

## Simplified synthetic procedure for (Z) to (E)-cyclooct-4-enol photoisomerization

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This article is a proof of the principle of a new synthetic procedure for sensitized photoisomerization of *cis*-cyclooct-4-enol in the corresponding *trans* isomer. By irradiation of the organic solution containing ethyl benzoate as sensitizer, which is part of a two-phase cyclohexane/water system, during irradiation a continuous extraction of the resulting *trans*-cyclooct-4-enol in the form of a silver complex is carried out. A theoretical model describing the thermodynamic equilibrium of this two-phase system is also derived. This model was used as a tool to optimize the experimental conditions of the photolysis. In this model, the stability constants of the silver complexes of the cyclooct-4-enol isomers, as well as the distribution constant of this compound between the organic and aqueous phases, participate as parameters, which parameters were experimentally established in the present study as well.

**Keywords:** Click chemistry, photoisomerization, (E)-cyclooct-4-enol

## INTRODUCTION

The term “Click Chemistry” [1-4] involves interactions between pairs of functional groups that rapidly and selectively react (“click”) with each other in mild, aqueous conditions. This concept has developed into a convenient and reliable two-step coupling procedure of two molecules widely used in biosciences [5], drug discovery [6, 7] and material science [8]. Especially biomolecule labelling requires reaction procedures that can be performed under physiological conditions (neutral pH, aqueous solution, ambient temperature) with low reactant concentrations to ensure non-toxic, low background labelling at a reasonable time scale while still preserving biological function. Among the plethora of possible reactions only a few generally fit the necessity of fast reactivity, selectivity, catalyst-free and biocompatibility criteria [9]. An example of such coupling is the inverse electron demand Diels–Alder (IEDDA) reaction [10] which goes between 1,2,4,5-tetrazines (s-tetrazines, Tz) and various dienophiles ([4+2] cycloaddition). It was observed that the use of *trans*-cyclooctene (TCO) as a precursor gave a tremendous rate difference compared to *cis*-cyclooctene and most importantly to the other cyclic alkenes with higher ring strain.

Unfortunately, synthesis of the *trans* isomer of cyclooctene derivatives is not easy and usually proceeds with low yields. This fact determines the high price of these compounds. The most common synthesis of the *trans* isomers follows the photochemical synthetic procedure described by Royzen *et al.* [11]. By this procedure,

corresponding Z isomer of cyclooctene is dissolved in a nonpolar aprotic solvent as cyclohexane and is placed in a photochemical reactor where it is irradiated with UV light in presence of sensitizer. During irradiation, the solution is continuously recirculated through a chromatography column filled with silica gel the top of which is covered by an additional amount of silica gel impregnated with AgNO<sub>3</sub>. In this way, the E isomer, obtained by photoisomerization of the Z cyclooctene, is retained over the silica gel doped with silver ions due to the formation of a silver complex and the Z isomer is transmitted through this layer given that its silver complex is by two orders of magnitude weaker than the former one. After unknown amount of time [11] recirculation is suspended and the captured E-cyclooctene is liberated by dissolving the silica gel containing its silver complex in 25% ammonium hydroxide and the compound is then re-extracted from the aqueous solution with an organic solvent. After evaporation of the organic solvent the E isomer is collected.

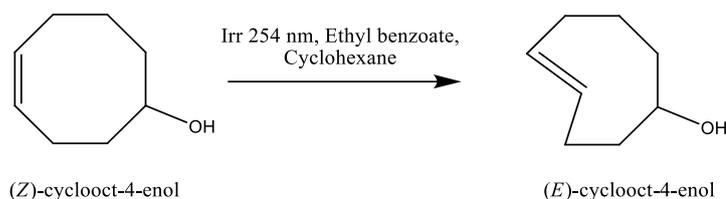
Some drawbacks of the procedure described [11, 12] are observed, though it leads to good yields of isomerization. First, the experimental setup used is not the simplest. A circulating pump is required and consumables such as hundreds of grams of silica gel and liter amounts of organic solvent are used. This makes the procedure unusable for milligrams of the substrate because it will spread throughout the system and this will lead to a significant reduction in yields. Second, before the start of photolysis, unknown circulation time might be required to achieve a concentration equilibrium of

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the substances dissolved in the organic solvent. Depending on the nature of the solutes and the polarity of the eluent, different rates of passage through the silica gel column can be obtained for the solvent and for the solutes. This leads to the attenuation of concentration fluctuations in the solution over time, as they are different for the substrate and for the sensitizer. After reaching the equilibrium some substrate will be retained on the

column causing unknown reduction of the concentration of the substrate in the irradiated solution.

In this paper, we suggest a simplified method for *cis* to *trans* isomerization of cyclooctene derivatives using (Z)-cyclooct-4-enol (*cis*-CO-4-OH) (CAS number: 4277-34-3) as sample compound (Scheme 1).



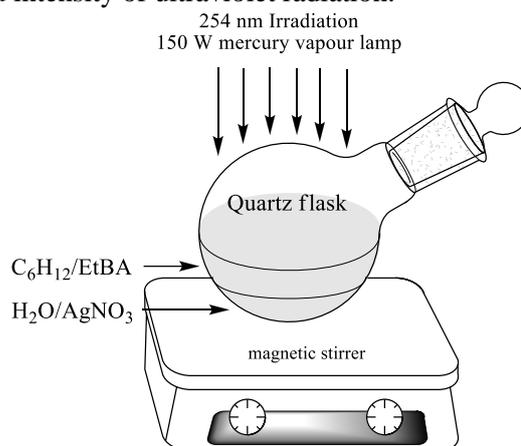
Scheme 1.

The advantage of this method is that it uses an extremely simple experimental setup, which allows the use of mg amounts of substrate and small amounts of organic solvent without affecting the yields for photoisomerization. In addition, precise control of the substrate and sensitizer concentrations in the irradiated solution can be performed. This is extremely important because it results in photoisomerization yields. With this method we obtain yields comparable to the more complex procedure using silica gel [11, 12] and 3 to 5 times higher yields than those of single-phase photosensitized isomerization with different sensitizers [13-15].

The experimental setup of the method is presented on

Scheme 2. We use a two-phase system consisting of two layers of liquids – an upper organic layer of cyclohexane in which the cyclooctenol and the sensitizer (ethyl benzoate) are dissolved and an aqueous layer containing silver nitrate on the bottom of the flask. Thus, by continuously stirring of the solutions during irradiation from the top of the flask, a continuous extraction of the resulting *trans*-CO-4-OH (CAS number: 85081-69-2) is ensured, and it is retained in the aqueous layer in the form of a silver complex. The progress of the photoisomerization was monitored by titration of the resulting *trans*-CO-4-OH in the aqueous layer over a period of time with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (TzPy) (CAS Number 1671-87-0). In the article we develop and discuss a theoretical model for the distribution of the different forms under which CO-4-OH exists in the two-phase system, taking into account different thermodynamic parameters of the system, such as

equilibrium and stability constants, constants of phase distribution and photostationary state. This model helps us to adjust the experimental conditions of the method such as to achieve maximum efficiency of photoisomerization for the specific conditions of the experiment, such as irradiation area and intensity of ultraviolet radiation.



Scheme 2.

## EXPERIMENTAL

*cis*-Cyclooct-4-enol (10 g 98% purity Career Henan Chemical Co) and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (54 g 98% purity Career Henan Chemical Co) are trade products which were purified prior to use by column chromatography. The photoisomerization was monitored by the amount of the *trans*-cyclooct-4-enol produced in the aqueous phase or that left in the organic phase by titration of the ethanol solution of tetrazine with known concentration. Quantity of the *trans*-cyclooct-4-enol was calculated by the change of the absorption band of the tetrazine at 540 nm in pure ethanol or at 570 nm in presence of silver ions. Absorbance was

recorded using UV-Vis-NIR Agilent Cary 5000 spectrophotometer. The same instrument was used for determination of the thermodynamic parameters of the system such as distribution and stability constants.  $K_D = 0.92 \pm 0.05$  constant of cyclooct-4-enol for the system cyclohexane/water was determined by measuring the absorbance shoulder at 200 nm of the solution of cyclooct-4-enol in cyclohexane before and after water extraction. The constant  $K_{AgZ}$  was calculated to be  $2.5 \pm 0.3 \text{ M}^{-1}$  by UV spectroscopy monitoring of the amount of cyclooct-4-enol left in cyclohexane after extraction with aqueous solutions of  $\text{AgNO}_3$  with different concentrations. The same approach was used for determination of the  $K_{AgE} = 2100 \pm 100 \text{ M}^{-1}$  constant. In this case the amount of *trans*-cyclooct-4-enol left in cyclohexane was determined by titration with tetrazine.

The photolysis of *cis*-cyclooct-4-enol to *trans*-cyclooct-4-enol was carried out by irradiation from the top under continued stirring and constant temperature of 20 °C with a 150 W mercury vapor lamp of the quartz flask filled with air saturated cyclohexane/water mixture containing substrate and the sensitizer ethyl benzoate. In all experiments the concentration of ethyl benzoate in cyclohexane was

such as to ensure optical density 1 at a wavelength 272 nm and optical path 1 cm.

*cis*-Cyclooct-4-enol:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.72 – 5.67 (m, 1H), 5.63 – 5.56 (m, 1H), 3.85 – 3.78 (m, 1H), 2.36 – 2.22 (m, 1H), 2.19 – 2.07 (m, 3H), 1.98 – 1.81 (m, 2H), 1.76 – 1.46 (m, 5H).

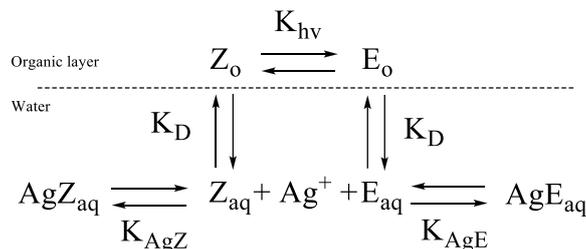
*trans*-Cyclooct-4-enol:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.64 – 5.51 (m, 1H), 5.45 – 5.32 (m, 1H), 3.51 – 3.41 (m, 1H), 2.31 (m, 3H), 2.02 – 1.88 (m, 4H), 1.72 – 1.53 (m, 3H).

## RESULTS AND DISCUSSION

### Theoretical background

Assuming that at the ultimate time of irradiation the isomerization of *cis*-CO-4-OH to *trans*-CO-4-OH and *vice versa* leads to reaching a photostationary state, the global equilibrium and the distribution of the components between the two-phase system can be expressed by the equations on

Scheme 3.



Scheme 3.

where letters Z and E denote the corresponding  $\pi$ -diastereomers of CO-4-OH and subscripts “o” and “aq” denote organic and aqueous phase at which the compounds exist, respectively.  $\text{AgZ}$  and  $\text{AgE}$  are the silver complexes of the *cis*- and *trans*-CO-4-OH, respectively.  $K_{hv}$  is the equilibrium constant of the photostationary state in presence of sensitizer, which is equal to  $K_{hv} = E_o/Z_o$ , where  $Z_o$  and  $E_o$  are the moles of *cis* and *trans* isomer, respectively. The equilibrium constant which presents the distribution of the CO-4-OH isomers in the two immiscible solvents can be written as follows:

$$K_D = \frac{Z_o V_{aq}}{Z_{aq} V_o} = \frac{E_o V_{aq}}{E_{aq} V_o},$$

where  $V_o$  and  $V_{aq}$  are the volumes of the organic and aqueous phase, respectively. The stability

constants  $K_{AgZ}$  and  $K_{AgE}$  of the corresponding silver complexes are equal to:

$$K_{AgZ} = \frac{\text{AgZ}_{aq} \cdot V_{aq}}{Z_{aq} \cdot (C_{Ag} - \text{AgZ}_{aq} - \text{AgE}_{aq})}$$

and

$$K_{AgE} = \frac{\text{AgE}_{aq} \cdot V_{aq}}{E_{aq} \cdot (C_{Ag} - \text{AgZ}_{aq} - \text{AgE}_{aq})}$$

where  $C_{Ag}$  is the total mole amount of silver ions.

We made two approximations presenting the global equilibrium of the system with this model.

First, we neglected the amount of silver complexes in the organic phase, assuming that they are almost completely dissolved only in water, and second, that

the distribution constant  $K_D$  has the same value for the E and Z isomers. The thermodynamic model of the two-phase system at equilibrium presented on

Scheme 3 can be expressed by the following system of equations:

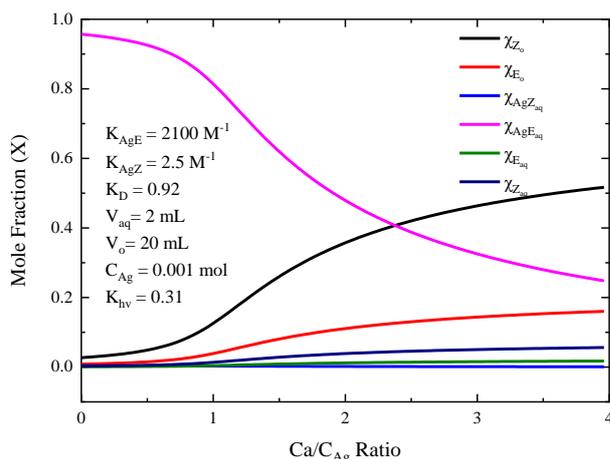
$$\begin{aligned} E_o &= K_{hv} Z_o \\ Z_{aq} &= \frac{Z_o V_{aq}}{V_o} \\ E_{aq} &= \frac{E_o V_{aq}}{K_D V_o} \\ K_{AgZ} &= \frac{Ag Z_{aq} \cdot V_{aq}}{Z_{aq} \cdot (C_{Ag} - Ag Z_{aq} - Ag E_{aq})} \\ K_{AgE} &= \frac{Ag E_{aq} \cdot V_{aq}}{E_{aq} \cdot (C_{Ag} - Ag Z_{aq} - Ag E_{aq})} \\ (Ca &= Z_o + E_o + Z_{aq} + E_{aq} + Ag Z_{aq} + Ag E_{aq}) \end{aligned}$$

By solving this system of equations, the mole fractions of the components of the two-phase model can be represented as a function of the total amount of CO-4-OH available in the system – Ca, as follows:

$$\begin{aligned} A &= K_{AgZ} + K_{AgE} K_{hv} \\ B &= K_D V_o + V_{aq} \end{aligned}$$

$$\begin{aligned} \chi_{Z_o} &= \frac{(K_D V_o (-K_D (1 + K_{hv}) V_o V_{aq} + V_{aq} ((Ca - C_{Ag}) A - (1 + K_{hv}) V_{aq})) \\ &+ \sqrt{V_{aq}^2 (4 Ca (1 + K_{hv}) A B + (A (C_{Ag} - Ca) + (1 + K_{hv}) B)^2))}{(2 Ca (1 + K_{hv}) A V_{aq} B)} \end{aligned}$$

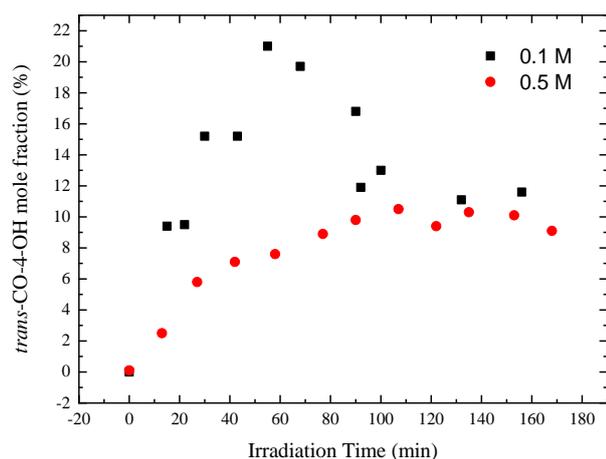
Hence, by replacing the term for  $Z_o$  into the equations above, the mole fractions of the other components of the system as functions of Ca can be easily deduced. These functions are represented graphically in Figure 1 and represent a specific case for the corresponding values of the equilibrium constants and volumes of the phases specified in the figure inset.



**Figure 1.** Mole fractions of the components of the system at global equilibrium as a function of CO-4-OH total mole – Ca, which follow the thermodynamic model of the two-phase system at global equilibrium presented on

Scheme 3.

As can be seen from Figure 1 under these conditions and an equimolar ratio between the amounts of CO-4-OH and silver ions, about 80% of the total amount of cyclooctenol will be in the form of a silver complex of the *trans* form, upon reaching global equilibrium. Thus, this theoretical model illustrates the advantage of the two-phase system in the photoisomerization of *cis*-CO-4-OH by providing a convenient way to synthesize *trans*-CO-4-OH, which can be isolated after treatment of the aqueous phase with 25% ammonium hydroxide and subsequent re-extraction. Although this procedure predicts 100% *cis* to *trans* conversion at optimal experimental conditions, as a result of side reactions between substrates and photoactive species, the predicted theoretical yield can never be reached. However, this model helps us to select the experimental conditions such as to minimize the rates of side reactions and thus maximize the yield of sensitized photoisomerization.

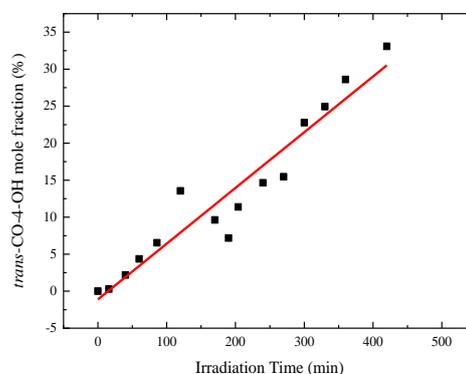


**Figure 2.** Sensitized photoisomerization of *cis*-CO-4-OH to *trans*-CO-4-OH in cyclohexane at two different initial concentrations of the substrate as a function of time.

## RESULTS AND DISCUSSION

Figure 2 presents the isomerization process of *cis*- in *trans*-CO-4-OH as a function of time for two different initial concentrations of *cis*-CO-4-OH. Photolysis of the *cis* form of CO-4-OH was performed in cyclohexane in the presence of ethyl benzoate. The amount of sensitizer was such that the optical density of the solution in the cuvette with an optical path length of 1 cm is equal to 1 at 272 nm wavelength. The amount of the *trans* isomer obtained was monitored by titration with a solution of TzPy in ethanol with known concentration. As can be seen from the figure, the initial concentration of cyclooctenol affects both the percentage of maximum transformation of *cis*- to *trans*-cyclooctenol and the shape of the function. This is an effect known in the literature [13, 15, 16], which is confirmed by our experiments. The reason for the concentration dependence of the photostationary state is the participation of substrates in side reactions, whose rate constants depend on the total concentration of cyclooctenol. These are polymerization reactions or interactions with radicals that are the product of photodestruction. All of these processes are bimolecular, but they follow pseudo-first-order kinetics because the concentration of the starting cyclooctenol that is a component of the reaction is orders of magnitude higher than that of short-lived radicals or photoexcited particles formed during photolysis. Thus, at high concentrations of cyclooctenol, the rates of side reactions become commensurate or even higher than those of *cis-trans* isomerization, since the concentration is a coefficient by which the rate constant of the side reaction is multiplied. For this reason, due to the continuous losses of cyclooctenol, the true photostationary equilibrium in

the isomerization of *cis*- and *trans*-cyclooctenol can be reached and determined by absorption spectroscopy only at low concentrations of the substrate. For this reason, single-phase photolysis of *cis*- to *trans*-cyclooctenol on a gram scale can only be done with large amounts of solvent, which requires subsequent concentration of the dilute solutions. The use of the two-phase method proposed in this article allows maintaining a low concentration of the substrate in the organic phase where photolysis takes place. By an appropriate ratio between the volumes of the two phases, a concentration of the substrate in the organic layer, by one or two orders of magnitude lower than the amount of all cyclooctenol distributed throughout the system, can be easily ensured.



**Figure 3.** Sensitized photoisomerization of *cis*-CO-4-OH to *trans*-CO-4-OH in a two-phase system as a function of time. Volume ratio of cyclohexane/water is 10. The initial concentration of the substrate is 0.074 M (0.174 mL *cis*-CO-4-OH in 20 mL cyclohexane).

To test the advantage of the two-phase photoisomerization of *cis*-CO-4-OH in the *trans* isomer over the single-phase one, we conducted an experiment, the results of which are presented in Figure 3. The figure shows the progress of photoisomerization of *cis*-CO-4-OH in the *trans* isomer as a function of time in a two-phase cyclohexane/water system in the presence of ethyl benzoate sensitizer. The experiment was performed at a phase volume ratio of 1:10 in favor of the organic layer. Under these conditions, about 70% of the total amount of *cis*-CO-4-OH (0.074 M, 0.00147 mol in 20 mL cyclohexane) is present in the organic layer as a free ligand. As can be seen (Figure 3), the dependence can be approximated by a straight line, which represents the kinetics of a zero-order reaction. This is because the substrate concentration is kept relatively constant over a wide range due to the global equilibrium between the forms distributed between the two phases. If we compare the experiments performed with approximately the same

total concentration of *cis*-CO-4-OH (about 0.1M) in single-phase (Figure 2) and two-phase (Figure 3) photoisomerization, we see that in the second case we have a 10% increase in the yield of the *trans* form, namely from 25% in the single-phase to 33% in the two-phase system. This result is probably due, on the one hand, to the decrease in the concentration of the substrate in the irradiated solution, which reduces the competitiveness of the side reactions and, on the other hand, to the continuous removal of the *trans* product from the organic to the aqueous phase, where it is retained in the form of a silver complex.

From the analysis of the experimental data in combination with the theoretical predictions for the distribution of the substrate in the different forms of the system, coming from the model described above, it is clear that the yield of the *trans* isomer increases at lower concentrations of the irradiated solution, which is achieved by increasing the volume of the aqueous phase compared to that of the organic. This, in turn, slows down the transformation process, as the slope of the dependence shown in Figure 3 depends inversely on the equilibrium concentration of *cis*-CO-4-OH in the irradiated solution. Finding the optimal experimental conditions and the maximum ratio (yield of the *trans* isomer in %) vs. (time) will be the goal of a future publication. In this article we wanted to illustrate the advantage of heterophase photoisomerization as a method for the synthesis of *trans* isomers of cyclooctene derivatives over other procedures already described in the literature.

## CONCLUSIONS

In conclusion, we point out a 3- to 5-fold increase in the yield of *trans*-CO-4-OH through photosensitized isomerization, as a result of the use of our proposed two-phase method. Thanks to the simplified experimental setup and with knowledge of the thermodynamic properties of the particular compound, better yields of sensitized photoisomerization can be achieved by precise control of the substrate concentration in the

irradiated solution carried out by changing the volume ratio of the organic and water phases, using the proposed two-phase method for the synthesis of *trans* derivatives of cyclooctene. That increase of the photoisomerization yields was achieved by using a very simple experimental setup consisting only of quartz flask and magnetic stirrer.

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