Poly(2-oxazoline)-Conjugates for Malaria Therapy

TECHNISCHE UNIVERSITÄT DRESDEN
Faculty of Chemistry and Food Chemistry
Chair of Macromolecular Chemistry

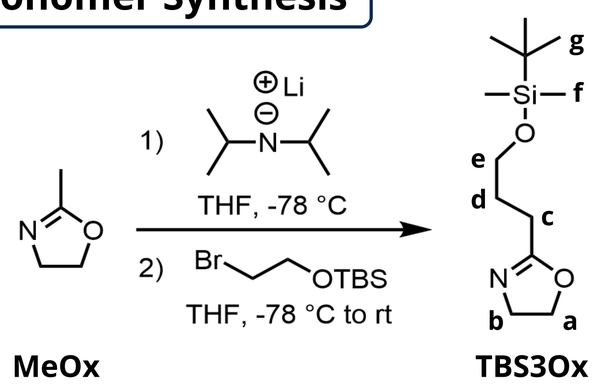
Martin Schmidt, Paul Naumann, Maximilian Franze, Rainer Jordan*
*Rainer.Jordan@tu-dresden.de

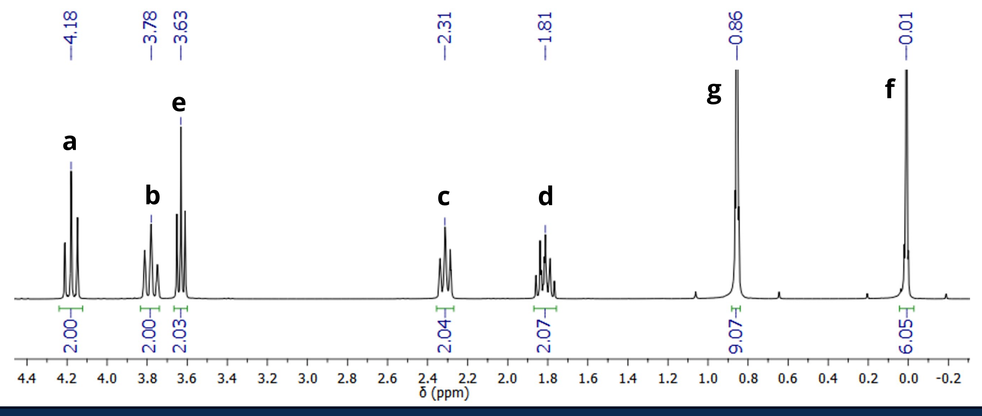
Introduction

Malaria is a deadly, parasitical disease, which caused 597 000 deaths in 2023.[1] Even with hospital treatment, the mortality of severe malaria is still 10-20 %.[2] Intravenous artesunate (ARS) is the current recommended treatment for severe malaria.[2] However, low solubility and stability at physiological pH, as well as unfavorable pharmacokinetics of ARS present room for improvement.[3, 4]

Poly(2-oxazoline)s (POx) are a highly adaptable class of polymers which have attracted attention as biocompatible drug delivery systems.[5, 6] This work aimed to synthesize well defined POx block copolymers to bind ARS via mild esterification reactions. To form soluble and stable POx-ARS conjugates for the possible treatment of malaria, different conjugate architectures were compared.

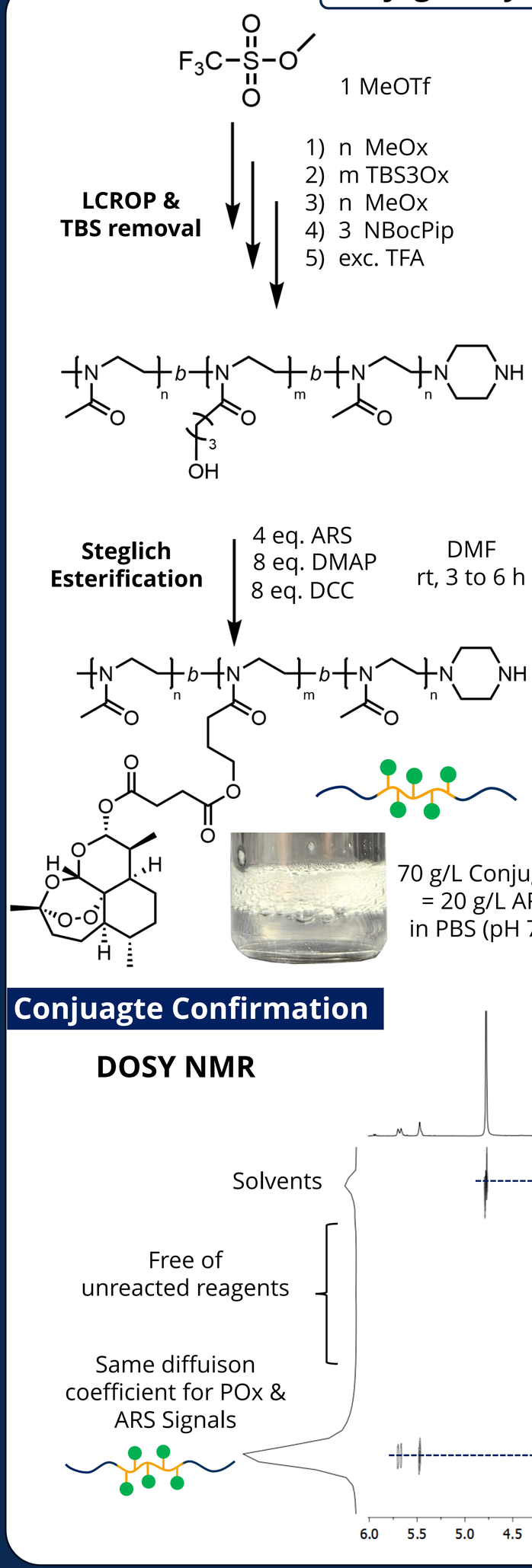
Monomer Synthesis



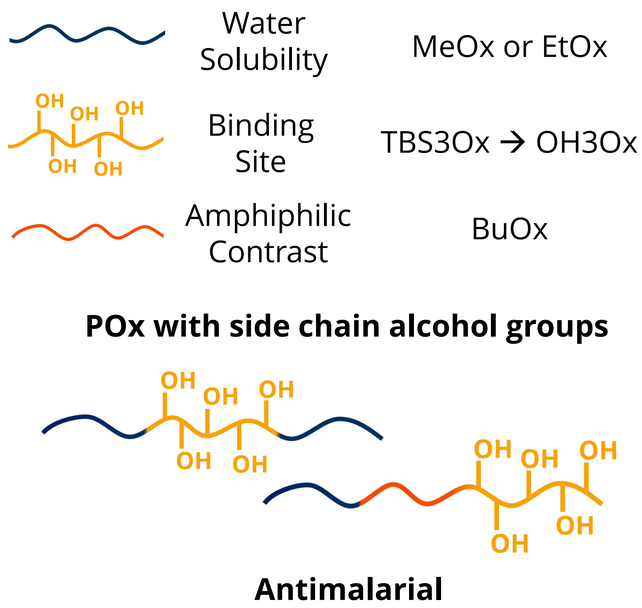


- ✓ One-pot reaction (η = 56 %)
- ✓ Suitable for longer alkyl chains (e.g. TBS5Ox, TBS10Ox)
- ✓ TBS-group stable through LCROP
- ✓ Copolymerization possible

Conjugate Synthesis

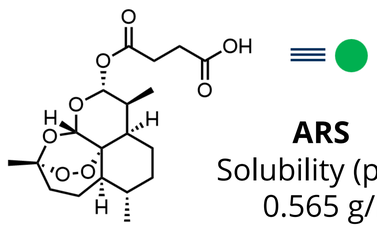


Polymer Design



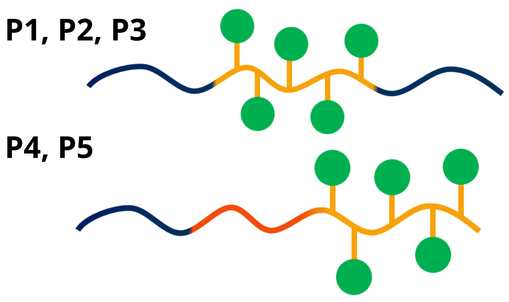
POx with side chain alcohol groups

Antimalarial



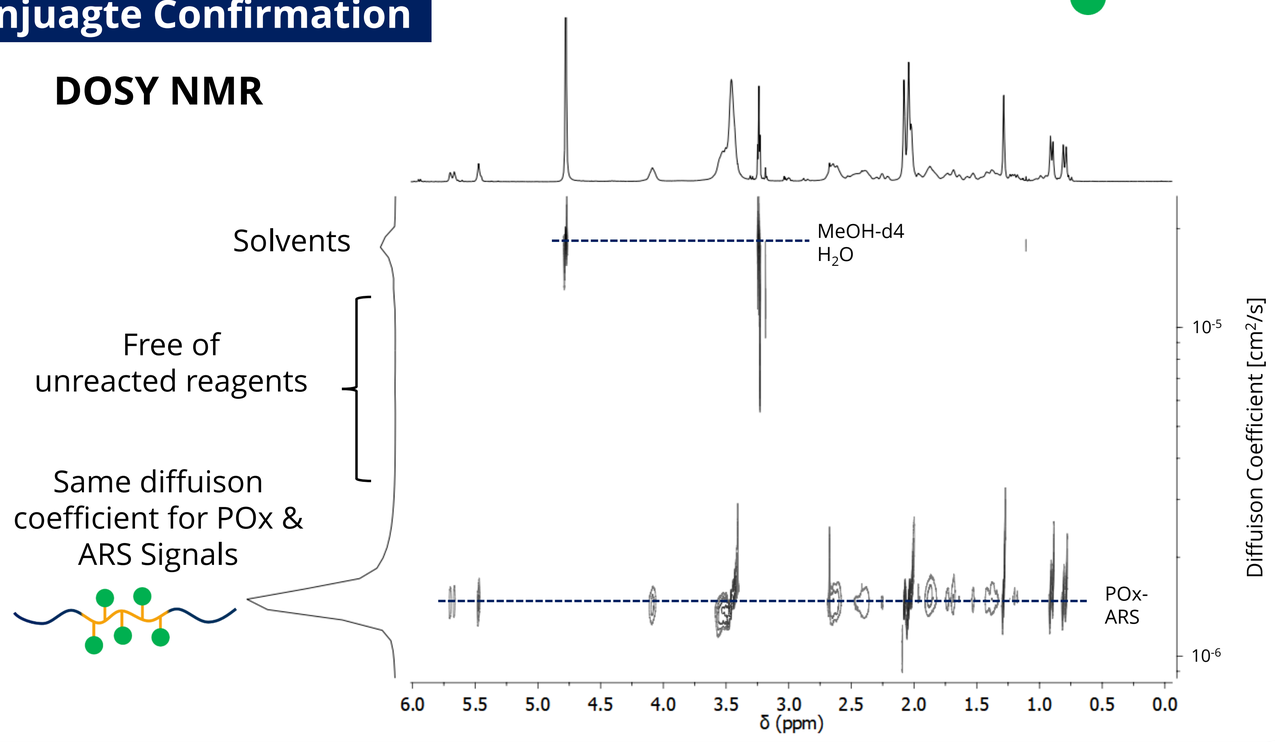
ARS
Solubility (pH 7.4)
0.565 g/L[3]

Soluble POx-ARS-Conjugates



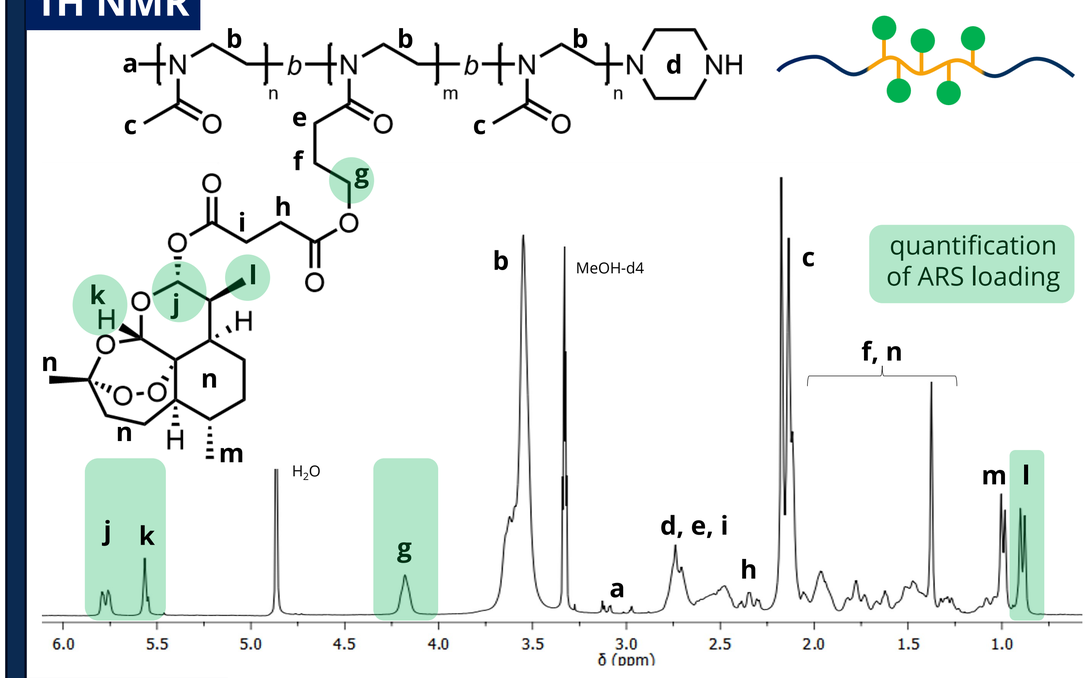
Conjuagte Confirmation

DOSY NMR



Analysis

1H NMR



Polymers

	Structure before Conjugation[a]	M_n[a] [kg/mol]	Đ[b]
P1	Me-MeOx$_{10}$-*b*-OH3Ox$_9$-*b*-MeOx$_{10}$-Pip	3.0	1.09
P2	Me-MeOx$_{26}$-*b*-OH3Ox$_9$-*b*-MeOx$_{26}$-Pip	5.7	1.10
P3	Me-EtOx$_{29}$-*b*-OH3Ox$_{11}$-*b*-EtOx$_{29}$-Pip	7.3	1.21
P4	Me-MeOx$_{32}$-*b*-BuOx$_9$-*b*-OH3Ox$_9$-Pip	5.1	1.09
P5	Me-MeOx$_{73}$-*b*-BuOx$_{11}$-*b*-OH3Ox$_9$-Pip	8.9	1.27

a: via 1H NMR; b: via SEC (DMAc, PMeOx standards).

Optimized POx-ARS Conjugates

	Units bound ARS[a]	LC ARS [%]*	Soluble ARS [g/L]**	Đ[b]	d[c] [nm]	PDI[c]
P1	6.2	45	19	1.18	113	0.054
P2	7.6	33	22	1.14	21	0.296
P3	6.8	26	12	1.12	25	0.092
P4	6.2	32	18	1.13	108	0.161
P5	5.0	18	9	1.17	75	0.195

a: via 1H NMR; b: via SEC (DMAc, PMeOx standards); c: via DLS.

$$*\text{Loading Capacity (LC)} = \frac{\text{mass bound ARS}}{\text{mass conjugate}} \times 100\ \%$$

** no visible precipitation in PBS buffer (pH 7.4)

Conclusion & Outlook

- ✓ Mild conjugation conditions
- ✓ High drug loading
- ✓ ARS solubility increase up to factor 39
- ? Efficacy
- ? Pharmacodynamics
- ? Pharmacokinetics

Literature

[1] World malaria report **2024**: addressing inequity in the global malaria response. Geneva: World Health Organization; 2024.
[2] WHO guidelines for malaria, 30 November **2024**. Geneva: World Health Organization; 2024; DOI: 10.2471/B09146.
[3] R. K. Haynes, Curr. Top. Med. Chem. 2006, 6, 509-537; DOI: 10.2174/156802606776743129.
[4] J. Achane et al., *Malar. J.* **2024**, *23*, 174; DOI: 10.1186/s12936-024-04986-z.
[5] R. Luxenhofer et al., Macromol. Rapid Commun. **2012**, *33*, 1613-1631; DOI: 10.1002/marc.201200354.
[6] T. Lorson et al., Biomaterials **2018**, *178*, 204-280; DOI: 10.1016/j.biomaterials.2018.05.022.