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The kinetics of the thermal rearrangement 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazoles, **1**, to the corresponding 1-ethyl-3,5-diphenyl-1-alkyl-1*H*-1,2,4-triazoles, **2**, was studied in 15-Crown-5 and octadecane at 330 °C. The reaction was very slow in octadecane but proceed well in 15-Crown-5. The reaction order for the reaction was not constant but changed from an initial second order rate law towards a first order rate law as the reaction progressed. This was confirmed by the concentration dependent reaction order, n_c , which was larger than the time dependent rate law, n_t . The rationale for the observation was, that at high substrate concentrations the reaction order was second order while at lower concentrations a competing solvent assisted reaction plays an increasing important role. The data were in agreement with a mechanism in which the neutral 4-alkyl-triazoles in an intermolecular nucleophilic displacement reaction form a triazolium triazolate, which in a subsequent nucleophilic reaction gives the observed product.

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Introduction.

We have reported studies of the thermal rearrangement of neat 4-alkyl substituted 4*H*-1,2,4-triazoles, to the corresponding 1-alkyl-1*H*-1,2,4-triazoles [1]. There is good evidence for a mechanistic pathway that involve an initial bimolecular nucleophilic displacement reaction that lead to the formation of a "salt", a triazolium triazolate, resulting in an activation of the triazole ring as a leaving group. Subsequent nucleophilic attack by the triazole anion at the alkyl group positions of the triazolium ion, yield the products. This reaction scheme is bimolecular in nature, Scheme 1. Thus, in the 4-alkyl-substituted triazoles the heterocyclic ring behaves as a leaving group, and give rise to products corresponding to both substitution and elimination reaction pathways [2]. Previous work excluded a concerted, unimolecular mechanism and radical reaction. This reactivity somewhat resemble that of quaternary ammonium salts, which may undergo substitution as well as elimination reactions. Recent results also appeared to rule out any unimolecular reaction steps [3].

The anion corresponding to 3,5-diphenyl-1,2,4-triazole is a good nucleophile, which reacts exclusively at the *N*-1 ring position. Reaction at the *N*-4 position was never observed, neither in thermolysis reactions nor with a variety of alkylation reagents [2,4].

To gain further insight into the mechanistic details of this reaction, we have conducted a kinetic study of the rearrangement of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole, **1**, in solution. Due to the high thermal stability of the triazoles, high

temperatures were required, making such studies difficulty to carry out. For that reason, a previous kinetic study dealt with reactions in melts of the pure triazoles. The results of that study supported the rearrangement mechanism described above. An interesting observation, however, was that rearrangements were also taking place in the crystalline state [5]. To get a better understanding of the details of the mechanism a study of the reactions in solution was necessary.

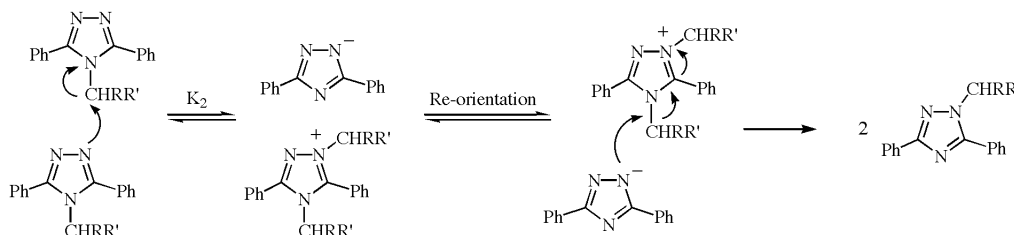
EXPERIMENTAL

The solvents used under the extreme conditions in this study, was octadecane, (C₁₈H₃₈), as a non-polar solvent and 15-Crown-5 as an example a better solvating but inert, non-nucleophilic solvent. The solvents were of analytical grades and freshly distilled prior to use. Flash points were exceeded in all experiments, and reactions were therefore carried out in nitrogen atmosphere. Under the reaction conditions no noticeable decompositions of the solvents was observed, (GC). The triazole we have studied here was 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole, **1**, which rearranged to the corresponding 1-ethyl-3,5-diphenyl-1*H*-1,2,4-triazole, **2**. Compounds **1** and **2** were prepared and purified as described earlier [1]. These compounds were fully soluble in the solvents at 80-90 °C in the concentration ranges applied in this study.

Instrumental Methods.

¹H and ¹³C NMR spectra were recorded on a JEOL JNM-EX400 FT NMR or a JEOL FX-100 NMR spectrometer, using CDCl₃ as the solvent and tetramethylsilane (TMS) as the internal standard. IR and GC-IR spectra were obtained on a Nicolet 20-

Scheme 1



SXC FT-IR (GC Carlo Erba 5160, 25 m, CP-Sil-5 CB). Mass spectra were recorded on a AEI MS-902 spectrometer at 70 eV (IP) and 200 °C inlet temperature. GC measurements were performed on a Varian 3700 gas chromatograph equipped with a BP-1 capillary column (24 m).

Kinetics.

Reaction rates were determined by heating solutions of known concentrations in the appropriate solvent, which also contained tetracosane, ($n\text{-C}_{24}\text{H}_{50}$) as an internal standard. For a kinetic experiment, the reaction mixtures were placed in sealed capillary tubes (1.5 x 60 mm). This operation was accomplished by placing the tubes with the open end immersed in a heated solution (ca. 80 °C) of the substrate of known concentration, in a flask which was then evacuate. When ambient pressure was restored by letting nitrogen into the flask, the tubes were filled with the solution of **1** in the appropriate solvent. The filled tubes were then sealed.

The tubes were then placed in refluxing nonadecane, ($\text{C}_{19}\text{H}_{40}$, bp 330 °C at 1 atm), which was kept under a nitrogen atmosphere. At various times, sample tubes were taken out, cooled in ice water, cleaned, crushed and the content dissolved in dichloromethane. The composition of the mixture was determined by GC, and the amount of **1** still present and **2** formed was measured by GC using the internal standard method. All the compounds were calibrated with respect to the internal standard. In all experiments a mass balance of better than 95 % was obtained. Twenty tubes were used for each kinetic experiment. The thermolyses in 15-C-5 was carried out using 4 different concentrations of **1**, covering approximately one order of magnitude (1.5×10^{-2} - 12.8×10^{-2} mol / kg).

Rate Expression.

Rate data was fit to the integrated rate expressions. Thus, to explore first order kinetics, $\ln[\mathbf{1}]$ was plotted vs time and k_1 was determined as the slope of the straight line. For second order kinetics was plotted $1/[\mathbf{1}]$ vs time, and the rate constant k_2 determined from the slope of the line. Representative examples are shown in Figures 1a and 1b respectively.

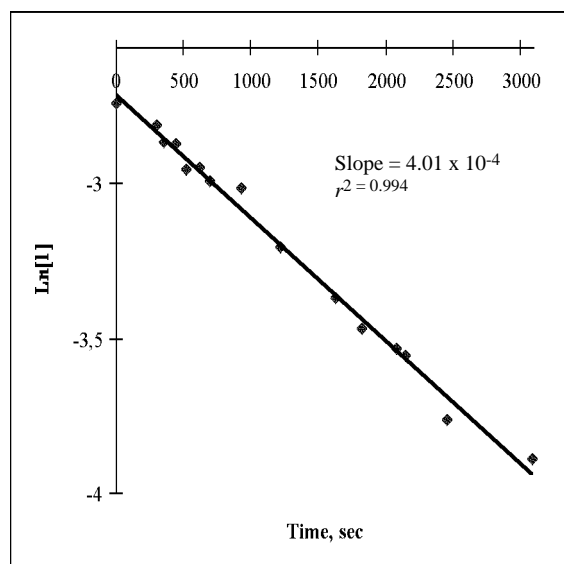


Figure 1a. A representative example of a plot of $\ln[\mathbf{1}]$ vs. time for $[\mathbf{1}]_0 = 0.0647$ mol/kg.

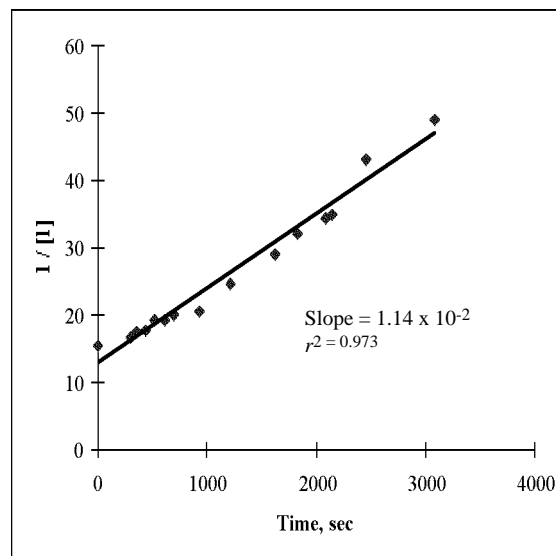


Figure 1b. A representative example of a plot of $1/[\mathbf{1}]$ vs. time for $[\mathbf{1}]_0 = 0.0647$ mol / kg.

Kinetics for the thermolysis of **1** in 15-C-5.

The results obtained for reactions in 15-C-5 is shown in Table 1. The data surprisingly appeared to agree reasonably well with first but also with a as second order rate law. The data therefore did not allow a clear assignment of kinetics to a reaction mechanism. The reason for this apparent inconsistency may be that we here have a kinetic system that is shifting from the one reaction order to the other as the reaction progress. To investigate this possibility we did a further investigation of the reaction order.

Table 1

The Rate Laws for the Thermolysis of **1** at 330 °C in 15-C-5.

| Concentration of 1 , Mol/kg x 10 ² | Correlated to First order rate expression $10^4 \times k_1$ (sec ⁻¹) | r ² | $\sigma \times 10^5$ | Correlated to Second order rate expression $10^2 \times k_2$ (kg mol ⁻¹ sec ⁻¹) | r ² | $\sigma \times 10^3$ |
|--|--|----------------|----------------------|--|----------------|----------------------|
| 1.57 | 2.78 | 0.966 | 3.2 | 3.79 | 0.894 | 7.7 |
| 3.53 | 4.17 | 0.986 | 3.1 | 2.20 | 0.977 | 2.1 |
| 6.47 | 4.01 | 0.994 | 1.7 | 1.14 | 0.984 | 7.8 |
| 12.8 | 6.56 | 0.995 | 2.5 | 0.99 | 0.987 | 6.2 |

The reaction-order was analysis using the differential method., determining the reaction order with respect to concentration, n_c , [6]. This was accomplished by measuring the initial rates for a series of reactions with different starting concentrations. In a double logarithmic plot of the log of the reaction rate versus log of the starting concentration, the slope, of what now should be a straight line, gives the concentration dependent reaction order, n_c . The intercept with the y-axis corresponds to the rate constant, k_r . The data obtained for the system here studied are shown in Table 2. The corresponding plot of $\log [\mathbf{1}]_0$ vs $\log (d[\mathbf{1}]_0/dt)$ is shown in Figure 2. A linear regression analysis shows that the data points lie on a straight line ($r^2 = 0.998$, $\sigma = 0.075$) with the slope 1.96. This is in very good agreement with a second order rate law.

Table 2

The Initial Reaction Rates for Thermolysis of **1** in 15-C-5 at 330 °C

| | | | | |
|-------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Concentration of 1 , mol/ kg | 1.57×10^{-2} | 3.53×10^{-2} | 6.47×10^{-2} | 12.8×10^{-2} |
| $d[\mathbf{1}]_0 / dt$ mol/kg . sec | 1.00×10^{-6} | 4.02×10^{-6} | 1.41×10^{-5} | |

The intercept value of -2.50 was also in reasonable agreement the second order rate constants reported in Table 1.

To investigate the possibility that the reaction order changed in the course of the reaction, we also determined the reaction order with respect to time, n_t . This was done by considering a single run and measure the slopes of the concentration/time graph at various times. This is equivalent to measuring the rate for a number of reactant concentrations. The experimental data are shown in Table 3.

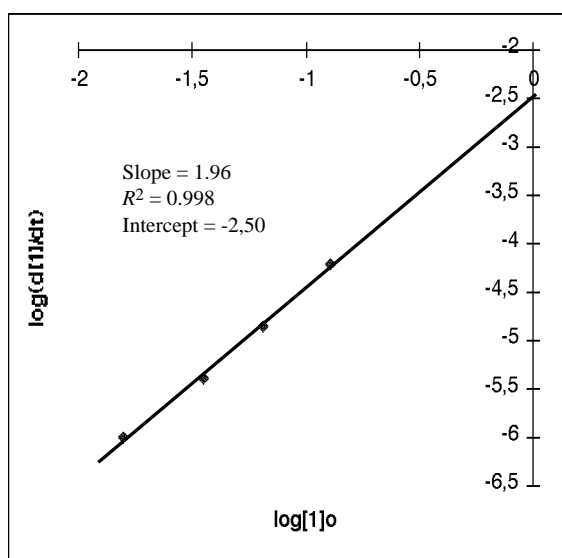


Figure 2. The concentration dependent reaction-order, n_c . The log-log plot of the initial reaction rates as a function of the starting concentrations.

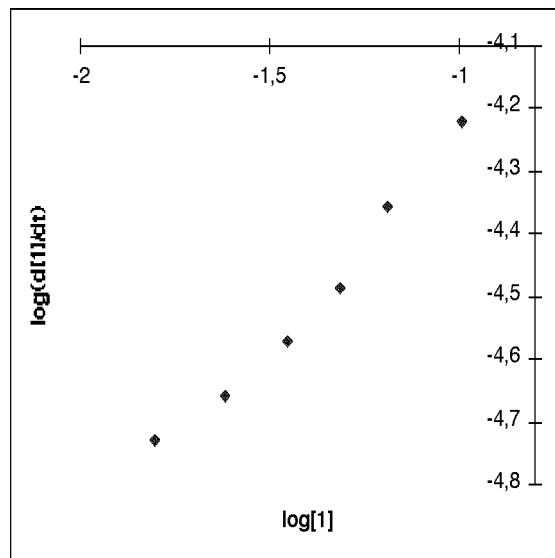


Figure 3. The time dependent reaction-order, n_t . The log-log plot of $\log[1]$ vs. $\log(d[1]/dt)$.

The reactions in octadecane are slow, and over time carbonation of the starting material took place. GC measurements using internal standard showed that after 146 hours merely 37 % of the substrate was left in the reaction mixtures, together with minor amounts of the rearrangement product, but without the presence of other reaction products. An explanation may be that at high temperatures in non-polar solvents, alternative radical reaction pathways may become important. For these reasons we did not proceed further with measurements in octadecane.

Results and Discussion.

When the $n_c > n_t$ it is usually interpreted that the reaction is auto-catalytic. However, there may be an alternative explanation that rationalizes the $n_c > n_t$ observed in this study. The solvent 15-C-5 solvent, being a non-polar solvent

Table 3

The Instantaneous Reaction Rate for Thermolysis of **1** in 15-C-5 at 330 °C. $[\mathbf{1}]_0 = 12.8 \times 10^{-2}$ mol/kg Followed to Approximately 70% conversion

| | | | | | | |
|---------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Concentration of 1 , Mol / kg | 10.2×10^{-2} | 6.47×10^{-2} | 4.82×10^{-2} | 3.53×10^{-2} | 2.41×10^{-2} | 1.57×10^{-2} |
| $d[\mathbf{1}]_t / dt$ mol / kg . sec | 6.02×10^{-5} | 4.40×10^{-5} | 3.27×10^{-5} | 2.68×10^{-5} | 2.19×10^{-5} | 1.87×10^{-5} |

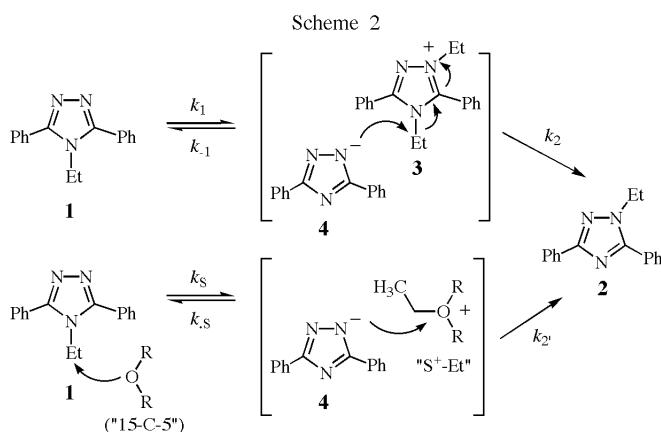
The logarithm of the concentration was plotted vs the logarithm of the instantaneous rate of the reaction, *i.e.*, $\log [\mathbf{1}]_t$ vs $\log (d[\mathbf{1}]_t/dt)$. This graph is shown in Figure 3. The points may fit to a line with slope corresponding to a time dependent reaction order, $n_t = 0.64$ ($r^2 = 0.988$, $\sigma = 0.051$). However, we also see that the slope for high concentrations tends to be larger than for lower concentration. This is another indication for the reaction order not being the same all the time and that the reaction -order changes from initially second order to first order as the reaction progress.

Kinetics for the Thermolysis of **1** in Octadecane, $C_{18}H_{38}$.

The reaction in this solvent were very slow even at 330 °C. The observed data were of poor quality, and attempts to extract meaningful rate expressions failed to yield realistic relationships.

has special solvating properties towards cations. In light of the proposed initial formation of the triazolium triazolate intermediate in the upper pathway in Scheme 1, solvation may explain why the reaction is facile in 15-C-5 and not in octadecane. The greater rate in 15-C-5 is consistent with the postulated existence of a solvent stabilized ion-pair like intermediate. At higher substrate concentrations, the intermediate could be a triazolium triazolate, while at low substrate concentrations a 15-C-5 "oxonium" triazolate ion pair. Support for this reaction scheme is also found in the very low reactivity in octadecane, that here is a poorly solvating solvent and which can not participate as a nucleophile in the reaction. A good approximation is to assume that salt formation is the

rate-determining step, followed by rapid conversion of the charged components into the neutral product. 15-C-5 has weak nucleophilic properties, which may become apparent under the reaction conditions described here. We therefore assume that 15-C-5 may react with **1** leading to the formation of an oxonium salt as indicated in the lower pathway in Scheme 2.



This reaction scheme leads to the following rate expressions, after using the steady-state approximation on ionic intermediates **3/4** and **4/S-Et** respectively.

Triazole Reaction:

$$V = K_1 k_2 [\mathbf{1}]^2 \quad (1)$$

Solvent Assisted Reaction:

$$V = K_S k_2' [\mathbf{1}] \quad (2)$$

Total Reaction:

$$V_{total} = K_1 k_2 [\mathbf{1}]^2 + K_S k_2' [\mathbf{1}] \quad (3)$$

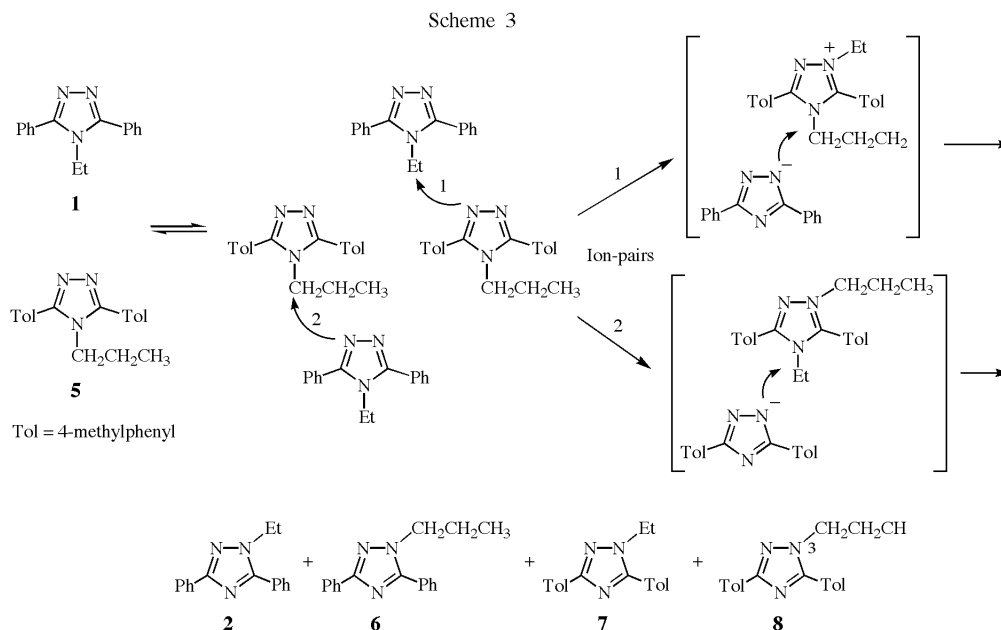
The equilibrium constant K_S includes the solvent concentration as a constant. These rate expressions are in agreement with a reaction scheme where initially the **[1]** concentration is still high, the reaction follows a second order rate law but as **1** is consumed, the solvent assisted reaction becomes prevalent, and the first order rate law more important.

Cross-over Experiments.

Assuming the proposed bimolecular triazolium triazolate mechanism takes place, the presence of another 4-alkyl triazole would give rise to formation of cross-over products. This effect was observed previously on thermolysis of melts containing mixtures of neat triazoles [3]. However, will it also take place in solution? To investigate this, mixtures of triazole **1** and 4-propyl-3,5-di(4-methylphenyl)-1*H*-1,2,4-triazoles, **5**, were thermolyzed in 15-C-5 solutions. Thus, a solution under nitrogen in a sealed tube containing 34.2 mg of **1** and 46.9 mg of **5** in 1.24 g 15-C-5 was thermolyzed at 330 °C for 75 minutes. GLC analysis of the product mixture with co-injection of authentic compounds and mass spectrometric analysis, clearly showed that all the expected products **2**, **6**, **7**, **8** were formed in a 10:18:22:41 ratio as shown in Scheme 3.

Conclusion.

The study of the kinetics of the thermal rearrangement 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazoles, **1**, to the corresponding 1-ethyl-3,5-diphenyl-1*H*-1,2,4-triazoles, **2**, shows that the reactions are extremely slow in octadecane but proceed well in 15-C-5. Acceptable mechanistic evidence could not be obtained in octadecane. In 15-C-5 solvent the reaction order was not constant but changed from an initial second- to a first order rate law as the



reaction progressed. This was further confirmed by the finding that the concentration dependent reaction order n_c was larger than the time dependent rate law, n_r , an observation normally characteristic of an auto-catalytic reaction. However, the rationale here is that at high substrate concentrations the reaction is second order in substrate, while at lower concentrations a competing solvent assisted reaction plays an increasingly important role. Each pathway proceeds therefore through a mechanism involving the formation of ionic intermediates. These results corroborate and strengthen the case for the presence of triazolium ions as intermediates in the thermal isomerization of 4-alkyl-3,5-diaryl-4*H*-1,2,4,-triazoles. The proposed mechanism was further supported by the cross-over results.

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