Universiteit Leiden

25th EPR Benelux Meeting 2017

Leiden
June 1st, 2017

Stichting
Dr. C.J. Gorter

BRUKER

25th Benelux EPR Society Meeting
Program

09:45 **Registration Coffee/tea**
10:30 **Opening (Edgar Groenen)**

Chair: Fred Hagen

10:35 Rigid spin labels for improved distance and dynamics in intrinsically disordered proteins and peptides.
Enrico Zurlo (Leiden, NL)

11:00 Nanometric distance measurements using high-spin metals: from model systems to self assembled spin-labels inside cells.
Vincent Ching (Antwerp, BEL)

11:25 Ultrafast mixing instruments for the study of presteady state kinetics of cytochrome c.
Batoul Srour (Delft, NL)

11:50 Solutions for high-end research to routine analytical tasks.
Sylwia Kacprzak (Bruker, GER)

12:15 **Lunch**

Chair: Etienne Goovaerts

14:00 Determination of nitric oxide concentration in placental tissue of pre-eclamptic patients by direct detection with Electron Paramagnetic Resonance (EPR).
Dominique Mannaerts (Antwerp, BEL)

14:25 Investigating the impact of ITPP on tumor oxygenation anti-tumor outcome upon combination with radiotherapy.
Ly-Binh-An Tran (Louvain, BEL)

14:50 Iron in the brain seen by EPR and SQUID magnetometry.
Lucia Bossoni (Leiden, NL)

15:15 **Tea/Coffee**

Chair: Freddy Callens

15:45 In-situ EPR detection of paramagnetic intermediates in water oxidation catalysis by a Co-P_i modified electrode surface.
Olaf Rüdiger (Mülheim, GER)

16:10 Investigating luminescence-based radiation dosimeters using EPR methods.
Kwinten Maes (Ghent, BEL)

16:35 Efficient cross-effect DNP for MAS NMR with trityl-nitroxide biradicals
Guinevere Mathies (MIT, USA)

17:00 **Closing remarks and drinks**

Abstracts

RIGID SPIN LABELS FOR IMPROVED DISTANCE AND DYNAMICS IN INTRINSICALLY DISORDERED PROTEINS AND PEPTIDES

Enrico Zurlo[1], Nico J. Meeuwenoord[2], Dmitri V. Filippov[2], Martina Huber[1].

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Spin-labeling and Electron Paramagnetic Resonance spectroscopy (EPR) have become powerful tools for structure determination in proteins and biomacromolecules. Usual spin labels, such as the disulfide-linked MTSL labels are flexible, owing to multiple single bonds separating the nitroxide from the protein backbone. We investigate spin labels rigidly linked to the backbone in a series of peptides derived from the KVKVLGDVIEV peptide[1], with the 4-amino-1-oxyl-2,2,6,6-tetramethylpiperidine-4-carboxylic acid (TOAC). These peptides mimic amyloid-aggregation proteins. They were found to form stable oligomers that are cell-toxic, and enabled X-ray crystallography to determine their structures[1].
We synthesized and characterized three TOAC-peptides (see Table) and one reference peptide (EZ). We show that the EPR rotation correlation times differ depending on TOAC position. Only one of the TOAC variants (T0EZ) showed aggregation by CD signatures similar to[1], same as the non-TOAC containing EZ peptide. Changes in room temperature EPR spectra suggestive of amyloid aggregation were found in T0EZ, but not in the other TOAC variants.

K11V		**Lys**	**Val**	**Lys**	**Val**	**Leu**	**Gly**	**Asp**	**Val**	**Ile**	**Glu**	**Val**		
T05EZ		**Lys**	**Val**	**Lys**	**Val**	**TOAC**	**Gly**	**Asp**	**Val**	**Ile**	**Glu**	**Val**		
T0EZ	**TOAC**	**Lys**	**Val**	**Lys**	**Val**	**Leu**	**Gly**	**Asp**	**Val**	**Ile**	**Glu**	**Val**	**Gly**	
T12EZ		**Lys**	**Val**	**Lys**	**Val**	**Leu**	**Gly**	**Asp**	**Val**	**Ile**	**Glu**	**Val**	**TOAC**	**Gly**

T0EZ and EZ acquire β sheet character under aggregation conditions (in H_2O, shaking at 1000 rpm at 310 K). Rotation correlation times (τ_r) by continuous wave EPR at 9 GHz are T05EZ: 0.40 ± 0.02 ns; T0EZ: 0.122 ± 0.005 ns; T12EZ: 0.32 ± 0.03 ns. For T0EZ τ_r increases to 0.162 ± 0.007 ns upon aggregation.

Conclusions
We propose that for rigid spin labels such as TOAC, the spin label position and the peptide host are crucial and that the TOAC label may interfere with peptide properties. The results are essential to design spin-labeled constructs for the investigation of intrinsically disordered proteins.

[1] Laganowsky *et al.*, Science 335 (2012) 1228.

Figure. *K11V oligomer structure according to X-ray structure from ref. [1.]*

Nanometric distance measurements using high-spin metals: from model systems to self-assembled spin-labels inside cells

H. Y. Vincent Ching,[a#] Paul Demay-Drouhard,[b] Dmitry Akhmetzyanov,[c] Florencia C. Mascali,[d] Hélène C. Bertrand,[b] Vasyl Denysenkov,[c] Eduardo M. Bruch,[a] Rodolfo M. Rasia,[d] Thomas F. Prisner,[c] Clotilde Policar,[b] Leandro C. Tabares,[a] and Sun Un[a]

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PELDOR

High spin Gd(III) (S=7/2) and Mn(II) (S=5/2) complexes have found uses as spin-labels for nanometric distance measurements[1,2] by pulse dipolar spectroscopy (PDS), which is a versatile biophysical tool for probing the structures and functions of complex biological systems. Compared to the more commonly used nitroxide (S=1/2) spin-labels, metal-based systems are more stable under reducing conditions (*e.g.* inside a cell). Furthermore, in the case of Mn(II), it is endogenous in biological environments and besides being found naturally in biomarcomolecules, it can often replace Mg(II) in others, such as kinases, nucleic acid constructs and nucleotide binding domains due to their similarity in size and charge.

Recently, we have prepared and studied model systems labelled with Mn(II)-DOTA centres by PDS, including pulsed electron-electron double resonance (PELDOR/DEER) at 94 GHz,[3,4] and relaxation-induced dipolar modulation enhancement (RIDME) at 94 and 263 GHz.[5] We have also performed PELDOR measurements at 94 GHz using genetically encodable metal spin-labels which are capable of self-assembly from naturally available components,[6] or in the case of Gd(III) the self-assembly occurs directly inside cells.[7] Details of these experiments and the intricacies of using high-spin metals in nanometric distance measurements will be discussed.

flexibility spin labels!
Mn spin

References

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6. H.Y.V. Ching *et al. J. Phys. Chem. Lett.*, **2016**, *7*, 1072
7. F.C. Mascali *et al. Angew. Chem. Int. Ed.*, **2016**, *55*, 11041

pseudosecular

$$\hat{S}_z^A \hat{S}_z^B \rightarrow \hat{S}_+^A \hat{S}_-^B + \hat{S}_-^A \hat{S}_+^B$$

µs timescale

ULTRAFAST MIXING INSTRUMENTS FOR THE STUDY OF PRESTEADY STATE KINETICS OF CYTOCHROME *C*.

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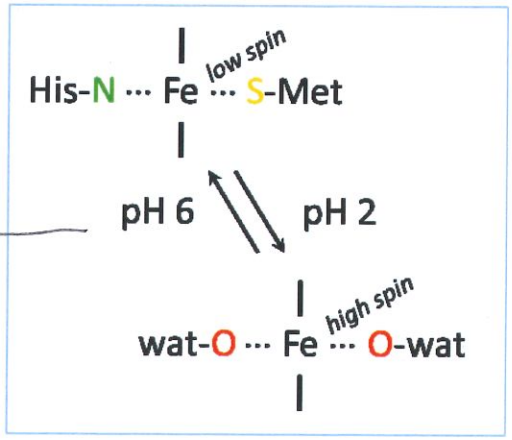
Detailed understanding of catalytic mechanism of redox enzymes under single turnover conditions and on the shortest possible timescale constitutes a main focus of current biochemical research. Two pre-steady state kinetic instruments that were recently developed by us have been used [(1)]. The first is a rapid-freeze quench instrument (MHQ, microsecond freeze-hyperquenching) that enables trapping of intermediates in a sub-millisecond timescale for characterization by Electron Paramagnetic Resonance. The second is a continuous-flow UV-Visible spectrometer with a dead time in the order of microseconds. These instruments enables the detailed kinetic analysis of the very onset of biocatalysis and protein folding.

The study of the refolding kinetics of acid denatured cytochrome *c* using the pH jump technique from pH 2 to pH 4 are presented. Cytochrome c was chosen as a model system to explore the usefulness of the new instruments for the study pre-steady state kinetics of any heme enzyme. Our results show that the intial refolding of denatured oxidised cytochrome *c* occurs very rapidly τ =10 µs, a phase that has not been observed before and is followed by partial refolding steps with time constants of 62 and 200 µs [(2)]. Additionaly, EPR analysis of the MHQ experiments shows the change from high spin to low spin of the heme iron of the folding intermediates.



µs ⇒ s range.

6 s

1000 UV–vis spectr.

Ultrafast freeze quench.

Figure 1. The ligation of the heme iron as function of pH.

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Soret band ~400 nm

ms SPECTROFOTOMETER.

EPR Freeze quench
80 µs – 12 ms

Nanopen
4µm – 2ms

SOLUTIONS FOR HIGH-END RESEARCH TO ROUTINE ANALYTICAL TASKS

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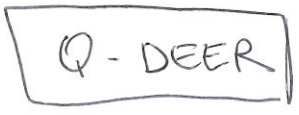
One of the main drivers for new developments in EPR is the demand for higher signal-to-noise. With a number of recent and upcoming product introductions we have made significant progress in this field.

The high power Q-Band pulse-EPR setup allows running DEER experiments with dramatically improved sensitivity, e.g. the measurement time of 22h in X-Band is reduced to 25min in Q-Band, thus increasing sample throughput by more than a factor of 50. To achieve this, a combination of a high power pulse amplifier (150W) and a large volume resonator are used allowing short inversion pulses of 10ns at 150 MHZ resonator bandwidth.
Limitations in excitation bandwidth are a severe handicap in pulse-EPR. The availability of high speed arbitrary waveform generators allows new methods in EPR based on pulse shaping for larger bandwidth excitation. With shaped broad band inversion pulses, the DEER modulation depth can be improved by a factor 2 – 3 and HYSCORE spectra can be measured with much higher S/N.

An ongoing project to substantially increase S/N is the development of a rapid scan unit. The direct registration of the EPR spectra via Rapid Scan method allows recording of absorption spectra, exciting complete spectrum in single shot. In addition due to the short time during which the spins are exposed to microwave field, the saturation effect is less pronounced compared to cw-EPR. This allows use of high microwave fields and consequently increases signal amplitude.
Currently Direct Rapid Scan (DRS) EPR Accessory is being designed by Bruker to further extend the functionality and performance of ELEXSYS and EMX plus systems. The preliminary information about accessory specification will be presented and its performance demonstrated with experimental results.

For a routine analytical tasks in a commercial use all technological advances have to be combined with a strong focus on usability. This is exemplified by the EMXnano bench-top spectrometer which features full instrument calibration with respect to field and signal amplitude, dedicated workflows and requires from the user only little technical knowledge.



• Arbitr. wave gen. AWG.

Determination of nitric oxide concentration in placental tissue of pre-eclamptic patients by direct detection with Electron Paramagnetic Resonance (EPR).

Dominique Mannaerts[1,2], Ellen Faes[1,2], Jacob Briede[3], Emeline M. Van Craenenbroeck[4,5], Marc Spaanderman[6], Yves Jacquemyn[1,2].

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Objective

Pre-eclampsia (PE) is a pregnancy specific disorder characterized by hypertension and proteinuria, which can result in severe organ damage, threatening the life of both mother and unborn child. PE is associated with placental oxidative stress, inflammation and elevated release of cytotoxic and anti-angiogenic factors. These circulating placental factors can affect the endothelium causing generalized maternal endothelial dysfunction. Nitric oxide (NO) is a free radical molecule derived from L-Arginine by NOS (Nitric Oxide Synthase), essential for adequate endothelial function. In the placental circulation, endothelial release of NO dilates the fetal placental vascular bed and thus ensures feto-maternal exchange. In this study, we explored the feasibility of NO concentration determination in normal placental tissue and compared this to placenta of pre-eclamptic patients.

Methods

Electron Paramagnetic Resonance (EPR) is the most direct and reliable method to detect free radicals in tissue. In this study, we used an iron-DETC solution (Fe (II) DETC2 (iron (II)diethyldithiocarbamate) as spin trap to stabilize free radicals for EPR detection. Patients are included at the moment of vaginal or caesarean delivery. Twenty-nine patients were included, of which 15 pre-eclamptic and 14 uncomplicated pregnancies.

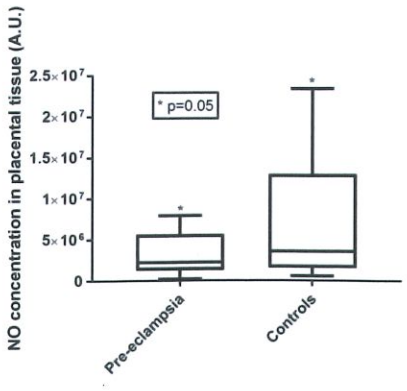
Results

NO concentration in placental tissue of uncomplicated pregnancies (7601225 ± 8206710 Arbitrary Units (A.U.)) was significantly higher compared to pregnancies with PE (3111020 ± 2366653 A.U., p=0.05). Results are presented in figure 1.

Conclusion

We were able to successfully detect NO in placental tissue. We hypothesize that due to an impaired placentation in the first trimester of pre-eclamptic pregnancies, local ischemia and endothelial damage occurs, resulting in altered placental NO production and oxidative stress. Larger study populations are however necessary to confirm these results including further studies into the mechanism how the type of delivery has an influence on NO concentration.

Figure 1.



Investigating the impact of ITPP on tumor oxygenation and anti-tumor outcome upon combination with radiotherapy

Ly-Binh-An Tran[1], Sofie Deschoemaeker[2], Arne Heyerick[2], Bernard Gallez[1]

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Background and purposes:
Normoxys' lead product, ITPP (*myo*-inositol trispyrophosphate), has been suggested to decrease tumor hypoxia. Nevertheless, the mechanisms underlying this effect are still unknown. Herein, we used EPR oximetry to confirm the impact of ITPP on tumor oxygenation in various models and to optimize the treatment schedule. The effect of this compound on oxygen consumption *in vitro* was then assessed as a potential explanation for its mode of action. We finally investigated if ITPP treatment could enhance tumor outcome in combination with radiotherapy.

Methods:
To validate the impact of ITPP on tumor oxygenation, 2 rat tumor models (9L-glioma and Rhabdomyosarcoma) and 4 mouse tumor models (FSaII, SiHa, MDA-MB-231 and NT2) were deployed. Charcoal, used as the oxygen sensor, was injected intra-tumorally one day before the experiment. L-Band EPR oximetry was performed to measure the tumor pO_2 before the administration of ITPP and at several time points after the treatment. Rhabdomyosarcomas were then exclusively subjected to various doses and various treatment schedules to explore which regime could offer the most elevated pO_2 value.

The impact of ITPP on oxygen consumption *in vitro* was tested on 4 cell lines (FSaII, SiHa, MDA-MB-231 and NT2) using X-band EPR spectrometer and ^{15}N-DPT (^{15}N 4-oxo-2,2,6,6-tetramethylpiperidine-d_{16}-^{15}N-1-oxyl) as the sensor. EPR linewidth was recorded every minute over 10 minutes and oxygen consumption rate (OCR) was determined by the slope of the decrease in oxygen concentration in the closed capillary tube over time. Since the inhibition of PI3K pathway has been shown to decrease oxygen consumption, LY294002, a PI3K inhibitor, was also included in the study as a comparator.

The optimal treatment schedule was applied in the following experiment where ITPP was combined with radiotherapy. Two rat models (9L-glioma and Rhabdomyosarcoma) were used; rats were randomly divided into 4 groups: untreated, radiotherapy alone, ITPP alone and ITPP combined with radiotherapy. The therapeutic effects were evaluated based on the tumor growth delay assay.

Results and conclusions:
Our data consistently demonstrate the improvement of tumor oxygenation in all 6 models upon the administration of ITPP. The presence of a dose-response relationship was also revealed. Interestingly, a cumulative effect was found when the second ITPP injection was given on the following day; whereas, additional consecutive treatments did not appear to further increase tumoral pO_2. Furthermore, the *in vitro* study indicated that ITPP could reduce oxygen consumption rate in cancer cells and this effect was quite comparable to LY294002, suggesting that ITPP might work via a similar mechanism as PI3K inhibition. Tumor oxygenation enhancement induced by ITPP, however, did not offer significant benefit in Rhabdomyosarcomas when combined with radiotherapy. The radiosensitization effect of ITPP on 9L-gliomas is currently under investigation.

Iron in the brain seen by EPR and SQUID magnetometry

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Iron is essential for many fundamental biological processes in the brain, including the synthesis of myelin, neurotransmitters, and DNA, oxygen transport, and mitochondrial respiration [1]. It is also known that age-related accumulation of iron in the brain is a risk factor for neurodegenerative processes, especially in Alzheimer's diseases (AD). Indeed, iron accumulation is found in the brain tissue of AD patients and is often co-localized with Amyloid plaques [2, 3].

Despite iron's central role in the pathophysiology of neurodegenerative diseases (NDs), the mechanisms of its toxicity and the specific molecular iron forms (MIFs) involved in the disease are still not well understood. Our aim is to quantify different MIFs in the brain, by exploiting the magnetic properties that iron displays, when bound to proteins, iron-oxide minerals, or when it is potentially chelatable. Additionally, we aim to elucidate the most-relevant MIFs in NDs and determine the MIF(s) underlying the relaxation-based contrast in Magnetic Resonance Imaging (MRI) observations, leading to signal voids in R_2^*-weighted sequences [4].

We provide a method, alternative to the current biochemical assays, to measure MIFs concentrations in post-mortem brain tissue. Our method is based on the combination of Electron Paramagnetic Resonance (EPR), SQUID Magnetometry and MRI [5]. We show that we can quantify the following MIFs: (i) Potentially-chelatable Fe(III); (ii) ferrihydrite-containing ferritin and (iii) potentially-toxic magnetite/maghemite nanoparticles.

We employed our method to the study of 36 patients (22 AD cases and 14 controls). We firstly show which MIF is mostly affected in our AD patient group. Secondly, we discuss possible associations between MRI relaxation rates (R_2^*) and the measured MIFs, in the framework of the existing theoretical models.

References:
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[4] van Rooden S, Doan NT et al., Neurobiol Aging. 36(1), 20-26 (2015)
[5] Kumar P, Bulk M, Webb A et al., Sci. Rep. 6, 38916 (2016)

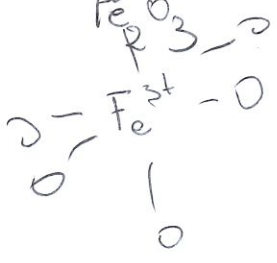
iron accumulation in Alzheimer's disease

Amyloid beta.

mostly ferritin / hemosiderin

↕

magnetite



In-situ EPR Detection of Paramagnetic Intermediates in Water Oxidation Catalysis by a Co-P_i Modified Electrode Surface

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The combination of electrochemistry with different in-situ spectroscopic techniques has the potential to provide valuable information towards understanding the mechanism(s) of electrocatalysts. Here we report an in-situ EPR study of cobalt-based phosphate-containing electrodeposited catalytic materials (CoPi) that can oxidize water. This type of system, owing to intrinsic cost, operation efficiency and ease of manufacture, represents a promising system for future large-scale water splitting applications. Our newly designed cell allows the determination of the paramagnetic species at each applied potential. Concurrently with the appearance of catalytic current at more oxidizing potentials, the initial S=3/2 Co(II) signal disappears and a S=1/2 Co(IV) signal becomes more intense. These results are in good agreement with ex-situ studies by McAlpin *et al.*[1] Multifrequency-multiresonance EPR measurements demonstrate the intermediate contains a protonated ligand (OH?) and has a large interaction with the phosphate buffer. In addition, the EPR spectro-electrochemical cell has been used to characterize biological samples. The hydrogenase enzyme can be immobilized on an electrode surface using a redox hydrogel.[2] Such system allows accurate redox control and the reduction of the enzyme from the oxidized states (Ni-A/Ni-B) to the reduced Ni-C state could be followed by EPR.

This setup could be used to study other relevant electrocatalytic systems under turnover conditions and gain valuable information on redox intermediates to understand the catalytic mechanism.

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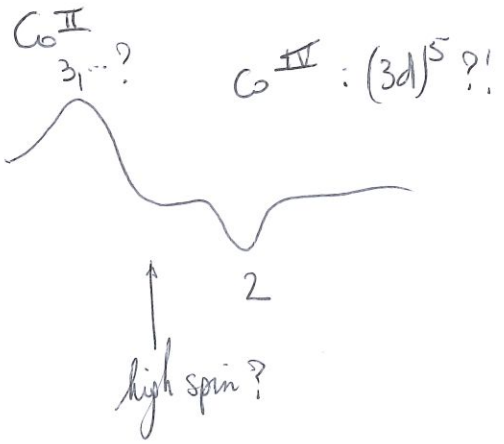

Investigating luminescence-based radiation dosimeters using EPR methods

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Solid state luminescence dosimetry developed considerably since the 1960s and is used for a wide range of applications, such as personnel, medical and environmental ionizing radiation dose assessment. Thermoluminescence (TL), Optically Stimulated Luminescence (OSL) and Radiophotoluminescence (RPL)-based methods and detectors all have their typical properties (sensitivity, dimensions, linearity, energy response, …) making them suited for specific purposes[1-3].

EPR is also known as a reliable dosimetric technique, using e.g. alanine, tooth enamel and sucrose for retrospective/accident dosimetry, detection of irradiated food, etc. Although EPR can, in general, not compete with the luminescence methods mentioned above, it can provide complementary insight into the defects and processes leading to luminescence.
In the present study we discuss results on two classes of materials, i.e. LiF:Mg,Ti /LiF:Mg,Cu,P and Al_2O_3:C /Al_2O_3:Mg,C relevant for TL and OSL/RPL respectively. All samples were measured in X- and Q-band both before and after X-ray irradiation. In powder samples of LiF:Mg,Cu,P a strong signal was detected (Fig. 1) that did not show (X)-radiation sensitivity. Upon irradiation also no other signals could be detected. The signal shown below or a very similar signal has been tentatively identified in literature[4] as related to Cu^{2+}, although its characteristics are not evidently compatible with such an assignment. Therefore further investigation appeared necessary and the first ENDOR experiments look promising. The Al_2O_3-based and LiF:Mg,Ti powder samples have no significant EPR signal present before irradiation, but do reveal a signal after irradiation. The present status of the research will be discussed.

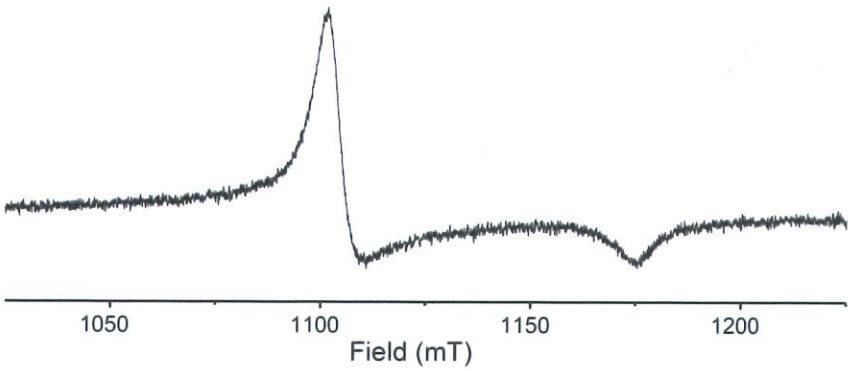

Figure 1: Q-band spectrum of LiF:Mg,Cu,P powder before irradiation.

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Efficient cross-effect DNP for MAS NMR with trityl-nitroxide biradicals

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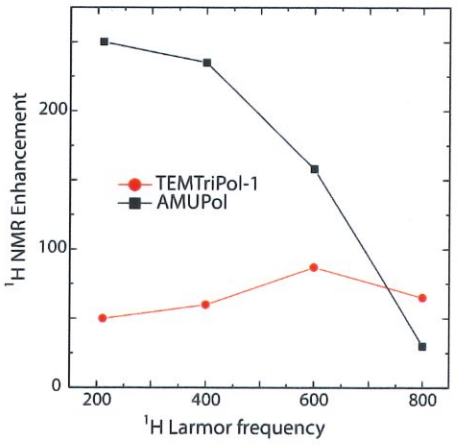
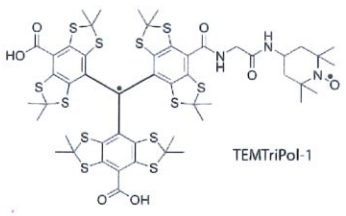
Dynamic nuclear polarization (DNP) is rapidly maturing as a method to enhance the sensitivity of nuclear magnetic resonance (NMR) experiments. In DNP, paramagnetic species are introduced into the NMR sample, often in the form of stable radicals or "polarizing agents". Via microwave irradiation at or near the electron Larmor frequency, the electron spin polarization is transferred to the nuclei, thereby enhancing the nuclear spin polarization and hence the NMR signal intensity. If the DNP and NMR experimens are performed at the same magnetic field and temperature, a maximum signal enhancement of γ_e/γ_{1H} =658 can be achieved for protons, where γ_e and γ_{1H} are the gyromagnetic ratios of electrons and protons, respectively.

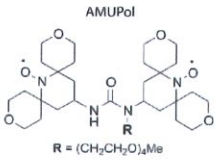
The cross-effect (CE) form of DNP is currently most successfully applied in magic-angle spinning (MAS) NMR structural studies. For CE DNP, biradicals, which are typically bis-nitroxides, are the most efficient polarizing agents. The chemical structure of these bis-nitroxides determines the NMR signal enhancement. The bis-nitroxide polarizing agent for CE DNP that currently gives the highest CE DNP enhancements is AMUPol (see Figure 1).

We investigated the performance of trityl-nitroxide biradicals, called "TEMTriPols", as polarizing agents for CE DNP. Compared to bis-nitroxides, TEMTriPols give higher enhancements at high magnetic fields (see Figure 1),[1] and, in addition, do not suffer from the detrimental depolarization effect.[2,3] In my talk I will describe what makes the TEMTriPols so efficient and discuss how the method of CE DNP can be improved even further.

Figure 1: Field dependence of the CE DNP enhancement for the biradical polarizing agents AMUPol and TEMTriPol-1. All samples contained 10 mM biradical and 1 M ^{13}C-urea in a frozen glassy matrix of d_8-glycerol:D_2O:H_2O 60:30:10 v:v:v (a.k.a. „DNP juice"). Enhancements are determined by comparing the signal strengths of ^{1}H-^{13}C cross-polarization MAS NMR experiments with and without microwave irradiation.







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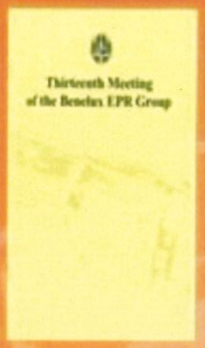
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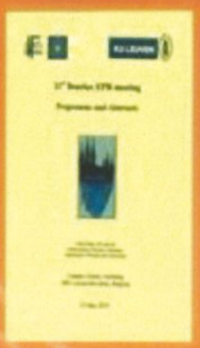
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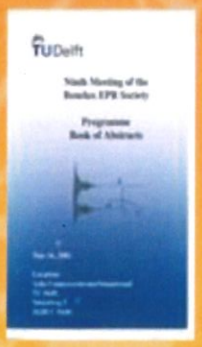
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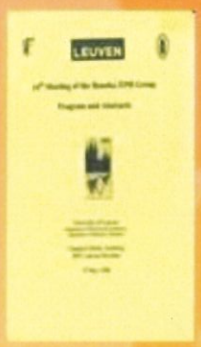
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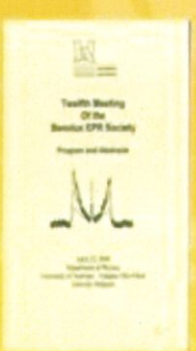
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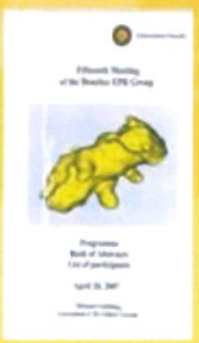
Fifteenth Meeting


Eighth Meeting
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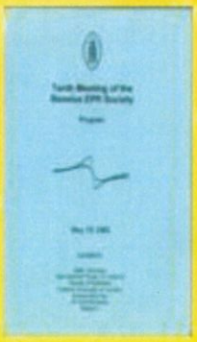
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