Enclosure 1b. Category 1 Application form – English version

APPLICATIONS ARE PREFERABLY DRAWN UP IN ENGLISH. AN ENGLISH TRANSLATION HAS TO BE ENCLOSED WITH APPLICATIONS SUBMITTED IN DUTCH.

The application form is available in English on the website https://vscentrum.be/.

Title of the application: Dynamics of poly(2-oxazoline)s

Name and first name of the applicant: Dietmar Hertsen

Institution: Ghent University

Research group / department: Center for Molecular Modeling, Department of Applied Physics

Title / position: PhD fellow

e-mail address: dietmar.hertsen@ugent.be

Total computing time that is needed, in node days: 2900

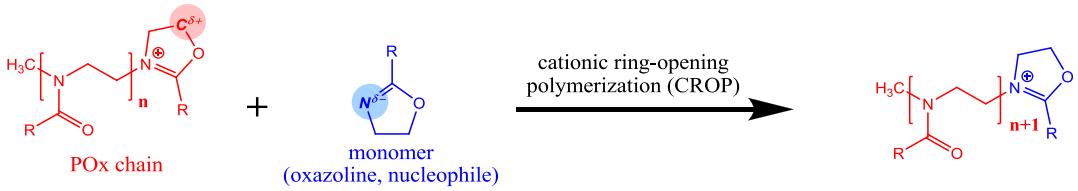
Total disk storage that is applied for: ~ 1 TB scratch, ~ 1 TB long-term storage

1. **Title of the research project (with IWETO link if available) within the framework of which computing time is applied for**:

POXylation as next generation PEGylation (promoter prof. Dr. ir. Veronique Van Speybroeck, IWT SBO 120049)

2. **Short description of the research project within the framework of which computing time is applied for (max. 1 A4 in Arial 12)**:

Poly(2-oxazoline)s (POx) are an interesting class of biocompatible polyamides whose physical and chemical properties can easily be tuned. These polymers are readily synthesized via cationic ring-opening polymerization (CROP) of various monomers, yielding polymers with distinct properties. The characteristics of the resulting pseudo-polypeptides can be altered even further by chemical functionalization of the residue side chains. Because of their versatility and biocompatibility, poly(2-oxazoline)s are candidate drug-delivery systems, providing a viable alternative to the gold standard in this field, polyethylene glycol (PEG). Their polymerization is still a bottleneck, however, and more computational efforts should be directed toward it.



The CROP rate is highly dependent on the monomer side chain and this effect has been successfully modeled by static ab initio calculations.[1] Since the effects at play are localized, model systems typically only include the last residue of the living polymer chain and the attacking monomer. However, our recent study of monomers with flexible, polar side chains, e.g. 2-methoxycarboxy-2-oxazoline (MestOx), has shown that nearby residues in the polymer chain are able to stabilize the CROP transition state (unpublished results). The size of the conformational space which has to be sampled to understand these interactions warrants a molecular dynamics (MD) approach.

In vivo, POx chains are involved in a complex equilibrium between hydration, intra- and intermolecular aggregation. The influence of different monomers on these phenomena is poorly understood, although they are the basis of clinically relevant supermolecular effects like micellation. Again, MD is the computational method of choice, since these effects are inherently dynamic.

[1] H. Goossens, S. Catak, M. Glassner, V. R. de la Rosa, B. D. Monnery, F. De Proft, V. Van Speybroeck, R. Hoogenboom, ACS Macro Lett. 2013, 2, 651–654.

3. **Financing institution or channel, financing the research project in full or in part (FWO, BOF, IWT, EU, ...): Please attach the confirmation letter as enclosure (see instructions in enclosure 3).**

SBO project POXylation as next generation PEGylation (IWT SBO 120049)

4. **Promoter of the research project**:

Prof. Dr. ir. Veronique Van Speybroeck

5. **Persons mandated by the Applicant to compute on the TIER1 within the framework of the present project: Please provide for every person:**

- **name and first name**
- **institution**
- **research group / department**
- **title / position**
- **experience with TIER1/TIER2 infrastructure in Belgium and abroad**

Dietmar Hertsen
Ghent University
Center for Molecular Modeling, Department of Applied Physics
PhD Fellow
vsc40473
experience with TIER2 at Ghent University

Hannelore Goossens
Ghent University
Center for Molecular Modeling, Department of Applied Physics
PhD Fellow
vsc40329
experience with TIER2 at Ghent University

Veronique Van Speybroeck
Ghent University
Center for Molecular Modeling, Department of Applied Physics
Full professor

vsc40021
experience with TIER1 and TIER2 at Ghent University

6. **Description of the computing task, justification for the computing time, disk storage and memory that are applied for, and description of the software tools required (max. 3 A4 in Arial 12). Please clearly provide the following in this regard:**

- **the number of nodes/cores that are applied for per computing task, with a subdivision of the computing time in sub-tasks indicating the sequence of the sub-tasks**
- **whether these tasks use diversification (OpenMP, MPI, hybrid OpenMP/MPI …)**
- **the estimated memory use of a computing task (maximum 64GiB/node)**
- **whether a vSMP system will be used**
- **the requirements for disk storage (estimated volume in GiB and the total number of files), more specifically for:**
  - **required input files (data set, parameter files, etc.)**
  - **SCRATCH volume used during the performing of the computing tasks**
  - **result files**

Semi-empirical and ab initio molecular dynamics simulations using the CP2K software package and MPI will be performed to study the hydration and polymerization of several poly(2-oxazoline)s (MeOx, EtOx, MestOx, ButenOx). vSMP will not be used.

The hydration behaviour will be investigated by means of semi-empirical MD simulations in the NPT/NVT ensemble. Three types of systems will be considered: a single hydrated polymer chain, a hydrated polymer chain and monomer, and two hydrated polymer chains. Polymer chains are made up of five residues. Typical systems include 150 water molecules (450 atoms). Based on preliminary TIER2 calculations on the delcatty cluster (Ghent University), it is estimated that 250 node days are required to complete this task:

	# atoms		# node days		
	chain	**monomer**	**chain**	**monomer**	**2 chains**
MeOx	69	13	15	15	25
EtOx	84	16	15	15	25
MestOx	114	22	20	20	30
ButenOx	104	20	20	20	30
			Sum		250

The cationic ring-opening polymerizations of these oxazolines will be modelled by ab initio molecular dynamics in the gas phase. For each reaction system, a metadynamics simulation will be performed (MTD), followed by a committor analysis (CA) and a transition path sampling (TPS). In the first step, around 100 ps will be simulated. In each of the last two steps, around 200 paths will be generated.

All homopolymerizations (4) and copolymerizations (6) will be examined. For each copolymerization, two monomer/polymer compositions will be selected. Based on preliminary TIER2 calculations on the delcatty cluster (Ghent University), it is estimated that 2650 node days are required to complete these calculations:

		# node days		
		MTD	**CA**	**TPS**
homopol.	**MeOx**	42	45	45
	EtOx	50	53	53
	MestOx	65	68	68
	ButenOx	60	62	62
copol.	**MeOx-MestOx**	110	112	112
	MeOx-ButenOx	105	107	107
	EtOx-ButenOx	110	116	116
	EtOx-MestOx	114	121	121
	MestOx-ButenOx	110	114	114
	MeOx-EtOx	94	97	97
Sum				2650

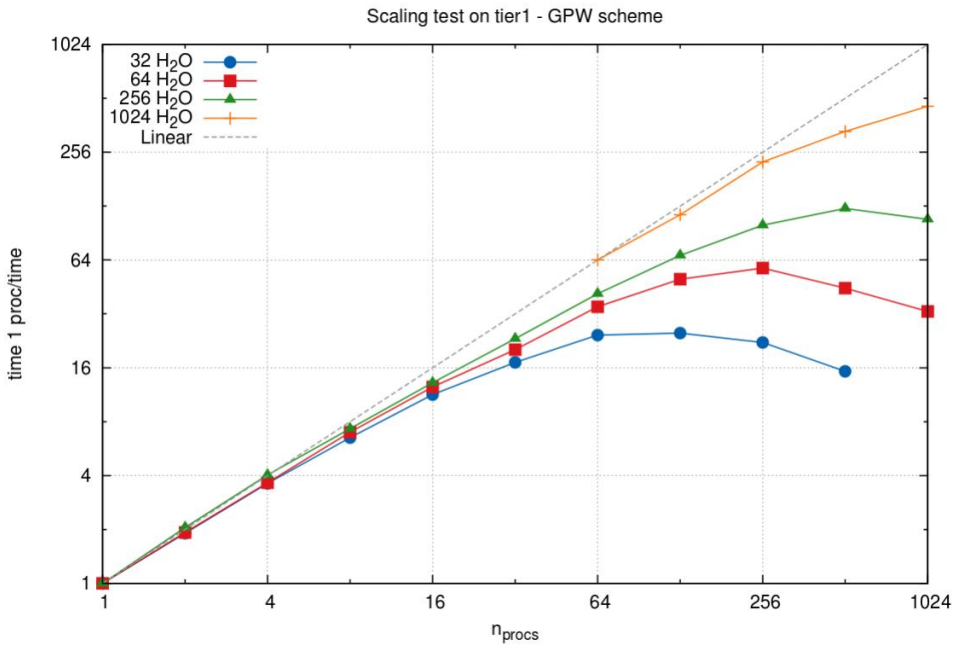
An estimate of the scratch and permanent storage size required is given below:

	scratch (GB)	permanent storage (GB)	# jobs	total scratch (GB)	total permanent storate (GB)
MD	1.0	5.0	12	12.0	60.0
MTD	1.0	5.0	10	10.0	50.0
CA	0.2	0.2	2000	400.0	400.0
TPS	0.2	0.2	2000	400.0	400.0
Sum				822.0	910.0

An overview of the computational resources needed:

computing time	2900 node days
scratch	822 GB
permanent storage	910 GB

Andy Van Yperen – De Deyne has tested CP2K extensively and concluded that the software package scales well on the TIER1 infrastructure (Ghent University):



7. **Please indicate why the TIER1 is the appropriate machine to perform the computing task (max. 1/2 A4 in Arial 12):**

The large conformational space of long and flexible POx chains limits the use of static molecular modeling methods. In order to obtain meaningful results, computationally expensive dynamical approaches are needed. Moreover, to understand the influence of the monomer side chain on the polymerization and chain hydration, a multitude of systems has to be probed. A TIER1 cluster is the only efficient choice in this case, both because of the number of systems and the cost per calculation.

8. **Summary of the software required to perform the computing task, and possible installation and compilation instructions (max. 2 A4 in Arial 12). Please clearly provide the following per item in this regard:**

- **a reference to the software's web page**
- **the software licence system (open source, GPL, etc.)**
- **if there is no free academic use of the software, state which licence makes the installation and the use valid on the TIER1 by the Applicant (+ add a copy of the signed licence)**
- **if need be, which licence server will be used (name + IP address)**
- **whether the software is already available on the TIER1 (see https://vscentrum.be/nl/tier1-rekenen) and, if this is not the case, compilation and installation instructions (possibly with reference to existing TIER2 installation)**

The CP2K software package will be used for all calculations (http://www.cp2k.org/). CP2K is freely available under the GPL license. The version (CP2K/20130228-ictce-4.1.13) is already available on TIER1.

9. **Period during which the task is to be performed:**

Our calculations will run for a time period of six months, starting as soon as possible.

10. **Describe the results that were obtained within the framework of computing time that was attributed during the past two years on the TIER1 or on other TIER1 or TIER0 supercomputers (max. 2 A4 in Arial 12):**

Not applicable.

UNIVERSITEIT GENT

DIRECTIE ONDERZOEKSAANGELEGENHEDEN

Afdeling **Onderzoekscoördinatie**

6 pp
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1/35378.

KOPIE

Aan prof. Richard Hoogenboom
Vakgroep organische chemie
Krijgslaan 281 S4
9000 Gent

uw kenmerk	**ons kenmerk**	**Datum :**
	DOZA/IL/DDC/GVH/13	30/01/2013
contactpersoon	**e-mail**	**tel. en fax**
Griet Van Hyfte	griet.vanhyfte@UGent.be	T +32 9 264 89 88 F +32 9 264 35 83

Betreft: **Vervroegde openstelling van een kredietlijn voor een onderzoeksproject**

Waarde collega

Gebruikmakend van de bevoegdheidsdelegatie voor het vervroegd openstellen van kredietlijnen noodzakelijk voor dringende aanwervingen en het ter beschikking stellen van werkingsmiddelen mij verleend door het bestuurscollege van 8 januari 2004, ga ik akkoord met een vervroegde openstelling van een kredietlijn ten bedrage van **€ 45.000** om versneld het opstarten van het onderzoeksproject *"POXPEG: Poxylation as next generation pegylation"* mogelijk te maken.

Ik heb akte genomen van de garantstelling **via kas D/01302/01**.

Het bedrag zal ter beschikking worden gesteld via projectcode **179J45A12** (budgetplaats:**B/13515/01-IV2**) en kan als personeels-en werkingsmiddelen worden besteed.

Ik geef hierbij opdracht aan de bevoegde directie om het nodige te doen.

Met collegiale groet,

Prof. P. VAN CAUWENBERGE
Rector

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Prjdef: B1351500 Doctyp: Contract

CC: de heer Y. De Clercq, regeringscommissaris