The History of Hungarian Cyclodextrin Research

Lajos Szente

Budapest

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Outline

- **The beginning: seminal role of Prof. Szejtli**
- **Early years in Chinoin: team building and networking**
- **First significant results: protection (patents) and dissemination (publication)**
- **The road from CHINOIN to CycloLab**
- **CycloLab short story**

„in the beginning…”

there was a dedicated person

(J. Szejtli), a carbohydrate chemist and

his vision:

a starch derivative can be a multifunctional auxiliary agent of real industrial significance

Who was József Szejtli ?

(a short introduction for new generation cyclodextrin researchers)

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Higly motivated scholar:

Photo: in 1954, in the chemistry lab of the University

Graduated in 1956, as a chemical engineer

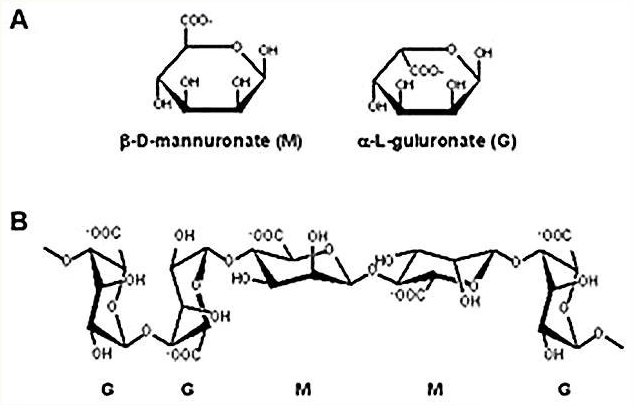
THE MECHANISM OF STARCH–IODINE REACTION

I. Critical investigation of actual viewpoints

J. HOLLÓ and J. SZEJTLI

One of his early, highly cited papers in 1957

Hungary seemed too small: Szejtli on board facing to Trondheim



invited by Royal Norvegian Academy

Note: crossing iron curtain in 1963 was not easy!

Potsdam, East Germany (1965-66) amylose helix and the host guest complexes: a step closer to cyclodextrins!

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Bundesarchiv, Bild 183-S99838
Foto: Rudolph | 5. August 1950

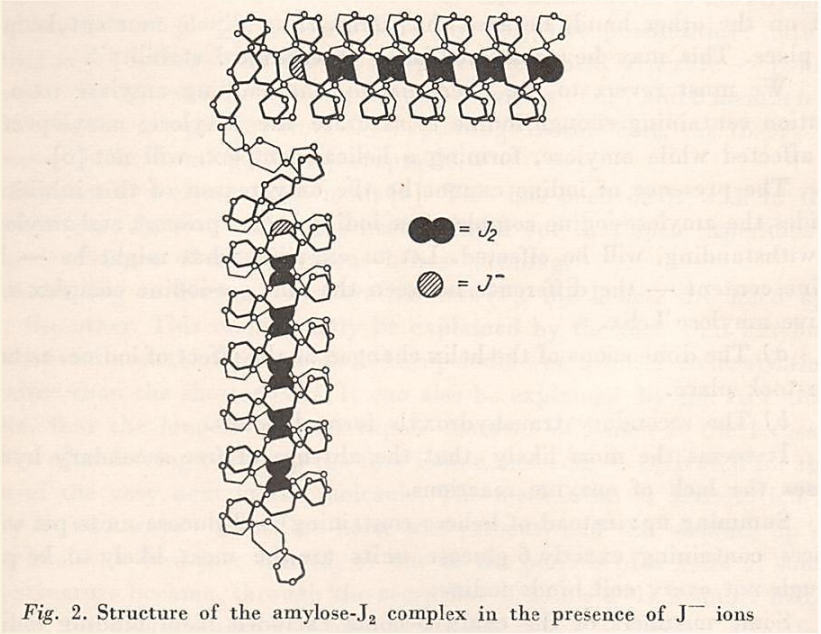

Fig. 2. Structure of the amylose-J_2 complex in the presence of J^- ions

J. Szejtli†, M. Richter and S. Augustat Molecular configuration of amylose and its complexes in aqueous solution, Biopolymers, Vol. 5. 5–16 pp. 1967.

Last citation in 2012!

From the foggy, cold East Germany to the Sunny Cuba (1967-70)

UNESCO delegate science/technology
advisor of the Cuban Government

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Szejtli presents his data to the Commandante in April 1970

(curtesy of Szejtli' family)

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No heavy arguments: Commandante was very convincing (note the big gun Fidel carries during scientific discussion)

Szejtli returns to Hungary and takes position as head of Biochemical Lab of Chinoin

Initiates systematic CD research and starts building team:

young, dedicated „victims” for a risky but challenging journey

Szejtli was a fortunate combination of engineer, scientist and entrepeneur

motto that describes the situation of CD technology in 1973-1975:

„ we have a lot of solutions,

looking for problems to solve”

This is how we sarted our „microchemistry”: only few grams of beta-CD available in 1975

S-3503: beta-cyclodextrin Sigma

At that time it was celled Schardinger-β-dextrin and supplied as a cyclohexane complex

(CycloLab archive)

Szejtli starts networking: connets universities in Hungary

Szejtli and his Hungatrian pioneer collaborators (1975-1985)

- **Enzymology/biotechnology**: Technical University (László, Bánky, Hoschke,)
- **Carbohydrate chemistry:** Debrecen (Lipták,A.)
- **Complex equlibria:** ELTE, (Körös, Barcza, Buvári)
- **Technology/CD-polymers:** ELTE (Tüdős, Zsadon)
- **Biology/ADME:** Joliot-Curie Radiobiology Inst. **First 14Clabeled CD in glucose core!!! made in Hungary in 1979.**

Challenging and rocky road to the radiolabeled BCD:

14C **CaCO3**→14C **CO2** →Tobacco leaf **photosynthesis** →14C **Starch** → CTG-ase enzyme **conversion** → isolation by **complex formation** → 14C **beta-cyclodextrin (chemical purity about 90 %!)**

Please, do not ask me about the YIELD!!

Early CD research with *„Homo Ludens”* mentality
(garden of Biochemical Lab of Chinoin)

Hard work and relaxing playtime: Cyclodextrins turned „from toy to tool”

Szejtli connetcs the best scientists around the world

International networking: Szejtli and his pioneer collaborators between 1975-1985

- **UK:** F. Stoddart, E. Davies, J. Pagington
- **France:** J-M. Lehn, D. Duchene,
- **Italy:** B. Casu, F. Carli, Chiesi Brothers
- **Germany:** W. Saenger, F. Müller, Frömming,
- **Japan:** Horikoshi, Komiyama, Osa, Nagai, Uekama, Otagiri,
- **USA:** Pitha, J.

International correspondence in 4 languages

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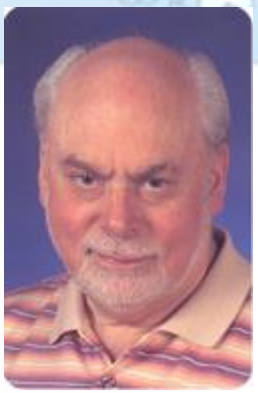
Dear Professor Stoddart,

Thank you very much for sending me your manuscript on the Transition Metal Complexes Cyclodextrins (Submitted to the Rec. Trav. Chim. Pays-Bas). I enjoyed much also your lecture at the Munich Symposium, but because of the very crowded program I could not "digest" all details. Now, spending my holydays at the Balaton-lake finally had enough time to read this excellent work with due attention. I should like to mention another specific type of CD-crown ether metal ion combinations. Some years ago we prepared a crown ether-appended-CD, which very effectively complexed the Na-p-nitrophenolate:

I am waiting with great interest the paper on the modified CD-based piezoelectric chemical sensors for benzene vapour. My laboratory's activity is focused on the industrial aspects of cyclodextrins, not only pharmaceutical applications, but virtually any potential uses of CDs. Please find enclosed our new brochure on CHINOIN's CD-products.

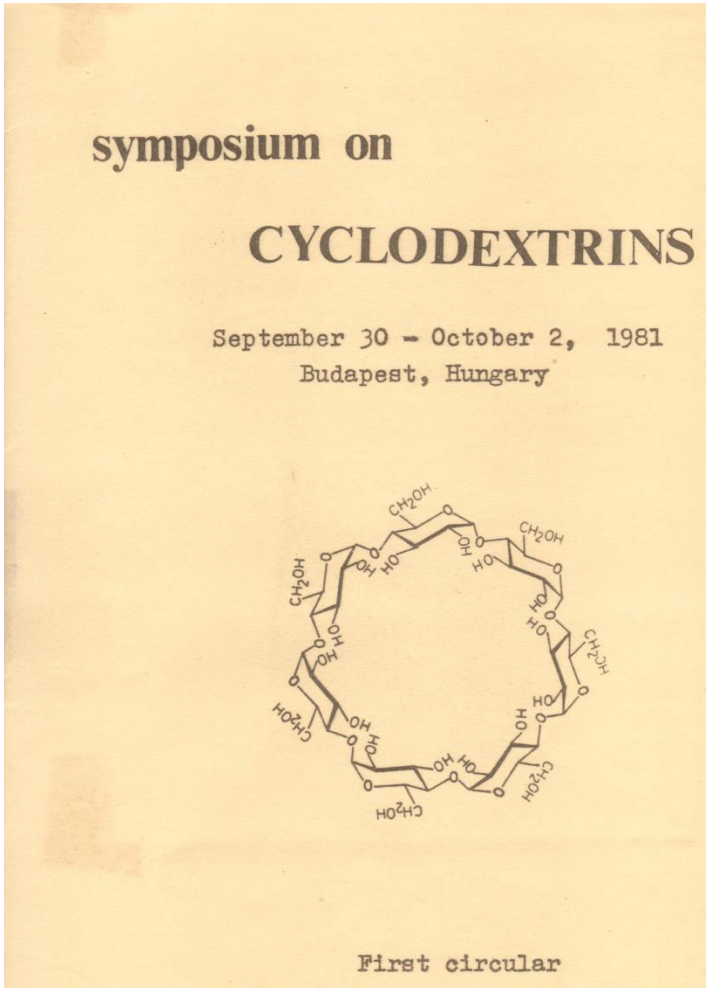


Sir Fraser Stoddart

Szejtli's letter to Stoddart about the assumed structure and utility of a CD-crown ther combination, in 1980

Besides annual domestic CD meetings,

Szejtli is organizes an International CD Symposium



1st circular and site of CD symposium: watch the shape of the macrocyclic Hotel building!

The „English-Connection”
Dissemination of knowledge: Cyclodextrin News

In November 1985 Szejtli and J. Pagington met in Budapest

co-editors of CD-News

„.. beginning of a beautiful friendship”

Japanese relationships and competition for over 10 years in manufacturing and application of CDs

Horikoshi (CTG-ase expert) and Szejtli in Budapest in 1981

Getting internationally acknowledged

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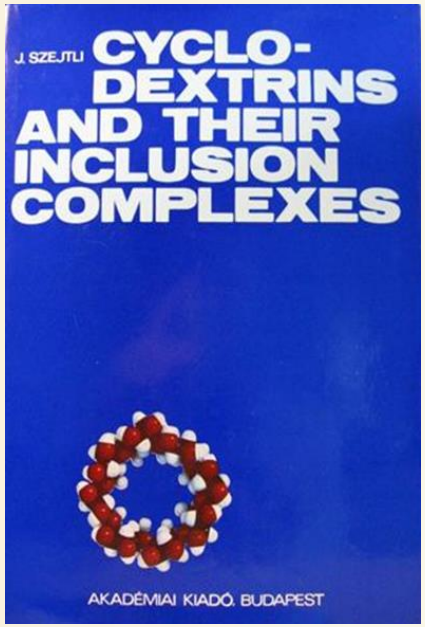
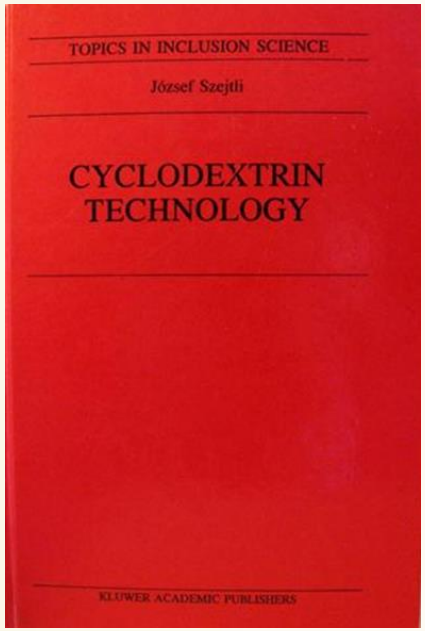
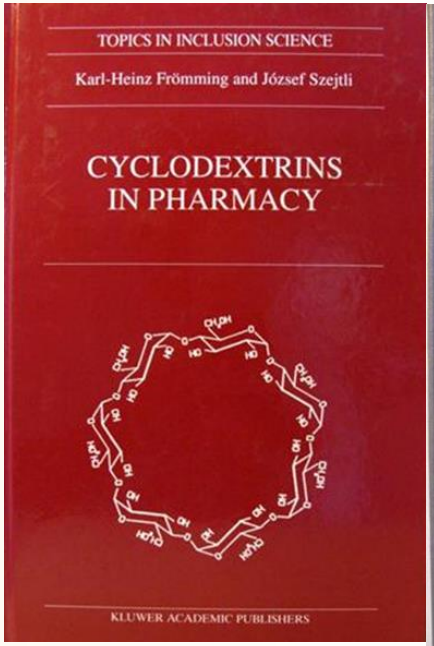


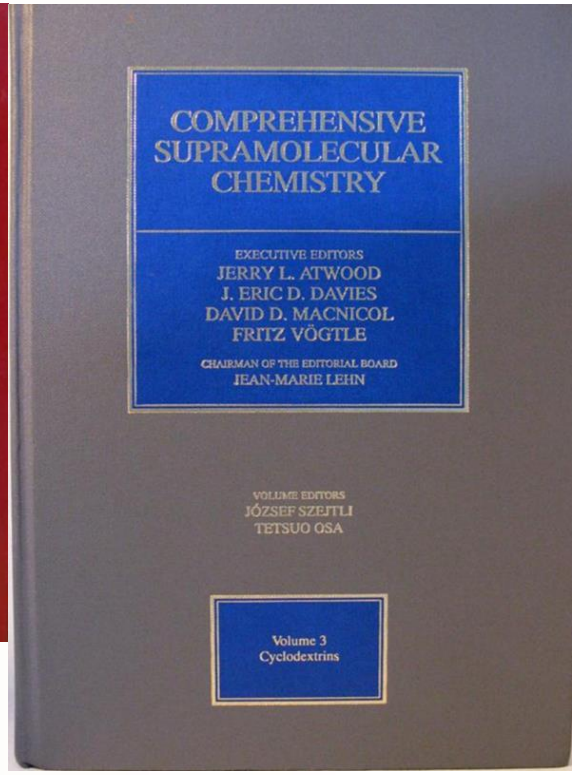
1981



1988



1990



1996

„If you want to be an expert, write a book, not just a review" (Szejtli, J.)

The road from Chinoin to CycloLab (1973-1989)

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- 1973. **Szejtli initiates a comprehensive CD R&D**
- 1975. **Szejtli's concept takes shape (products and processes)**
- 1979. **Chinoin optimizes 100 kg/batch scale manufactruring of betaCD, in 25 kg/batch alfaCD and gammaCD**
- 1973-1980 **all significant IP protection in place, great body of seminal publications, books, etc.**
- 1977-85 **12 project proposals with technology documentations**
- 1982. ***lege artis* safety/tox. studies for α-, β- and γCD in place**
- 1985. **Szejtli completes manufacturing of HPBCD and DIMEB (first DMF for HPBCD to Janssen 50 kg/batch scale)**
- 1987. ***Szejtli's group becomes independent unit within Chinoin***
- **1989. Cyclolab Ltd is established**

CycloLab is a spin-off of Chinoin Pharm. Chem. Works, *Ltd.*

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the team

- 15 qualified scientists
  - 13 PhD
  - 2 MBAs
  - By profession:
    - chemists
    - chemical engineers
    - biologists
    - pharmacists
- 15 qualified technicians

the resources

- 2,000 m^2 own facility
  - 2 galenic/technology labs
  - 3 analytical labs (GC, HPLC, CZE)
  - 3 synthetic chemistry labs
  - 150 m^2 cGMP approved clean room („ C area”)
  - cGMP-compliant plant with an annual capacity of 5 Mt

Quality systems:

- ***ISO 9001:2000***
- ***cGMP***

CYCLOLAB®: The world's largest and single all-round Cyclodextrin Laboratory

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Experience

Over 35-years experience in all fields of Cyclodextrin-technology

- ~ 400 technical/scientific papers
- ~ 10,000 citations to CYCLOLAB's publications
- ~ 650 technical reports to our customers
- ~ 150 different cyclodextrin derivatives produced on lab scale
- ~ 60 patents/applications
- ~ contribution in ~ 30 products on the market (3 of them drugs)
- Drug Master Files (Type IV.) and CTD

The world's most comprehensive and up to date CD literature database (over 63.000 entries)

Expertise & Technology

Nano-sizing, crystal engineering

Nano-encapsulation, formulation

Solubilisation, stabilisation

Controlled release, delivery systems, targeting

CD-related analytical services

cGMP-Manufacturing

CycloLab as a start up (1989-1993)

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- Focus on services for pharmaceutical R&D (sponsors Janssen, Chiesi)
- Results:
- Encapsin™ 2-HPBCD excipient
- a Brexin™ piroxicam/betaCD complex based product and further 10-year long collaboration

Non-Pharmaceutical Services (1989-1995)

Our major customers

- **Nestlé:** instant food and beverage, deep-frozen ready foods for micowave, CD-assisted flavour/colorant protection
- **Procter and Gamble:** laundry wasing powder, deodorizers, controlled-releaase perfumes (Bounce® and Febreeze®)
- **Beiersdorf:** CD-enabled cosmetics (Nivea Eucerin® brand, Q10, ceramid, retinol)

Examples
Of the
Pharmaceutical Developments
at CycloLab
(1989-1993)

First Customer: Chiesi Pharmaceutici

First CD-based pharmaceutical product where CycloLab assisted in early phase development (already generic!)

German connections (Schwarz Pharma)
CycloLab assists in CD-stabilised PG development

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Life cycle mangement of Voltaren Ophthalmic

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Development of a HP gammaCD enabled Diclofenac Eye Drop

Voltaren Ophtha CD

From test tube to the market in 4 years

The hard times of CycloLab (2004-2006)

Outer factors affecting negatively CycloLab's business

- Non-bioequivalence nature of CD-enabled ORAL drug formulations (generic firms disappointed)
- Turbulent IP situations around two parenteral excipients HPBCD, SBEBCD (unique patenting patterns in USA and in Europe)
- Mergers of previous clients (Hexal-SANDOZ-Novartis, Genentech-Roche etc.) the running projects slow down or even discontinue
- A number of „amateur studies" destroy reputation of CD- enabled products and technologies
- A number of vendor audits and due diligency processes may affect negatively the business: information fishing, technological intelligence concerns (Am I too paranoid?)

Intern factors affecting negatively CycloLab's business

The Cyclodextrin Company

1. Unique stakeholders structure

- 15! small shares for a little company with few major shareholders
- Sometimes difficult to make decision

2. Investors pursue CycloLab to grow big: number of due diligencies, investing offers

3. „*One-man-show*" character of the company

- Sudden death of founder hits the business

A long dilemma: Should CycloLab remain SME or grow big?

The Cyclodextrin Company

We decided to remain small because:

- **SME service provider firm reacts promptly, efficiently, is smart-swift, quickly deciding** (attributes that the Sponsor firms appreciate)

- **Acquisitions, mergers with big firms would have probably resulted in dilution of CycloLab's attributes our merit, our brand, our legacy, creativity, quick decision nature, ….. even CycloLab could have disappeared** *(„to be or not to be?")*

- **We shall never know what could have happened if we had completed the acquisition, maybe we were very rich today, who knows ?**

Bright future of CycloLab (from 2006)

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Reasons for being optimistic

- **Increasing sales in fine chemical business (focusing and investing in offering unique derivatives, chiral recognition agents, columns etc..) Sigma-Aldrich, Acros-Thermos Fisher sell CycloLab' cyclodextrins, too**
- **Serum-free culture media additives (water soluble lipids, Sigma, Invitrogen)**
- **Significant service provided in Sugammadex development** (multiyear Organon cooperation)
- **Opening toward the applied nano-science**
- **cGMPcompliant manufacturing of a generic excipient, a chemiaclly modified cyclodextrin on large scale**

New era of cyclodextrin science and technology: an empty nanocavity acts as a drug active!

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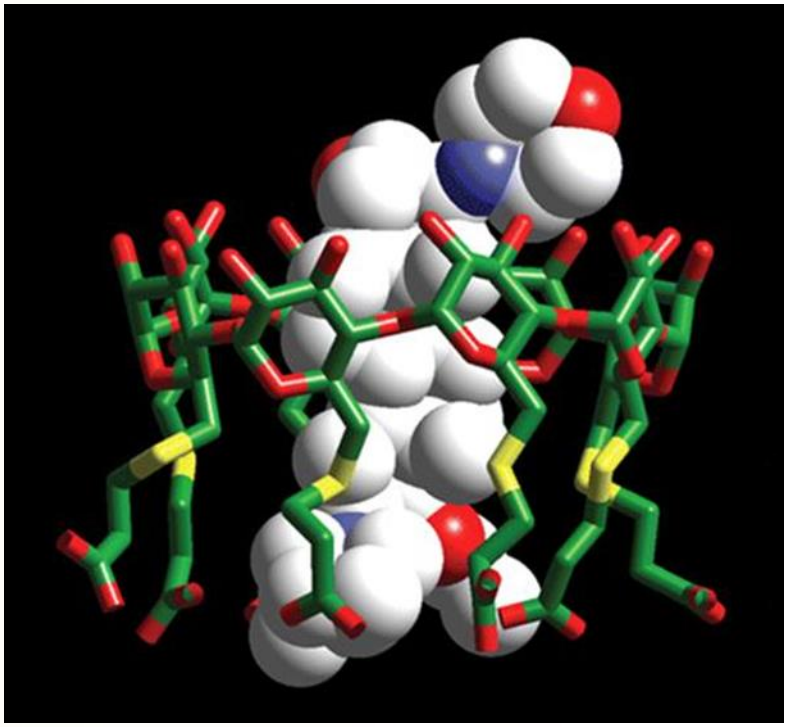
Probably the greatest intellectual challenge for us: to be a part of selection and chemical tuning of an „artificial receptor”

Commercial sucess: the product has great turnover

Akzo-Organon → Schering Plough → Merck



Scientific value: on the cover of Angewandte Chemie Intl. Ed. 2002

(Malcolm-Campbell price to the scientists)

CycloLab as a pharmaceutical manufacturer (2008-2010)

The Cyclodextrin Company

cGMP- manufacturing of *Dexolve™*

(USP Betadex Sulfobutyl Ether Sodium)

-**Working with a heavily patented compound → CycloLab patented a proprietary synthesis**

-**Technology development, optimization, validation of a composite isomeric mixture!** (never had access to originator's product to be copied!)

-**Technology scale up from lab scale to 50 kg/batch scale** (Type IV DMF filed to US-FDA and Health Canda)

- **Investing in the manufacturing area: regulatory approval, vendors-audited site**
- **Annual capacity 5-6 metric tons**
- **Relevant supply agreements with major pharmaceutical companies**
- **CycloLab' revenue streamline dramatically changes**

This was possible only becasue CycloLab has a well organized

GREAT TEAM of:

- Creative synthetic chemists
- Precise analytical chemists
- Pragmatic chemical engineers
- Reliable technologists
- Accurate QA/QC experts

cGMP–compliant Spray-Drying unit with about 5 metric tons annual capacity

The entire construction of the Manufacturing site was financed by CycloLab' money earned from R. and D. (no investors)

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Remembering József Szejtli

In 2013, CycloLab established the Szejtli award with the aim to :

- **preserve Szejtli's legacy and his ground-breaking achievements in the area of Cyclodextrin technology**
- **encourage young scientists working on cyclodextrin**

- **The award is presented bi-annually during the International Cyclodextrin Symposia to a young cyclodextrin scientist who demonstrates outstanding results in the field of cyclodextrins**

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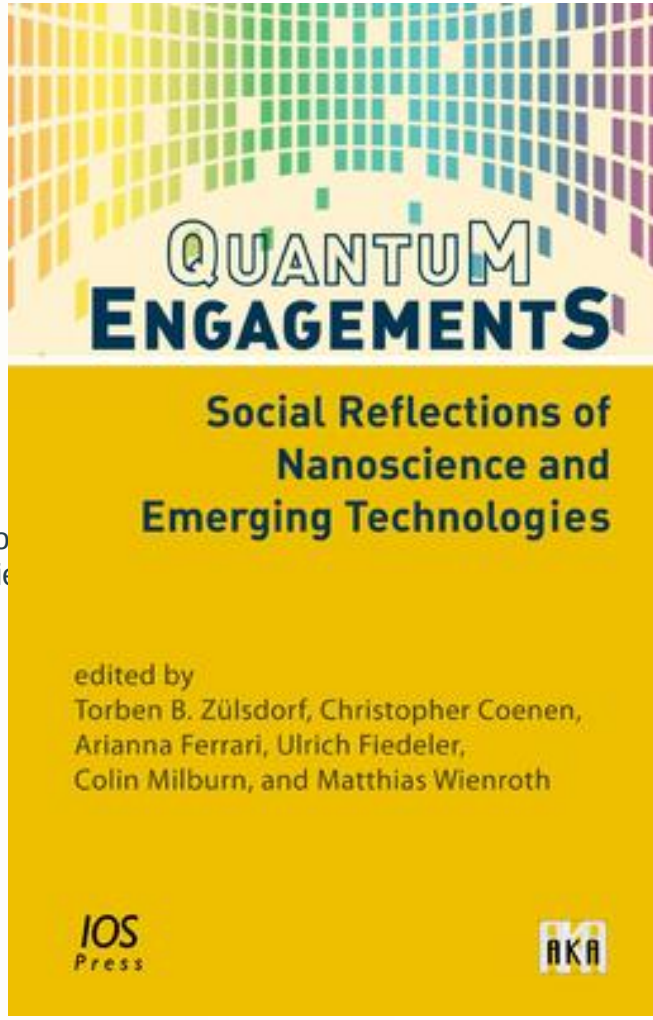
In 2011, an assay uses Szejtli's personal motivation as an example on how trust and dedication affect applied science

How to Trust a Molecule? The Case of Cyclodextrins Entering the Nanorealm

Sacha LOEVE[a,1] and Mickaël NORMAND[b]
[a]*Post-doctoral fellow in Philosophy,*
Centre d'Etude des Techniques, des COnnaissances et des PRAtiques, CETCOPRA,
University of Paris 1 Panthéon – Sorbonne, France
(sacha.loeve@univ-paris1.fr)
[b]*Ph.D. Student in Chemistry,*
Catalysis and Organometallics, J.-F.Carpentier's team, UMR CNRS 6226,
University of Rennes, France

(mickael.normand@univ-rennes1.fr)
"Quantum Engagements. Social Reflections of Nanoscience and Emerging Technologies, To
B. Zülsdorf, Christopher Coenen, Ulrich Fiedeler, Arianna Ferrari, Colin Milburn, Matthias Wie
195-216"
DOI : 10.1607509539



Many thanks are due to:

- **Pioneer collaborators involved in early Hungarian CD research at Universities**
- **All former colleagues at Chinoin**
- **My current colleagues in the CycloLab' team for their excellent contribution, perseverance and tireless dedication**

Thank you all for your attention!