

Selective synthesis of cyclododec-2-en-1-yl ethers via palladium-catalyzed allylic substitution reaction: a kinetic study

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Abstract: The palladium-catalyzed reaction between isomeric cyclododec-2-en-1-yl acetates and primary aliphatic alcohols was found to result in high yields of the reaction products obtained. The selectivity with respect to cyclododec-2-en-1-yl ethers formed as reaction products ranged from 73% to 93%. The kinetics of the reaction of acetoxy cyclododec-2-enes with alcohols was studied within the temperature range of 328–358 K. A kinetic equation best fitting the experimental data was provided.

Key words: Alkoxylation, acetoxy cyclododec-2-enes, kinetic model

1. Introduction

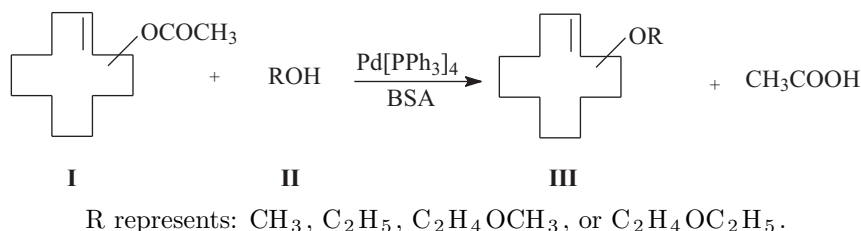
Among the numerous compounds used in the perfume industry nowadays, methoxy- and ethoxycyclododecanes as well as (2-methoxyethoxy)- and (2-ethoxyethoxy)cyclododecanes hold an important position. The commonly accepted procedures for the preparation of these compounds are multistage, and some of the reaction steps are associated with the formation of highly toxic, explosive, or expensive chemicals.^{1–4} On the other hand, in the reactions of allylic monoacetates derived from cyclopolyenes, acetate groups are easily substituted with some alcohols in the presence of transition metal catalysts, which is known as the Trost–Tsuji reaction.^{5–11} The allylic ethers thus obtained can be turned into the corresponding saturated cyclic compounds by selective hydrogenation of the carbon–carbon double bond, with the oxygen-containing functionalities remaining intact.

The aim of the present work was to evaluate quantitatively the catalytic substitution reaction between isomeric cyclododec-2-en-1-yl acetates (I) and primary aliphatic alcohols (II) to the cyclododec-2-en-1-yl ethers (III) in the presence of triphenylphosphine complex of palladium ($\text{Pd}^0[\text{PPh}_3]_4$) as catalyst, and to verify its conformity to a certain kinetic model.

The corresponding reaction scheme is given below:

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1.1. Reaction network and general model formulation

Relevant information about the mechanism of alkoxylation of cyclododec-2-en-1-yl acetates can be obtained from the dependence of the quantitative distribution of the products on reaction conditions. The products formed as a result of the alkoxylation of cyclododec-2-en-1-yl acetates (I) are, generally, the cyclododec-2-en-1-yl ethers (III). Unsaturated ketones and alcohols are also present as minor reaction products. Some decomposition of the acetoxy cyclododec-2-enes and condensation reactions leading to the formation of products of higher molecular mass are also likely to take place.

In accordance with the desirable end-products' distribution, the reaction network can be expressed by the parallel formation of π -allyl and π , σ -complexes and their subsequent decomposition to the above-mentioned products. In order to simplify the reaction network, the number of reaction species involved was reduced by lumping all monoacetates (I) as well as all monoethers (III) and by-products (marked as others) into single components, respectively. These assumptions led to modification of the complicated reaction network to the simplified scheme given below (Figure 1), where Pd(0) is a representation of the catalytic species; K_1 , k_2 , and k_3 are the composite equilibrium and rate constants, respectively. In other words, the initially complicated reaction network was reduced to 2 parallel decomposition reactions involving the complexes formed (Figure 1).

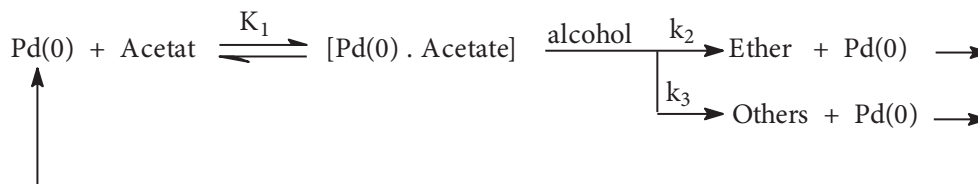


Figure 1. Simplified reaction network.

The application of the well-known quasi-steady-state approximation approach¹² to the reduced reaction scheme (Figure 1) gave the following differential kinetic equation:

$$\frac{dC_I}{dt} = -(k_2 + k_3) \times C_{Pd(0)} \times C_I / F \quad (1)$$

where

$$F = 1 + K'_1 C_I + K'_2 C_{III} + K'_3 C_{III}^2 + K'_4 C_I^2 + K'_5 C_I C_{III} \quad (2)$$

Here K'_i are composite equilibrium constants, and F represents the so-called complex formation function.

Some of the potential complexes can be quite unstable, and the corresponding monomials in the denominator (Eq. (2)) did not reach significant values within the experimental conditions studied. After neglecting the formation of such inactive intermediates, many different models can be derived from the general kinetics equation (1).

2. Experimental

2.1. Catalytic substitutive alkoxylation

Cyclododec-2-en-1-yl acetate (>97% purity by GC) and $\text{Pd}^0[\text{PPh}_3]_4$ were prepared by the methods described previously.^{13,14} Tetrahydropyrene, methanol, ethanol, 2-methoxyethanol, and 2-ethoxyethanol were purchased from a commercial source (Merck). The experiments were carried out in a 25-mL thermostated 3-necked glass reactor fitted with a thermometer and magnetic spinbar under argon atmosphere. $\text{Pd}^0[\text{PPh}_3]_4$ (0.1–0.3 mmol), cyclododec-2-en-1-yl acetate (3.0–9.0 mmol), and N,O-bis(trimethylsilyl)acetamide (BSA) (6.0–18.0 mmol) were dissolved in 4.0–6.0 mL of tetrahydropyrene and the mixture was thoroughly stirred. Following heating to the reaction temperature (328–358 K), aliphatic alcohol (6.0–18.0 mmol) was subsequently added. Aliquots of 0.5 mL were taken out at certain time intervals for analysis. Both the nonreacted starting reagent and reaction products were separated from the solvent and the catalyst by vacuum distillation. The kinetic studies were performed in a similar way, using certain amounts of the starting materials and the catalyst.

2.2. Analyses

IR spectra were measured on a Specord M-80 spectrometer ($400\text{--}4000\text{ cm}^{-1}$) using thin sample films. GC-MS analyses were performed on a Hewlett-Packard 5890II, 5970B instrument, with $25,000 \times 0.2\text{ mm}$ column, stationary phase consisting of 95% methyl silicone and 5% methylphenylsilicone, and helium as a carrier gas. Analyses of the samples taken at certain time intervals and the purity of products were checked by employing GLC (PerkinElmer Sigma-2000 chromatograph with a flame-ionization detector), with nitrogen as carrier gas, at flow rate of 1 mL/min, $50,000 \times 0.32\text{ mm}$ column, stationary phase Carbowax 20M, oven temperature 180 °C, injector temperature 250 °C. Column chromatography was performed on Kieselgel 100 (Fluka AG) with hexane, dichloromethane, and methanol as eluents.

3. Results and discussion

3.1. Catalytic substitutive alkoxylation

The yield of the starting isomers of cyclododec-2-en-1-yl acetate (I) (3 isomers) following their purification was found to be 83.6%. In the initial experiments, methanol was used as the component containing active hydrogen. According to some published data¹⁵ and our own results, the substitutive alkoxylation of acetoxy cyclododec-2-enes can occur at temperatures as low as 328 K. The experiments within the temperature interval from 328 K to 358 K showed higher conversions with increasing reaction temperatures, as expected. The conversion should, however, be kept at optimum level, depending on the overall economic efficiency of the process. For this reason, the experiments were carried out at 348 K, using aliphatic alcohols, BSA, and $\text{Pd}^0[\text{PPh}_3]_4$ at a molar ratio to cyclododec-2-en-1-yl acetates of 2:2:0.033, respectively. The conversion of the substrate at the reaction duration of 9 h was approximately 50% (Figure 2).

The selectivity towards the formation of isomeric methoxycyclododec-2-ene at 348 K increased up to 92.3% (Figure 3).

With longer reaction durations at 358 K, the amount of cyclododecene was found to increase, due to the parallel decomposition of cyclododec-2-en-1-yl acetates.

Further substitution reactions of allylic acetates (I) were carried out in the presence of ethanol, 2-methoxyethanol, and 2-ethoxyethanol as reagents. The experimental observations supported the expected increase in the reaction rate for substrates of higher acidity (Figures 2 and 3).

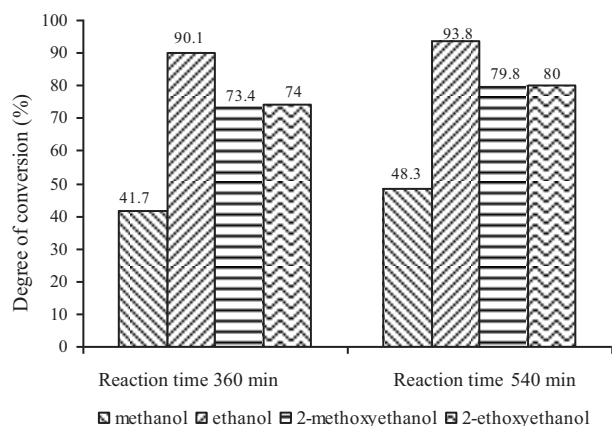


Figure 2. Dependence of the conversion on reaction time. Reaction conditions: temperature 348 K; amount of catalyst $\text{Pd}^0[\text{PPh}_3]_4$: 0.2 mmol; tetrahydropyran: 5 mL; acetates: 6.0 mmol; alcohol: 12.0 mmol; BSA: 12.0 mmol.

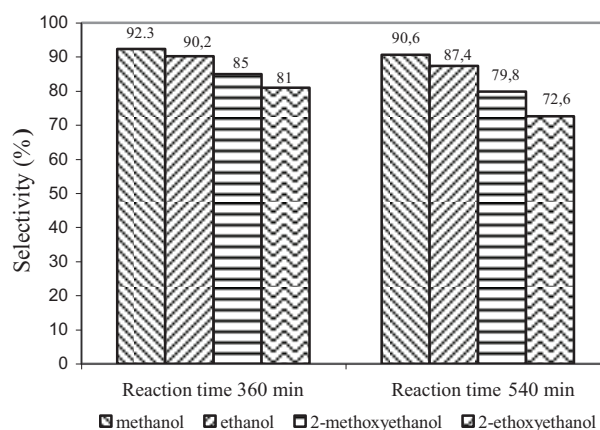


Figure 3. Dependence of selectivity on the reaction time. Reaction conditions: $\text{Pd}^0[\text{PPh}_3]_4$: 0.2 mmol; tetrahydropyran: 5 mL; acetates: 6.0 mmol; alcohol: 12.0 mmol; BSA, 12.0 mmol.

With ethanol, high conversion (90.1%) and selectivity (90.2%) towards the target product were achieved in less than 6 h, following the reaction onset (Figures 2 and 3, Run No. 2). For the reaction with 2-methoxyethanol, in 6 h, relatively good conversion (73.4%) and selectivity (85%) towards the isomeric (2-methoxyethoxy)cyclododec-2-ene were achieved (Figures 2 and 3, Run No. 3). Similar results were obtained with 2-ethoxyethanol as reagent. Further increases in the reaction duration did not affect the conversion values. Moreover, the selectivity towards the ether product dropped, due to side condensation processes, resulting in the formation of products with higher average molecular mass.

3.2. Kinetics of substitutive alkoxylation reaction

No data on the kinetics of this reaction have been found in the literature so far. Therefore, we attempted to study the kinetics phenomena associated with the substitution reaction between isomeric cyclododec-2-en-1-yl acetates (I) and primary aliphatic alcohols (II) at the constant molar ratio between the initial concentrations of acetate and alcohol $C_{I,0}/C_{II,0} = 1:4$, employing different catalyst concentrations. The experimental reaction temperature ranged from 328 K to 358 K, and reaction duration was set at 6 h.

In order to reduce the computing time, the fitting procedure between the experimental data obtained and the different models derived from the kinetic equations (1) was conducted by the so-called short-cut differential method.¹⁶ By doing this, a number of reaction rate kinetics models were eliminated early in the process on the basis of negative parameters or unexpected trends in the calculated concentrations. The refinement of the parameters for the remaining rival models was carried out by the fourth-order Runge–Kutta method combined with the method of Marquardt.¹⁷ The best fit, evaluated on the basis of the values of the sum of squares of residuals (SSR) and the values and significance of the parameters, was performed by the following rate equation:

$$\frac{dC_I}{dt} = -k_{eff} \times C_I \quad (3)$$

where $k_{eff} = (k_2 + k_3) \times C_{\text{Pd}(0)}$.

The Table summarizes the results obtained from the fitting procedure by using the model, corresponding to Eq. (3).

Table. Effective rate constants for the substitutive alkoxylation of cyclododec-2-en-1-yl acetates and alcohols and the 'lack of-fit' test.*

Compound with active hydrogen	T (K)	$k_{eff} \times 10^3$, L/mol min	$S_{um} \times 10^3$	'Lack of-fit' ratio
Methanol	328	0.4	0.008	0.01
	338	0.7	1.217	0.76
	348	1.2	8.012	5.01
Ethanol	328	3.1	16.050	10.03
	338	4.3	21.410	13.38
	348	5.1	1.202	0.75
	358	13.2	3.060	1.91

*Reaction conditions : $[PPh_3]_4$, 0.1 mmol; tetrahydropyran, 2.55 mL; acetates, 3.0 mmol; alcohol, 12.0 mmol; BSA, 6.0 mmol; reaction duration 6 h.

The parameters from the Table can be expressed as a function of temperature by the common Arrhenius equation (Figure 4):

$$k_{eff} = A_{eff} \exp(-E_{eff}/RT), \text{ where the gas constant } R \text{ is } 8.3143 \text{ J mol}^{-1} \text{ K}^{-1}.$$

The activation energy values E_{eff} for the reactions with methanol, ethanol, and 2-methoxyethanol were calculated as 52.1, 43.7, and 87.1 kJ mol⁻¹, respectively. Therefore, the substitution reaction of the isomeric cyclododec-2-en-1-yl acetates with 2-methoxyethanol was found to be more sensitive with respect to the reaction temperature. The overall comparison between the experimental concentrations of the cyclododec-2-en-1-yl acetate and those calculated on the basis of Eq. (3) is illustrated in Figure 5.

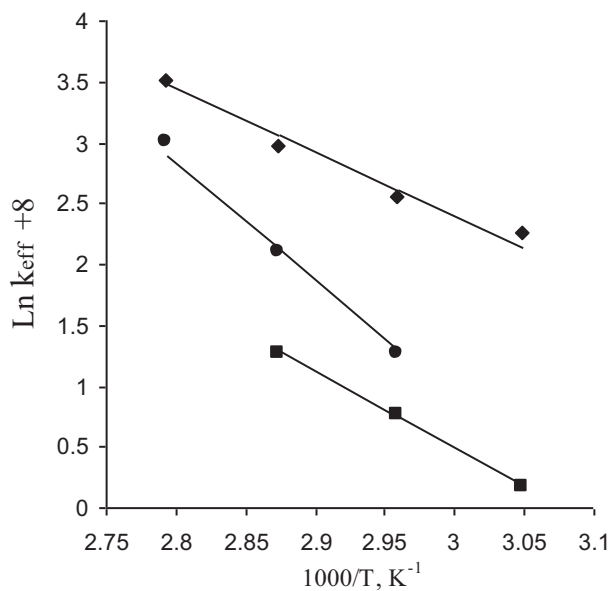


Figure 4. Arrhenius plot of kinetic parameters by the substitution reaction of isomeric cyclododec-2-en-1-yl acetates and primary aliphatic alcohols: (■) - methanol, (◆) ethanol, (●) 2-methoxyethanol; □ Eq. (3).

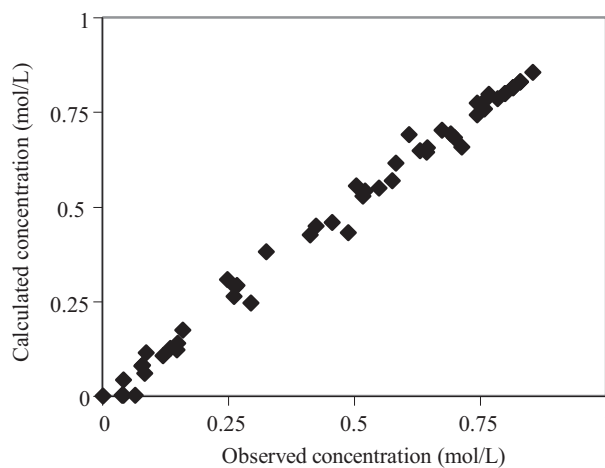


Figure 5. Parity plot comparing measured and calculated concentrations.

Since the catalytic reaction studied occurs in liquid phase, the enthalpy and entropy of activation were not calculated, due to the difficulties associated with various effects of interaction between both the reactants and active complex with the reaction medium.

The model predictions are in good agreement with the experimental data obtained at all conversions, and so the results from this study can be successfully applied to simulate a specified plant-scale reactor system.

4. Conclusions

The substitutive catalytic alkoxylation of isomeric cyclododec-2-en-1-yl acetates with primary aliphatic alcohols in the presence of palladium/triphenylphosphine complex $\text{Pd}^0[\text{PPh}_3]_4$ takes place with good selectivity at high substrate conversions.

The maximum attainable yield of ethers can be obtained at a molar ratio of aliphatic alcohols, BSA, $\text{Pd}^0[\text{PPh}_3]_4$ to cyclododec-2-en-1-yl acetates of 2:2:0.033 for reaction duration of 6 h and temperature of 348 K.

A simplified reaction network is derived on the basis of both the quantitative distribution of the products and preliminary information on the potential inhibition effects of the reactants and products involved. The reaction system can be described by the pseudo-first-order kinetics model. Any further improvement of the model requires more detailed information about the fundamental chemistry of the system studied.

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