up of "fatty-acid-like" cyclic-anhydride-tail

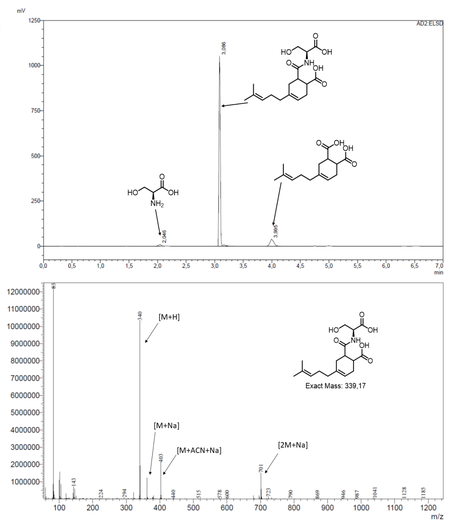
- Fast microwave-assisted reaction in 50 mmol-scale
- Maleic Anhydride (MSA) in THF or solvent-free with citraconic anhydride (CA)
- High yield (up to 96 %)

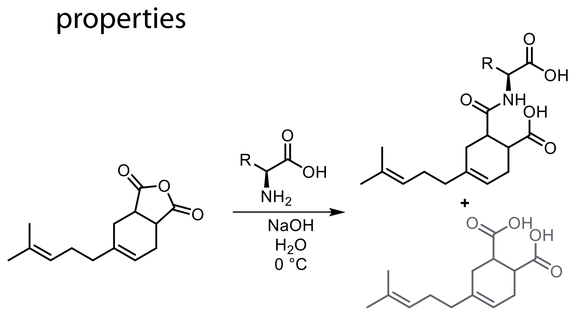




2) Nucleophilic ring-opening with amino acids

- Coupling in Water or Water/Acetone at 0 °C
- Dropwise addition of anhydride to amino acid solution
- Yields mixture of product-surfactant and hydrolysis by-product
  - ➢ Both potentially employing surfactant properties

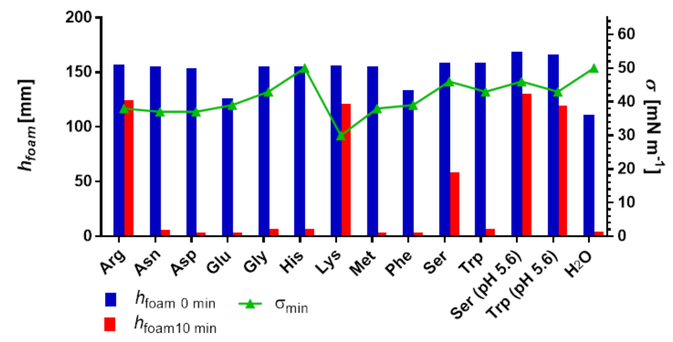




Linker	Nucleophile	Yield *Y*	Purity	Linker	Nucleophile	Yield *Y*	Purity
MSA	H_2O	99 %	99 %	MSA	Lys	89 %	73 %
MSA	Arg	68 %	61 %	MSA	Met	94 %	88 %
MSA	Asn	46 %	52 %	MSA	Phe	70 %	90 %
MSA	Asp	88 %	61 %	MSA	Ser	71 %	85 %
MSA	Glu	99 %	74 %	MSA	Trp	46 %	92 %
MSA	Gly	91 %	85 %	CA	H_2O	99 %	99 %
MSA	His	91 %	88 %	CA	Ser	90 %	90 %

Physicochemical characterization

- Surface tension analysis with Dataphysics DCAT 21, Wilhelmy-plate method
- Foam analysis was conducted with a Krüss DFA100 at concentrations of 4 mmol/l and an air flow of 0.4 l/min applied for an interval of 20 s
  - ➢ Maleic-anhydride-surfactants showed higher decrease of surface tension, especially at lower pH
  - ➢ Citraconic-anhydride-surfactants decay after short time in acidic pH
- Amino acid headgroup significantly enhances foamability and increases foam-stability
- Cationic Amino acids Arg and Lys form stable foam at pH 7
  - ➢ **Lys** applied as mixture of mono- and bi-acylated product
  - ➢ **Lys** and **Arg** potentially antimicrobial due to cationic moiety
- Reduction of pH to skin-friendly 5.6 creates stable foam with MSA-serine and MSA-tryptophan for above 10 minutes



Antimicrobial properties

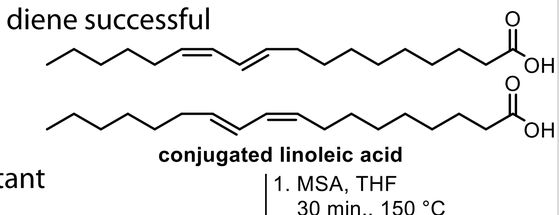
- Antimicrobial activity was analyzed against the yeast Candida vishwanathii, Escherichia coli as gram-negative and C. glutamicum and B. subtilis as gram-positive bacteria
- only N-(myrcene-MA)-phenylalanine exhibited some antimicrobial activity

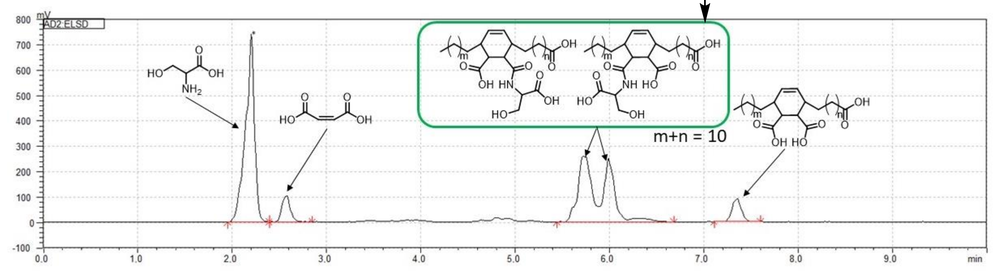
Diels-Alder adduct	Amino acid	*Bacillus subtilis*	*Corynebacterium glutamicum*	*Escherichia coli*	*Candida vishwanathii*
Myr-MA	Phe	40 + / 20 -	40 + / 20 -	40 X / 20 -	nd
Myr-MA	Arg	nd	nd	nd	nd
Myr-MA-OEt	Arg-OEt	40 + / 20 -	40 ++ / 20 + / 10 ○ / 5 -	40 X / 20 -	40 + / 20 ○ / 10 -
Myr-CA	Arg	nd	nd	nd	nd
Myr-CA-OEt	Arg-OEt	40 + / 20 -	40 ++ / 20 + / 10 + / 5 ○	40 + / 20 -	40 + / 20 -

nd = no inhibition detected at highest concentration, ++ = large inhibition area, + = clearly visible inhibition area, • = small inhibition area, X = weak inhibition, ambiguous test results and - = no inhibition detected

Follow up: Long-chain surfactants

- Linoleic acid can be obtained from safflower oil and isolated by precipitating with urea and then conjugated using a basic catalyst
- Application of conjugated linoleic acid (CLA) as diene successful
- Longer chain yields in higher hydrophobicity and change of physicochemical properties
- prolonged carbon chain might enhance surfactant and antimicrobial activities





Conclusions & Outlook

- Two-step synthesis of three-component-surfactants successful with high yields under fast microwave-assisted conditions
- Amino acid head-group enhances foaming properties and surface activity
- Lysine and Arginine show promising properties in foamability and surface activity and could show antimicrobial activity
  - ➢ Determination in further experiments necessary
  - ➢ Properties of mono- & bi-acylated product need to be evaluated

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