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Asymmetric Michael Addition and Deracemization of Enolate by Chiral Crown Ether

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Abstract: Crown ethers anellated to glucose units have been used to catalyse the enantioselective Michael addition of methyl phenylacetate to methyl acrylate in high chemical yields in up to 84% enantiomeric excess. A novel CH-acid deracemization has also been discovered and the mechanistic rationale of the asymmetric induction is discussed.The proposed mechanism of the addition was also substantiated by molecular mechanics calculations.

Introduction

Catalytic asymmetric C-C bond formation reactions are of special interest in organic synthesis.[1] The mechanism leading to asymmetric induction in transition states in the case of asymmetric reactions catalysed by chiral crown ether complexes is not well understood. Many optically active crown ethers have been synthesized, of which only a few have been applied as catalysts in asymmetric reactions,[2a-j] there is still a need for collecting further data for a better understanding of the mechanism of the chiral catalysis in these processes.

In this paper, in the Michael addition section we describe our contribution to the asymmetric carbon-carbon bond-forming reaction in the Michael addition of methyl phenylacetate (**1**) to methyl acrylate (**2**) catalyzed by chiral crown - potassium tert-butylate complex in a detailed form (Preliminary publication ref. 2j). The mechanism suggested by us for the reaction is substantiated by a molecular mechanics calculation, the details of which are also presented here under the Molecular modeling title.

To the best of our knowledge we are the first group who observed the time-dependency of the ee values in the reaction and gave a rationale explanation for it. The related experiments and the mechanistic reasonings are collected in the Deracemization section of the article.

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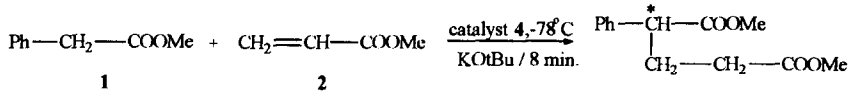
Michael addition

The model reaction selected for testing the catalytic activity of the crown- macrocycles (**4**) was the addition of methyl phenylacetate (**1**) to methyl acrylate (**2**),[2a] employing potassium tertiary butoxyde as a base as well as the structure of crown ether catalysts **4** can be seen in Fig. 1.



1 2 3

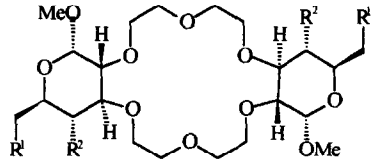


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Figure 1

The crown ethers **4a-l** all have a C_2-symmetry axis obtained by alkylation under liquid - liquid phase transfer catalytic (PTC) conditions from crown ether **4a**. The synthetic procedures leading to **4a-j** were published earlier [3a-i] while syntheses of **4k,l** are collected in this Experimental.

The reactions were carried out at -78°C in toluene. The reagents were used in the following ratios : methyl phenylacetate : methyl acrylate : KOtBu :crown catalyst as 1.3 : 1 : 0.34 : 0.064. The asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by measuring the optical rotation of the product ester (**3**) and comparing to the literature value[2d] and by ^{1}H-NMR using (+)-Eu(fod)$_3$ as a chiral shift reagent. The results of the experiments are presented in Table 1.

Table 1. Asymmetric Michael addition of methyl phenylacetate to methyl acrylate in the presence of **4**, in toluene, for 8 min

Entry	Catalyst	R^1	R^2	Yield of **3** (%)	ee for *S*-**3** (%)	Notes
1	**4a**	OH	OH	44.0	7.5	
2	**4b**	OH	Bn	66.3	0.2	
3	**4c**	OTs	OH	67.5	0.4	
4	**4d**	Br	OH	37.1	1.2	
5	**4e**	Br	OBz	89.3	3.2	
6	**4f**	OTs	OTs	31.3	1.7	
7	**4g**	OAc	OAc	75.0	17.6	
8	**4h**	O—CH(Ph)—O		59.5	17.5	
9	**4i**	OMe	OMe	100.0	76.4	
10	**4j**	OBu	OBu	100.0	80.0	
11	**4k**	O-hexyl	O-hexyl	69.3	46.0	
12	**4l**	O-octyl	O-octyl	69.2	29.2	
13	**4j**	OBu	OBu	47.0	25.3	solvent CH_2Cl_2
14	**4j**	OBu	OBu	82.3	84.4	time 1 min
15	**4j**	OBu	OBu	100.0	76.4	time 16 min
16	Dibenzo-18-crown-6			60.0	-	
17	no catalyst			43.5	-	

It can be seen that under such conditions all catalysts (derived from glucose) cause asymmetric induction leading to the product with the same (*S*) configuration. Both chemical yield and optical purity depend on the substituents (R^1 and R^2) of the catalyst. The crown ethers fully alkylated at the sugar units (**4i**, **4j**, **4k**) produced the best asymmetric induction (entry 9-11, Table 1). The catalyst **4j** (R^1=R^2=OBu) yielded the highest optical purity (entry 10, 80% ee). The yields and the ee-values are comparable to or better than those described in the literature for similar catalytic reactions.[2b,c,d]

To explain the stereochemical outcome of the reaction (Fig. 2) it can be supposed that there exists an equilibrium between ion pair complexes formed by the Z-enolate[2h] - metal ion - crown ether and the result is believed to be controlled by the relative stability of these complexes (at least at the very beginning of the reaction, see later).

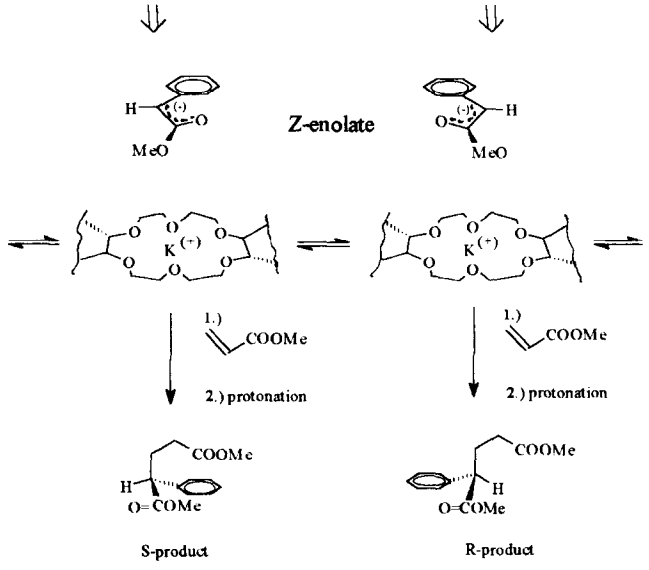


Figure 2.

In this equlibrium - because of the better fit of the Z-enolate in its Si-side-upwards - this ion-pair dominates, and after trapping the anion by the acrylate this situation will be frozen (trapped) resulting in the *S*-product-excess - after protonation of the adduct (anion) in a fast irreversible process. The result might also be modified by the solvent due to the different degree of the ion-pair aggregation and solvation (entry 13 in Table 1).

Molecular Modeling

Our proposed mechanism of the reaction was further analysed by molecular mechanics calculations. A relatively simple theoretical methodology to explain the observed stereoselectivity in asymmetric Michael additions was recently published by Brunet et al.[2h] Their calculations were limited to simple geometry

optimisation of feasible ion-pair complexes formed along the deprotonation. Since the stereoselectivity originates from the discrimination between these complexes, the rationalisation of the process requires their most stable conformation must be obtained. The computational effect of their limitation, however, is that the conformational space of intermediate complexes could not be explored and therefore the steric energies of local minima were compared. Although stereoselectivities calculated by this method were in fair agreement with the observed ones, the multiple minimum problem described above urged us to perform an extended conformational analysis on corresponding ion-pair complexes. The crown-ether **4i** was used as a model in our calculations.

According to the proposed mechanism our conformational analysis can be identified as a two-step process. Complexation of the potassium ion with the crown-ether **4i** is the first step of the reaction and therefore the conformational analysis of this complex should also be performed first. Due to the complexity of the system, this represents a challenging task. The conformational space of the crown ether cannot be treated without the consideration of the potassium ion complexed in its electrostatic field. The cyclic structure of the host revealed that a pseudosystematic algorithm for conformer generation might be optimal, the relative orientation of the potassium ion, however, requires the application of a Monte Carlo based random method. Conformational searches of such complexity can be adequately performed by the MacroModel package.[2k] The conformational space of the crown ether was explored using the systematic unbounded multiple minimum (SUMM) search algorithm. The positions of potassium ion were generated by Monte Carlo multiple minimum algorithm connected to the MOLS option of MacroModel.

SUMM algorithm

Within the framework of this method, conformer generation for cyclic structures is based on the ring-maker approach.[2l] The definition of a closure bond allows the opening of the macrocycle temporarily, in this opened state the variation of the torsional angles followed by reclosure of the ring leads to a new conformer. The resulting structure is then subjected to energy minimisation. The SUMM method[2m] operates by selecting values for torsional angle variation from a fixed set appropriate for a systematic search conducted at initially 120 deg resolution which can be increased along the process. This algorithm, therefore represents an intermediate between the fully systematic and random techniques, which is ideal for conformational searching.[2n]

MCMM/MOLS algorithm

Host-potassium interactions were studied by the particularly effective MCMM/MOLS algorithm using the low energy conformers of the crown ether **4i**. Minimum energy structures were calculated using Monte Carlo conformational search combined with the MOLS routine available in MacroModel.

The MOLS routine allows automatic docking of a ligand in a binding site by a combined conformational search procedure based on variation of the internal degrees of freedom of the crown ether (rotatable bonds). External degrees of freedom of the ligand (relative rotations and translations with respect to the fixed geometry

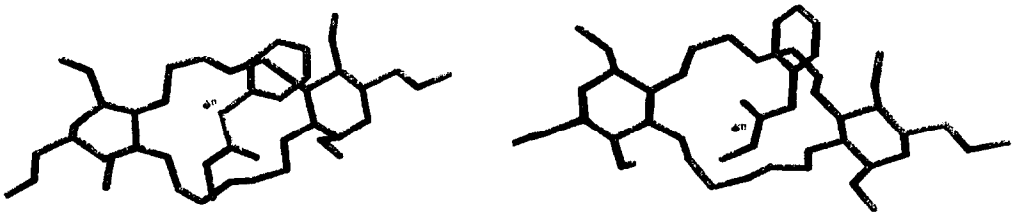
of the host) can be treated at the same time. In the case of metal ions only the degree of translational freedom should be considered.

The internal degrees of freedom of **4i** were varied using the previously described SUMM conformational search option of MacroModel. The combined MCMM/MOLS procedure was applied to allow the simultaneous random translation of the potassium ion with respect to the crown ether with increments of 0.5-1.0 Å for the translation of the centre of mass of the ligand along the *x,y,z* axes.

Finally, all these conformations were subjected to energy minimisation. The resulting minimum energy complex structures were sorted by energy and the unique structures within a 50 kJ/mol energy window above the global minimum were stored in a MacroModel multistructure file for further interactive study using the three-dimensional graphical interface of MacroModel.

Translations of potassium ion within the electrostatic field of the crown ether in combination with a 1000 step SUMM conformational search of the substrate enabled us to look for all possible low energy conformation for the potassium ion complex of **4I**. The most characteristic feature of the minimum energy complex is, that the potassium ion is located above the plane of the crown ether. This asymmetric orientation results, that attack of the anion formed from the phenylacetic acid ester could not take place with equal probability from the two sides of the crown ether. One can conclude that the anion would interact only from the more preferred side, and therefore further calculations concerning the other side might be omitted.

Conformational analyses of the corresponding ion-pair complexes were performed using an extended methodology. Backbone atoms of the crown ether as well as the potassium ion were fixed applying 35 kJ/A^2 constraint sets, which was introduced by a harmonic restoring potential. All substituents and the atoms of the anion were allowed free to move. The original MCMM/MOLS procedure was extended to the anion, in which the internal degrees of freedom were varied using the MCMM algorithm. Translation and rotation of the anion was allowed with respect to the crown ether with increments of 0.5-1.0 Å for the translation of the centre of mass of the ligand along the *x* ,*y* ,*z* axes and, 30-180 degrees for the rotation of the whole ligand around the *x*, *y*, *z* axes, respectively.



a b

Figure 3.

Minimum energy conformations of pro-*S* (a) and pro-*R* (b) complexes are depicted on Fig. 3. It is interesting to note, that the planar structure of the anion was distorted during the complexation with the potassium ion in both cases. The steric energy of the pro-*S* complex was found to be lower by 5.2 kJ/mol than that of the pro-*R* ion-pair. The enantioselectivity of 78% calculated from this energy difference is in good agreement with the corresponding experimental value (76.4%).

Comparing our result to previously reported values obtained by simple geometry optimisation clearly demonstrates, that exploring the conformational space of the complexes is a condition for quantitative prediction of selectivity. The accuracy of our method allows design of new and hopefully more selective chiral crown ethers for the catalysis of asymmetric Michael addition. Considering the fact, that the method suggested by Brunet et al. predicts the correct side of attack, it should be useful for preliminary qualitative analysis.

Deracemization

More important consequences were drawn from the observation that the ee values were dependent on time. It can be seen from Table 1. the reaction is very fast even at -78°C, as after one minute of reaction time 82.3% of the starting material (of the acrylate) has been converted into product, ee of which is as high as 85% (entry 14, Table 1). After 8 min time the reaction is completed, but at the same time the ee slightly decreased to ee 80%. After 16 min the ee value is 76 % (entry 15, Table 1).We also observed that the rate of the ee-decrease is somewhat retarded by the methyl phenylacetate excess because in its absence the ee value goes down more quickly to ee 40% (after 8 min reaction time) and - which is very important - the ee stabilises around this value further on with time (Table 2).

Table 2. Deracemization experiments with (±)-**3** (1.49 mmol) by KOtBu (0.39 mmol) and crown ether catalyst **4** (0.073 mmol), at -78°C, 8 min., in toluene

Entry	Catalyst	R^1=R^2	Notes	ee for S (%)
1	**4k**	O-hexyl	-	36.0
2	**4k**	O-hexyl	1.0 mmol of KOtBu	28.3
3	**4k**	O-hexyl	20°C	18.5
4	**4k**	O-hexyl	THF	23.2
5	**4k**	O-hexyl	(+)-**3**(ee 75% for S)	33.2
6	**4j**	O-Bu	-	39.9
7	**4j**	O-Bu	(+)-**3**(ee 75% for S)	40.5
8	**4j**	O-Bu	0.37 mmol of **1** also added	5.1

From these facts one can deduce that the ee values in Michael reaction are determined and shaped by two factors; the kinetically controlled result of the asymmetric C-C bond formation is continuously modified by another process; a deprotonation of the endproduct by the crown potassium base complex and reprotonation of the anion formed. Fig. 4. shows a possible arrangement of the anion before its protonation to give *S*-**3** and *R*-**3**.

It follows that the highest ee values are obtained at the very beginning of the reaction, which worsens with time so taking the conversion into account there is an optimum time for getting good yields still with highest possible ee. This seems to be true for all similar reactions in which the newly formed asymmetric carbon still has a C-H acidic proton.

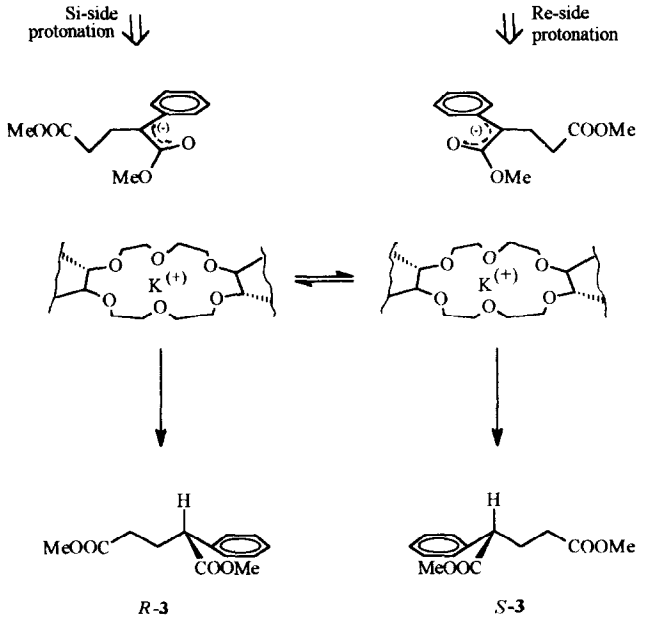


Figure 4.

On the other hand, the position of the deprotonation-protonation process in the presence of our chiral catalyst is around 40% for S so one can hope that placing the product-racemate into a mixture imitating the asymmetric Michael reaction conditions (of course the two reagents should be omitted) a so called deracemization occurs. And really it has been found that the (±)-**3** treated in this way quickly showed optical activity, the measure of which was increasing with time and after 8 minutes at -78°C its value corresponds to a product with almost 40% ee for *S* (entry 6, in Table 2). A similar tendency can be seen in the case of using tetra-O-hexyl-derivative **4k** (33-36% ee value, entry 1,5 in Table 2.).

Making the desired antipode from a racemate by deracemization is very attractive, modern route as one can get the racemate in a separate reaction using the best and cheapest synthetic method and subsequently, in a process called deracemization, both antipodes of the racemate (not only 50% of it) can be converted into the desired antipode, theoretically in 100% yield. The method has been reviewed excellently just recently [6b,c].

Good deracemization procedures have been published for CH-acids by Vedejs's,[4a,b] Hünig's,[5a-e]

Fehr's,[6a,b] Krause's[7] and Trost's[8] groups using one equvivalent of a chiral proton source for the enantioselective protonation of the enolates under kinetically controlled conditions. Successful deracemization experiments by catalytic enantioselective protonation of enolates are known from the literature and have been reviewed by Fehr.[6b]

For the explanation of our catalytic method we suppose that KOtBu; being practically insoluble in toluene at -78°C, goes into solution by a complex formation with the crown ether **4** and as a consequence, both the deprotonation of **3** and subsequently the reprotonation of the enolate from **3** (by t-BuOH or **3**) can proceed exclusively in the presence of the chiral crown **4**.

Further work is in progress on this novel deracemization to make it more useful for preparative purposes. We will also try to improve the ee values in Michael reactions and in other C-C bond forming reactions catalysed by chiral crown ether-potassium base complexes.

Experimental

Optical reactions are measured on a Perkin Elmer 241 polarimeter. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 100 MHz JEOL FX 100 spectrometer. All δ values are reported in ppm, TMS was used as internal standard. Thin layer chromatography (TLC) is perfomed using silicagel coated plastic sheets (Merck silicagel 60 F_{254}) and UV and / or iodine reagent for detection. Chromatographic purification refers to flash chromatography using Merck silicagel 60 (70-230 mesh ASTM). Elemental analysis were performed on a Perkin Elmer 240 automatic analyzer.

Bis(methyl-2,3-dideoxy-4,6-di-O-hexyl-α-D-glucopyranosido[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (4k). To a solution of 1g (1.9mmol) of the tetrahydroxy-compund **4a** in 7ml THF was added 14.8ml (105 mmol) hexyl bromide, 7.5ml 50% NaOH and 0.061g (0.19mmol) tetrabutylammonium bromide PT catalyst. This mixture was stirred at 40°C for 100 h. The water layer was extracted with dichloromethane (3x25ml), dried (Na_2SO_4), filtered off and concentrated *in vacuo*, to give 0.75g (45.8%) of **4k** as a yellow oil. $[\alpha]_D^{20}$ +47.3 (c=1, $CHCl_3$). ^{1}H-NMR δ: 4.77 (d, 2H, J=3.4Hz, 2x anomeric H), 3.73-3.46 (m, 28H, OCH_2 CH_2O, CH, other CH_2), 3.37 (s, 6H, 2xOMe), 1.81-1.10 (m, 40H, 20xCH_2), 0.86 (t, 12H, 4xCH_3) Anal. calcd. for $C_{46}H_{88}O_{14}$ (864), C 63.9, H 10.18, found C 64.00, H 10.15.

Bis(methyl-2,3-dideoxy-4,6-di-O-octyl-α-D-glucopyranosido[2,3-b][2',3'-k])-1,4,7,10,13,16-hexaoxacyclo-octadecane (4l). Terahydroxy compund **4a**: 2.0g (3.8mmol) in 15 ml THF octyl bromide: 40 ml (100mmol), 50% NaOH solution 15ml. The reaction procedure was performed in the same manner just like the previous one, **4l** was obtained as a thick oil. Yield: 2.75g (77.1%). $[\alpha]_D^{20}$ + 19.7 (c = 1.0, $CHCl_3$). ^{1}H-NMR δ: 4.77 (d, 2H, J=3.5Hz, 2x anomeric H), 3.73-3.46 (m, 28H, OCH_2 CH_2O, CH, other CH_2), 3.37 (s, 6H, 2xOMe), 1.81-1.10 (m, 56H, 28xCH_2), 0.86 (t, 12H, 4xCH_3) Anal. calcd. for $C_{54}H_{104}O_{14}$ (976.1), C 66.42, H 10.65, found C 66.51, H 10.39.

Michael addition reactions. Methyl phenylacetate (1.49mmol) in dry toluene (1.0ml) was added to a

suspension of potassium tert-butoxide (0.93mmol) in toluene (1.0ml) under argon and the mixture was stirred for 15 minutes at -78°C. A solution of the crown-compound (0.073mmol) in toluene (1.5ml) was then added and the mixture stirred for another 15 minutes. A solution of methyl acrylate (1.14mmol) in toluene (1.0ml) was added and the mixture was stirred for 8 minutes, then was poured into saturated aq. NH_4Cl (10ml), extracted with toluene (3x10ml) and the combined extacts were dried. The residue obtained after removal of the solvent was subjected to silica gel column chromatography and was eluted with hexan-EtOAc 6:1 to yield the product. The ee was monitored by measuring the optical rotation of the product ester (**3**) and comparing that to the literature value.

Calculations. All computations were run on a SGI Indy R4400 workstation. Molecular mechanics calculations as well as conformational analyses were performed by the MacroModel 5.0 program package. The standard AMBER* force field was applied in all cases. Electrostatic energies were calculated using the built-in electrostatic energy equation with distance dependent dielectric constant. Due to the pure electrostatic interactions between the crown ether and the potassium ion, cut-off distances were set to 8 Å for van der Waals and 20 Å for electrostatic interactions. Atomic charges of the **4i**-potassium complex as well as the phenylacetic acid anion were obtained by ZINDO1[20] semiempirical calculations for the corresponding preoptimised geometry.

Conformational analyses were performed using the SUMM and MCMM/MOLS algorithm in 1000 steps. The final resolution of 30 deg with an energy window of 50 kJ/mol was used in SUMM calculation. Maximal and minimal ring closure distances were set to 3.5 Å and 0.5 Å respectively. Maximal translations and rotations were set to 0.5 Å and 30 deg, respectively in MCMM/MOLS calculations. Structure comparisons were based on the positions of nonhydrogen atoms in each case. Molecular mechanics energies were minimised using the Polaak-Ribiere conjugate gradient method with the convergence criterion set to 0.01 kJ/Å mol.

Deracemization experiments. A suspension of potassium-tert-butoxide (0.043g, 0.39mmol) in toluene (1.0ml) was added to a solution of racemic 2-phenyl-glutaric dimethyl ester (0.3g, 1.49mmol) in toluene (1.0ml). This mixture was stirred for 15 minutes at -78°C. A solution of the crown catalyst (0.073mmol) in toluene (1.5ml) was added and stirred for 8 minutes, then the mixture was poured into saturated aq. NH_4Cl (15ml), extracted with toluene (3x15ml) and the combined extacts were dried. After standard work-up and column chromatography the enantiomer mixture was obtained. The ee% was monitored by measuring the optical rotation of the deracemized product.

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