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# Thermodynamic aspects of the [3+2] cycloaddition reaction of triphenyl-substituted TACs and the ethyl oleate

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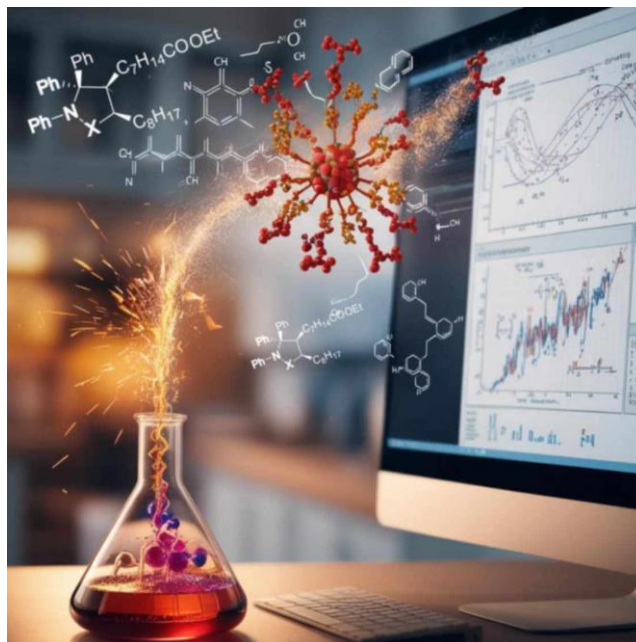
**Abstract:** The [3+2] cycloaddition reactions of triphenyl-substituted TACs and the ethyl oleate were examined on the basis of the DFT thermodynamic calculations. Free thermodynamic potentials of the reaction, values of the equilibrium constants K and equilibrium degrees were estimated on the basis of results derived from the vibrational analysis. Obtained results were compared with

experimental studies on the model reaction with the participation of the C,C,N-triphenylnitrone.

The [3+2] cycloaddition (32CA) reactions are the most universal and selective protocol for the preparation of different-type five-membered heterocycles [1,2]. Many of these compounds exhibit great potential in the pharmacy, biotechnology and other areas [3]. In the last time, results of some works regarding the application of the oleic acid and its esters were published [4].

The scientific value of some of these papers is however disputable. For example, some time ago, *Kumar* and coworkers [5] suggest that the [3+2] cycloadditions of nitrile N-oxides with oleic acid esters are realized under mild conditions, and with the full regioselectivity.

Very recent [6] reexamination of this case shed however a completely different light on the reactivity of the mentioned molecular system. In the continuation of this study we decided for the examination of the analogous reaction with the participation of selected phenyl-substituted allylic-type three atom components (TACs). As the model compound, we selected the C,C,N-triphenylnitrone **1a** due to its high reactivity in the previously described 32CAs [7]. Several reaction samples were tested with the monitoring of the reaction environment by HPLC technique (see Experimental Part). Unfortunately, in any case even trace amounts of expected cycloadducts were not detected. We assumed, that this was a consequence of the low thermodynamical stability of potential cycloadducts, determined by high sterical hindrances. For the verification of mentioned hypothesis we performed the DFT quantumchemical calculations regarding both theoretically possible reaction paths (Scheme 1). In analyzing the thermodynamic aspects of cycloaddition, individual paths were treated as independent reactions. Quantum chemical calculations were used to determine the values of the free thermodynamic potentials of the reaction. On their basis, the values of the equilibrium constants K and equilibrium degrees of conversion were calculated. It was found (Table 1), that in the benzene solution for both reaction paths of the reaction **1a**+**2** the values of the enthalpy of the formation are negative. The entropic factor determine however high positive values of the respective Gibbs free energies. As the consequence respective reaction constants are lower than $10^{-9}$. Next, estimated equilibrium conversion rates are equal 0. The increasing polarity of the reaction environment determine the further decreasing of the K value.

Therefore, from thermodynamical point of view, it is impossible to obtain satisfactory conversion within the analysed process. In a similar way similar processes with the participation of sulfur analog of the nitrone **1b** were analysed. It turned out that the thermodynamic parameters of this reaction are even less encouraging.
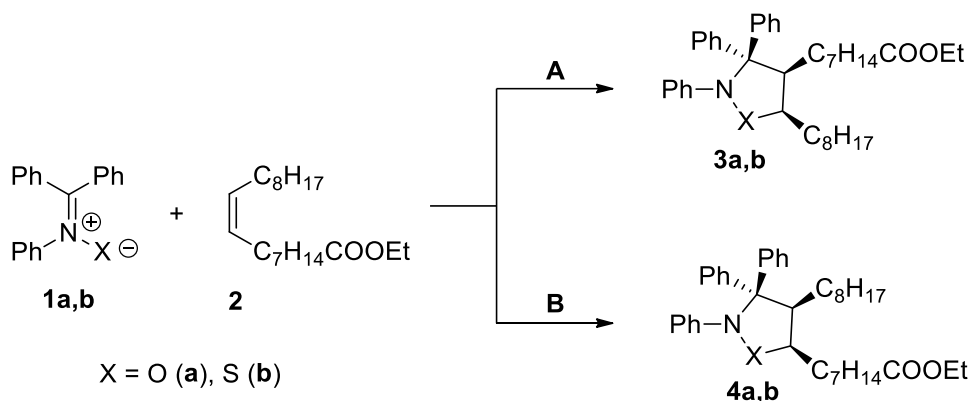


Scheme 1.

Table 1. Thermodynamical parameters for the [3+2] cycloaddition reactions between triphenyl-substituted TACs (**1a,b**) and the ethyl oleate (**2**) in different solutions according to the B3LYP/6-311G(d) (PCM) calculations ($\Delta H$ and $\Delta G$ are in kcal/mol; $\Delta S$ are in cal/molK).

| | Solvent | Reaction path | | | | | | | | | |
| | | **A** | | | | | **B** | | | | |
| | | $\Delta H$ | $\Delta G$ | $\Delta S$ | $K \cdot 10^{10}$ | $\alpha$ | $\Delta H$ | $\Delta G$ | $\Delta S$ | $K \cdot 10^{10}$ | $\alpha$ |
| **1a+2** | benzene | -2.1 | 15.5 | -59.1 | 35.1 | 0.000 | -1.3 | 16.2 | -58.5 | 15.0 | 0.000 |
| | acetone | -0.8 | 16.7 | -58.8 | 7.940 | 0.000 | 0.2 | 18.0 | -59.6 | 1.600 | 0.000 |
| | water | -0.7 | 16.7 | -58.3 | 8.160 | 0.000 | 0.4 | 18.1 | -59.5 | 1.330 | 0.000 |
| **1b+2** | benzene | -0.5 | 17.1 | -58.9 | 4.900 | 0.000 | 1.3 | 19.4 | -60.7 | 0.272 | 0.000 |
| | acetone | 2.4 | 20.1 | -59.3 | 0.115 | 0.000 | 4.2 | 22.4 | -61.2 | 0.006 | 0.000 |
| | water | 2.8 | 20.4 | -59.3 | 0.071 | 0.000 | 4.6 | 22.9 | -61.5 | 0.003 | 0.000 |

## Materials and methods

### General

Melting points were determined on a Boetius apparatus and were uncorrected. ^{1}H-NMR spectra were taken on a Bruker (500 MHz) spectrometer, using TMS as an internal standard, and CDCl₃ as a solvent. Liquid chromatography (HPLC) was done using a Knauer apparatus equipped with a UV-VIS detector. FTIR spectra were done with Thermo Scientific Nicolet 6700 spectrometer. A pellet was made from KBr. For monitoring of the reaction progress, LiChrospher 100-10-RP column (4x240 mm) and 55% THF as the eluent at flow rate 1 ml/min were used. Commercially available chemicals (Sigma-Aldrich, POCh) were used.

Preparation of the C,C,N-triphenylnitrone

The solution of 0.015mol of the diphenyldiazomethane (prepared according to the known procedure [8] in the 10mL of the petroleum ether was cooled to the 0°C and mixed with the cooled solution of the 0.0015 mol of the nitrosobenzene in the 10mL of the benzene. After 24h the crystalline product was filtered off and recrystallized from the toluene. Finally, 2.5g (64%) of the triphenyl nitrone was obtained as a yellow crystals. M.p.: 225-226°C ( Ref[7]: 224-227 °C);^{1}H NMR (ppm): 7.17-8.12 (15H, m); IR (cm$^{-1}$): 3047, 1592, 1488, 1452, 1439, 1346, 1235, 1074, 957, 772, 760, 704, 691, 654, 612 UV-VIS (nm): 206, 234, 312.

Reaction of the C,C,N-triphenylnitrone with ethyl oleate

REACTION PROCEDURE A

A solution of the 0.005 mol of the C,C,N-triphenylnitrone and 0.010 mol of the ethyl oleate was stirred at the at ambient temperature and normal pressure, for 48h. The reaction mixture was monitored using HPLC technique. Any reaction progress was not detected.

REACTION PROCEDURE B

A solution of 0.005 mol C,C,N-triphenylonitron and 0.010 mol ethyl oleate was heated in toluene at 80°C, under a reflux cooler at normal pressure, for 48 hours. The reaction mixture was monitored using HPLC technique. In the postreaction mixture, only some amount of the benzophenone was detected, next to unreacted reactants.

Quantumchemical calculations

Quantumchemical calculations were performed using the B3LYP/6-31G(d) level of theory. Earlier, the same algorithm was used for the interpretation of the reaction course of different type cycloaddition processes [9-12]. The optimization process was performed using the FOPT keyword. For all optimized molecules, the vibrational analysis was performed.

Assuming that at the initial moment the reaction mixture consists only of equimolar amounts of C,C,N-triphenylnitrone and the appropriate nitroalkene, the following expression for the equilibrium constant $K$ was obtained for each of the two regioisomeric reaction paths:

$$K = [2 \, \alpha - (\alpha)^2]/[1 - 2 \, \alpha + (\alpha)^2] \quad (1)$$

Where after transformation we get the quadratic equation of the variable $\alpha$:

$$(K + 1) \, (\alpha)^2 - 2 \, (K + 1) \, \alpha + K = 0 \quad (2)$$

One of the solutions of equation (2) determines the equilibrium transformation rate of a single second-order reaction:

$$\alpha = 1 - [1/( \, K + 1)^{1/2}]$$

## Conclusions

Continuing the research on the [3+2] cycloaddition reaction of substituted allyl triatomic components (TAC) with fatty acids or their esters, the course of the reaction between C,C,N-triphenylnitrone 1a and ethyl oleate was investigated. Based on the information obtained with the support of quantum chemistry, from the thermodynamic point of view, it is not possible to obtain a satisfactory conversion in the analyzed processes.

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