

# Hydrolytic kinetic resolution of racemic glycidyl esters on a polymer supported chiral salen cobalt(III) complex

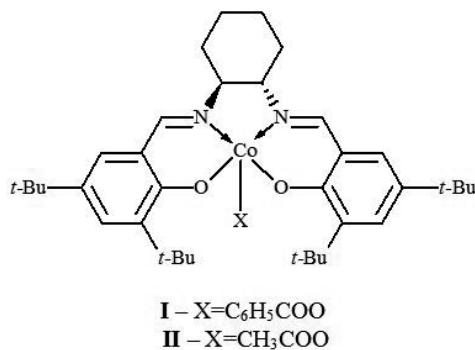
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## 1. Introduction

The hydrolytic kinetic resolution (HKR) of racemic epoxides occurring in the presence of chiral salen cobalt(III) complex I (Scheme 1) has been discovered accidentally by Jacobsen and coworkers during the studies of the catalytic activity of this complex in the reaction of epoxides with benzoic acid [1]. The presence of a diol with an enantiomeric excess above 98% was observed besides the expected products (a chiral epoxide and an ethylene glycol monoester) after complete reaction. It was formed as a side product in the reaction of hydration of one of the epoxide isomers occurring under influence of the water molecules introduced as an impurity to the reaction mixture. This finding turned the attention of Jacobsen's group to water as the best attractive reactant for the kinetic resolution of racemic epoxides. Simultaneous producing two valuable products (a chiral epoxide and a diol) contributed to the rapid spread of the HKR technology on an industrial scale [2].

The kinetic studies performed in the presence complex II (Scheme 1) led Jacobsen to a conclusion that cooperative acting of two catalytic moieties of the complex plays a key role in epoxide hydration. One of them is responsible for epoxide activation and the second delivers OH anions [3]. The privileged bimolecular path of the reaction of epoxide hydration has inspired Jacobsen and other researchers to undertake the attempts to improve the activity and stability of salen catalysts by developing the systems which will facilitate the mutual contact between two catalytic moieties. Dimeric [4, 5] and oligomeric [6, 7] catalytic systems, and those with (salen)Co(III) complexes immobilized on organic [8, 9] and inorganic [10] supports were developed as a result. The new catalysts were characterized by much higher activity than that observed for complex II.



Scheme 1. SalenCo(III) complexes

The studies performed in our group showed that the very active and stable catalysts for the HKR of *rac*-epichlorohydrin can be obtained as a result of immobilization of chiral salen cobalt(III) complexes on the appropriately designed low cross-linked polymer gels bearing hydroxyl groups. The gels were synthesized by suspension polymerization of mixtures of 2-hydroxyethyl methacrylate with styrene and divinylbenzene or different dimethacrylates as cross-linking monomers [11]. Herein, we present the results of the HKR of racemic glycidyl esters on the polymer supported salenCo(III) complex catalyst developed in our laboratory.

## 2. Experimental part

### 2.1 Materials

Racemic glycidyl acetate, propionate and butyrate, which were used as models in the HKR process studies were obtained according to the two-stage procedure developed in our laboratory and described previously in Ref. 12 [12]. The catalyst with a chiral (salen)Co(III) complex (0.314 mmol Co/g) immobilized on a polymer gel was synthesized as described in Ref. 11 [11]. The starting polymer support was synthesized by suspension polymerization of the mixture of 2-hydroxyethyl methacrylate (20 mol-%), styrene (77 mol-%) and diethylene glycol dimethacrylate (3 mol-%).

### 2.2 General procedure for the HKR of racemic glycidyl esters

All catalytic tests were performed in 5 ml vials equipped with magnetic bars and Teflon screw caps. The vials were charged with the polymer catalyst (0.5 mol-% Co), a racemic glycidyl ester (acetate, propionate or butyrate) and an organic solvent (methyl-*tert*-butyl ether, methylene chloride, tetrahydrofuran or acetonitrile) in 1/1 v/v ratio. Cyclohexanol (20  $\mu$ l), as an inner standard, and water (0.7 eq.) were next added to the reaction mixture as well. The vials were sealed and placed into a plate of a magnetic stirrer. The mixtures were gently mixed at 25°C. The samples for analysis (4  $\mu$ l) were periodically removed from the mixtures by means micropipettes. They were diluted with anhydrous diethyl ether (2 ml) and passed through plugs of silica gel to remove water residuals. The conversion of glycidyl esters and enantiomeric excess of *S*-isomers were determined using a 7980A Agilent gas chromatograph equipped with a split-splitless injector, a FID detector, and a Chiraldex G-TA column (Gamma Cyclodextrin Trifluoroacetyl, 20 m x 0.25 mm x 0.12  $\mu$ m).

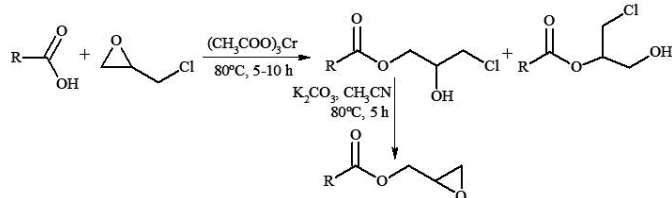
### 2.3 Spectral analysis

FTIR spectra were recorded using a FTIR Nicolet iN10 MX microscope equipped with a FTIR micro-compression diamond cell. Samples for analysis were prepared by flattening several polymer beads between a pair of diamond windows placed in the micro-compression cell.

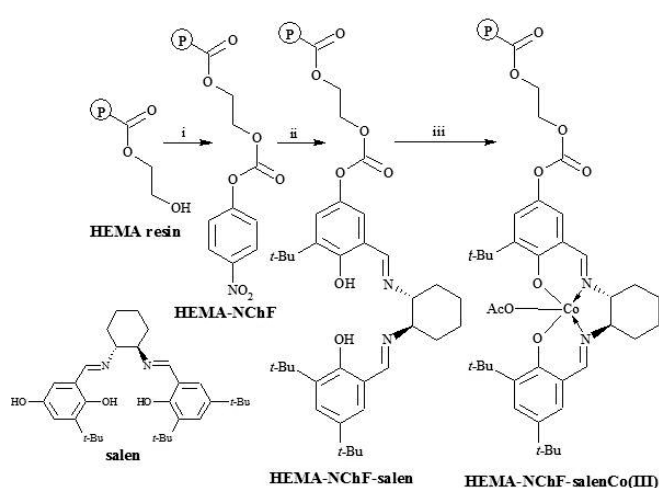
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### 3. Result and discussion

Glycidyl esters are synthesized mainly using the two-stage procedure including the reactions of addition of carboxylic acids to *rac*-epichlorohydrin and dehydrohalogenation of 3-chloro-2-hydroxypropyl carboxylates (Scheme 2). The yield of glycidyl esters depends largely on the selectivity of the first stage of synthesis. Our previous studies showed that a high selectivity and regioselectivity of the addition is achieved in the presence of chromium(III)acetate as a catalyst [13]. Using this catalyst at the first stage and the procedure of dehydrohalogenation described in Ref. 12 [12], at the second we synthesized racemic glycidyl esters of acetic, propionic and butyric acids. The esters were then used as models to study the HKR on a polymer supported salenCo(III) catalyst. The catalyst was prepared using the previously developed multi-stage procedure, including salen ligand synthesis, modification of the **HEMA resin** under the influence of 4-nitrophenyl chlorformate (**HEMA-NChF**), salen ligand immobilization (**HEMA-NChF-salen**), cobalt(II) ion coordination and their oxidation to a cobalt(III) form (**HEMA-NChF-salenCo(III)**) (Scheme 3).



Scheme 2. Synthesis of glycidyl esters



Scheme 3. Salen catalyst synthesis

i – 10 eq. 4-nitrophenyl chlorformate, 5 eq.  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 24 h, room temp., ii – 2 eq. salen, 1 eq. 4-dimethylaminopyridine (DMAP), 2 eq. *N,N*-diisopropylethylamine (DIPEA), iii – 1: ( $\text{CH}_3\text{COO}$ ) $_2\text{Co}$  4  $\text{H}_2\text{O}$ , 2:  $\text{CH}_2\text{Cl}_2$ : $\text{CH}_3\text{OH}$  (3:1 v:v), air, acetic acid (2-4 eq.), 1 h, 25°C.

A course of the multi-stage transformation of the **HEMA resin** to obtain **HEMA-NChF-salenCo(III)** was monitored by recording the FTIR spectra of polymeric beads using a FTIR microscope. This technique is commonly used for analysis of chemical transformations in solid phase organic synthesis [14] and can be regarded as a counterpart of TLC chromatography used in classical organic synthesis. FTIR microscopy makes possible of registration of changes in the chemical structure of polymer particles based only on the spectrum of a single polymer bead (Fig. 1).

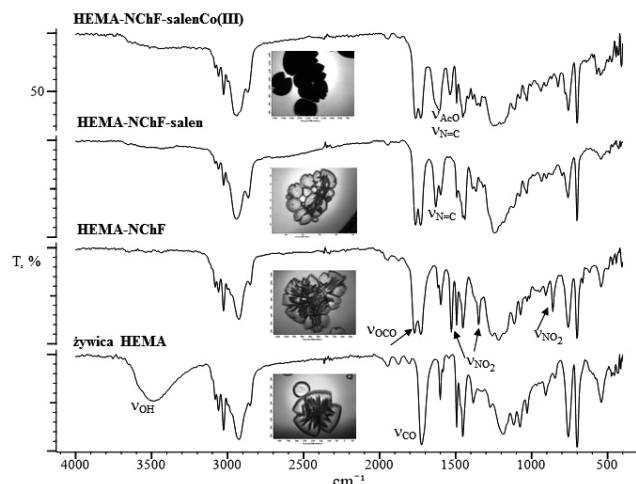
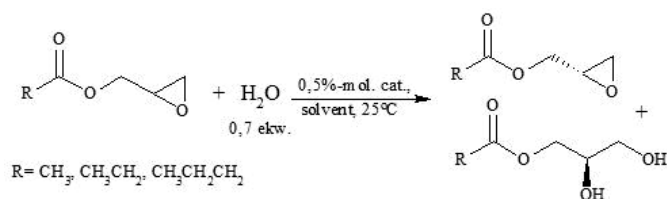


Fig. 1. Comparison of FTIR spectra of the **HEMA resin** and products of their modification

Immobilizing 4-nitrophenyl carbonate units resulted in a disappearance of the broad absorption band at 3500  $\text{cm}^{-1}$  characteristic of OH groups in the **HEMA resin** and an appearance of the new band at 1730  $\text{cm}^{-1}$  (C=O in carbonate units) and 1530, 1350, 860  $\text{cm}^{-1}$  ( $\text{NO}_2$  group stretches). Substitution of 4-nitrophenoxyl group by the OH-substituted salen ligand resulted in a disappearance of the bands corresponding to  $\text{NO}_2$  groups and an appearance of the band at 1630  $\text{cm}^{-1}$  (C=N group stretching vibration). These findings confirm the covalent attaching of salen ligand moieties on the polymer gel. Changes in absorption in the range of 1630–1605  $\text{cm}^{-1}$  observed as a result of cobalt(II) ion immobilization and their oxidation to a Co(III) form confirm the involvement of the C=N groups in complexing these ions (spectrum d). An additional absorption bands found in the spectra of the final complex at 1539  $\text{cm}^{-1}$  indicates the presence of acetate counter-ions.

The catalytic studies performed in this work were aimed the exploration of the usefulness of **HEMA-NChF-salenCo(III)** in the HKR process of another group of epoxy compounds – racemic glycidyl esters.

A gas chromatography method was applied for monitoring the HKR progress. Three capillary columns with two different chiral stationary phases recommended for analysis of epoxide enantiomers were at our disposal: Chiraldex G-TA columns (20 m x 0,25 mm x 0,12  $\mu\text{m}$  and 40 m x 0,25 mm x 0,12  $\mu\text{m}$ ) and a Cyclodextrin 3P column (30 m x 250  $\mu\text{m}$  x 0,12  $\mu\text{m}$ ). Attempts of chromatographic resolution of racemates of the glycidyl esters of linear C2–C10 carboxylic acids were performed. The resolution was achieved only for acetate, propionate and butyrate, using the Chiraldex G-TA columns. Thus, these three esters were selected as models for studding the HKR process (Scheme 4) at 25°C, using 0.7 eq. water in relation to the esters. Before the catalyst and water were added, the racemic esters were diluted in a volume ratio of 1/1 with acetonitrile, methylene chloride, methyl-tert-butyl ether or tetrahydrofuran.



Scheme 4. HKR of racemic glycidyl esters

An influence of the solvent on the HKR were studied using racemic glycidyl acetate as a model (Fig. 2). It was found that the highest resolution rate was achieved using methylene chloride as

a diluent. The HKR went slightly slower in the presence of THF. These solvents, as well as methyl-*tert*-butyl ether, for which the resolution rate was also satisfactory, swelled the beads of the polymeric catalyst well. It facilitated an access of the reactants to the salen complexes anchored to the polymeric gel and their activation. The slowest rate of the HKR was found when acetonitrile was used for diluting the ester. This polar solvent is characterized by the least affinity to the polymer catalyst used.

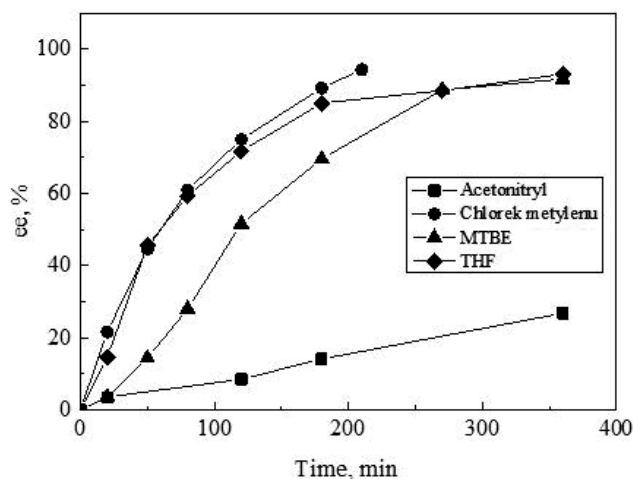


Fig. 2. An effect of the solvent nature on the rate of the HKR of racemic glycidyl acetate

Comparing the kinetic curves obtained for the HKR of individual glycidyl esters it was found that the rate of the resolution of racemic substrates was similar. Thus, it is rather difficult to conclude that the HKR rate depends in a specific way on the length of acid radicals. For each of the esters, an enantiomeric excess of about 96% was obtained within 210–360 minutes.

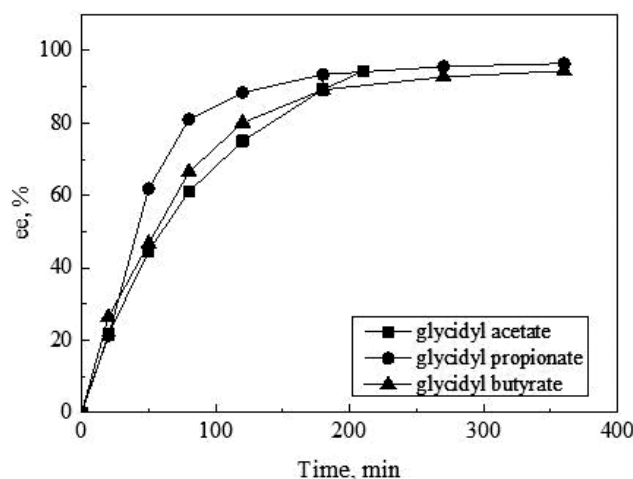


Fig. 3. The rate of HKR of racemic glycidyl esters

## Summary

The possibility of the use of the chiral salen cobalt(III) complex immobilized on the styrene-methacrylate gel in the HKR of racemic glycidyl acetate, propionate and butyrate were studied. The solvents which were compatible with the polymeric catalyst improved its activity. An essential influence of the length of an acid radical on the HKR rate was not detected. *S*-glycidyl esters with about 96% ee could be obtained in the presence of the polymer supported catalyst bearing *R,R*-salen cobalt(III) complexes.

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### Odpowiedzialność społeczna Grupy ADAMED nagrodzona

Odpowiedzialne społecznie prowadzenie biznesu (CSR) jest od wielu lat wpisane działalność Grupy ADAMED. Z programami edukacyjnymi i zdrowotnymi organizacja dociera każdego roku do coraz większej liczby osób, a sposób ich realizacji i przestrzegane standardy zdobywają uznanie interesariuszy. Starania Grupy ADAMED zauważają także niezależni eksperci - w tym roku firma została laureatem Białego Listka CSR Polityki oraz zajęła drugie miejsce na Liście Firm Odpowiedzialnych Społecznie. (kk)

(<http://adamed.com.pl/>, 31.05.2016)

### Dziesięcioro naukowców nagrodzonych w Innovators Under 35

Konkurs „Innovators Under 35” organizuje „MIT Technology Review” – najstarszy magazyn poświęcony technice, którego wydawcą jest renomowany Massachusetts Institute of Technology. Wybierani są w nim liderzy innowacji, którzy nie ukończyli 35. roku życia, a „dzięki swojemu wkładowi w rozwój nowych technologii w nieoczniony sposób przyczyniają się do znalezienia odpowiedzi na wyzwania współczesnej rzeczywistości oraz poprawy życia wielu osób na świecie”. W drugiej polskiej edycji konkursu eksperci wybrali trzy kobiety i siedmiu mężczyzn.

Wśród nagrodzonych znalazła się Marta Krupińska – twórczyni platformy Azimo, umożliwiającej szybkie, łatwe i bezpieczne transfery pieniędzy. Kolejną z nagrodzonych kobiet jest Patrycja Wizińska-Socha, która rozwinęła wszechstronne rozwiązanie telemedyczne – Pregnabit, pozwalające na monitorowanie stanu zdrowia dzieci w łonie matki. Trzecia z laureatek, Katarzyna Kamińska, za pomocą komputerowego modelu TherVira stworzyła nowy rodzaj leków rozmiaru pojedynczych cząstek, które mają na celu walkę z grypą. Kolejny z nagrodzonych, Arkadiusz Stopczyński, zaprojektował Smartphone Brain Scanner – mały i tani system EEG, który za pomocą sygnału telefonii komórkowej wysyła wyniki i pozwala na diagnozowanie epilepsji w trudno dostępnych miejscach. Z kolei Petros Pysillos rozwinął przenośne urządzenie – Matia, które pomaga osobom niewidomym, opisując otaczający ich świat za pomocą słów, muzyki i bodźców stymulujących zmysły. Inne osobiste, podręczne urządzenie MySpiroo stworzył Łukasz Kołtowski. Umożliwia ono zdalne monitorowanie pacjentów cierpiących na przewlekłe choroby układu oddechania, np. astmę. W drugiej polskiej edycji konkursu nagrodzono także Grzegorza Wróblewskiego za technologię, która pozwala tworzyć giętkie i przezroczyste elektrody – przy niskich

kosztach i na dużą skalę. Nowatorskie technologie pomagające w produkcji elektroniki organicznej, urządzeń organicznych i przewodzących polimerów rozwija z kolei Bartłomiej Kołodziejczyk. Kolejny laureat – Krystian Piecko stworzył rozwiązanie DataWalk, oparte na analizie i pozyskiwaniu danych, które ma zapobiec oszustwom i praniu pieniędzy. Wśród laureatów znalazł się także Rafał Flis – autor platformy Social Wolves, promującej postawy obywatelskie, za pomocą której angażuje młodych ludzi do pracy przy projektach społecznych. (kk)

(<http://naukawpolsce.pap.pl/>, 24.06.2016)

### INVENT ARENA 2016 – sukces IChP

W dniach 16–17 czerwca br. Instytut Chemii Przemysłowej uczestniczył w prezentacji wynalazków na Międzynarodowej Wystawie Innowacji Technicznych, Patentów i Wynalazków „INVENT ARENA 2016” w Trzcińcu (Czechy).

Złotym medalem nagrodzono „Sposób usuwania impregnatu z drewna impregnowanego olejami zawierającymi wielopierścieniowe węglowodory aromatyczne”, którego autorami są: dr hab. inż. Robert Brzozowski, prof. IChP, dr inż. Stefan Szarlik z IChP oraz inż. Zbigniew Kołodziej, inż. Wojciech Kołodziej, Michał Kluczek i Piotr Pałucki z Instytutu Urządzeń Ekstrakcyjnych

Srebrny medal otrzymał „Sposób utylizacji ścieków z procesu wytwarzania biodiesla” autorstwa mgr inż. Tadeusza Porębskiego, mgr inż. Sławomira Tomzika, mgr inż. Katarzyny Polarczyk, mgr inż. Dawida Bernego.

Tematy prezentowane były na stoisku Stowarzyszenia Polskich Wynalazców i Racjonalizatorów. (abc)

(<http://www.ichp.pl/> 07. 07. 2016)

### PGE na podium wśród „Liderów Polskiej Gospodarności 2016”

PGE Polska Grupa Energetyczna otrzymała Brązowy Laur w kategorii „Pracodawca 2016 roku” w rankingu „Liderzy Polskiej Gospodarności”. W pierwszej edycji rankingu „Liderzy Polskiej Gospodarności”, organizowanym przez „Gazetę Bankową”, wyróżniono polskich przedsiębiorców, polityków, menedżerów i naukowców, którzy w tym roku przyczynili się do budowania pozytywnego wizerunku polskich spółek i instytucji zarówno w kraju, jak i za granicą. Nagrodę dla PGE, w imieniu prezesa zarządu Henryka Baranowskiego, odebrał wiceprezes zarządu ds. handlu Bolesław Jankowski. Gala wieńcząca konkurs odbyła się 31 maja br. w Domu Dochodowym w Warszawie. (kk)

(<http://www.gkpgpe.pl/>, 06.06.2016)

*Dokończenie na stronie 399*