A Stopped-Flow Kinetic Study of the Reaction of *trans*-1-(Dimethylamino)-1,3-butadiene with Dimethyl Dicyanofumarate

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Received December 21, 1991

Key Words: Zwitterion formation and decay, kinetics of / Cycloadditions

trans-1-(Dimethylamino)-1,3-butadiene and dimethyl dicyanofumarate react in acetonitrile and dichloromethane at -40°C with a second-order rate constant of 10^7 to 10^8 $\mathrm{l\ mol^{-1}\ s^{-1}}$. This was determined by following the decay of the UV absorption of diene and dienophile with a stopped-flow spectrofluorimeter. After disapperance of the reagents a new absorption ($\lambda_{max} = 400$ nm, $\lg\varepsilon = 2.514$) is recorded which decays by a first-order process. The analysis of the kinetic data ($E_a = 14.5 \pm 0.1$ kcal mol^{-1}, $\lg A = 14.71 \pm 0.05$, $\Delta H^{+} = 14.1 \pm 0.1$ kcal mol^{-1}, $\Delta S^{+} = 7.2 \pm 0.2$ cal mol^{-1} K^{-1}, $\Delta G^{+} = 11.95 \pm 0.01$ kcal mol^{-1}) in combination with stereochemical studies on the cycloaddition of the *E/Z* isomeric dienophiles dimethyl dicyanofumarate and dicyanomaleate leads to the interpretation that the new species is a zwitterion.

The systematic study of (4 + 2) cycloadditions between a diene and a dienophile as a function of substitution has shown that these reactions do not occur via one single mechanism[1,2]. Evidence has been presented that biradical and zwitterionic structures are the most plausible intermediates[3–5]. These conclusions derive from indirect evidence, most often from stereochemical studies. If a cycloaddition takes place with loss of stereochemistry in the reactants an intermediate is indicated. If further the rate of reaction is measured as a function of the solvent polarity a distinction between a biradical and zwitterionic pathway is possible, Huisgen[6,7] has shown this in a very elegant manner for (2 + 2) cycloadditions. The measurement of activation volumes can also support the discrimination between different pathways, even allowing the recognition of concurrent concerted and two-step mechanisms[3]. Direct observation of zwitterions has become possible in recent years. Hartmann and Heuschmann[8] have established the structure of a zwitterion which is formed from a tetrazine and a ketene N,N-acetal by X-ray crystallography and have discussed its significance in the cycloaddition process. We have characterized zwitterions formed from bis(1,1-dimethylamino)-1,3-butadiene and TCNE[9] or dimethyl dicyanofumarate[10] which, however, do not cyclize to (4 + 2) adducts. Quast et al.[11] have carried out similar studies on 1,3-dipolar cycloadditions of electrophilic azides to a ketene aminal. Direct kinetic measurements on zwitterions have not been reported so far. It has also not been known what the kinetics of disappearance of such species should be like. Here we present results of measurements obtained by stopped-flow techniques which suggest that we have observed for the first time a transient zwitterion and determined the activation parameters for its disappearance in the cycloaddition of *trans*-1-(dimethylamino)-1,3-butadiene to dimethyl dicyanofumarate.

trans-1-(Dimethylamino)-1,3-butadiene (**1**) reacts with dimethyl dicyanofumarate (**2**) or dimethyl dicyanomaleate in high yield to give a (4 + 2) cycloadduct **3** the structure of which has been determined by NMR spectroscopic techniques[12]. The cycloaddition of the *E/Z* isomeric dienophiles provides one identical product. A careful analysis of the reactions suggests a non-concerted formation of **3**. The substitution patterns of diene and dienophile are in favor of a zwitterion as intermediate and not a diradical.

Results and Discussion

If 8.0×10^{-3} M solutions of the reactants in acetonitril are mixed in a stopped-flow spectrofluorimeter connected to a rapid-scan unit at -40°C, a new absorption is recorded after 6 ms with $\lambda_{max} = 400$ nm (Figure 1). Due to the time resolution of the spectrometer (mixing time 2 ms) the shortest time after which a spectrum can be recorded (recording time 5 ms) is ca. 4–6 ms. The new absorption occurs at a longer wavelength than that of the reactants and might be interpreted as being due to a charge-transfer (CT) complex. It was, however, noticed that the absorptions of the reactants had already disappeared when the spectrum was recorded. This shows that the new spectrum cannot be due to a CT complex where a new band must appear in addition to the absorptions of the reactants[13]. At -40°C the absorption decays by a first-order process with $k = 10.7$ s^{-1} ($\tau_{1/2} = 0.065$ s). Time-resolved measurements at $\lambda_{max} = 400$ nm allowed the determination of $\varepsilon = 327$ M^{-1} cm^{-1}. This value was calculated on the basis that all starting material had been converted to the new species.

The disappearance of reagents was monitored with the stopped-flow equipment at -40.3°C and at $\lambda = 276$ nm (5.0×10^{-5} M solutions in acetonitrile). The reaction is so fast that only the decay of a residual absorption can be followed. It can be analyzed by a second-order rate law and gives $k_2 = (3.8 \pm 0.05) \times 10^7$ $\mathrm{l\ mol^{-1}\ s^{-1}}$, corresponding to a first half-life time of 0.55 ms. At the higher concentration of 8.0×10^{-3} M which was used for the measurements at $\lambda = 400$ nm, $\tau_{1/2}$ would correspond to 0.35 ms. This high rate constant supports the observation that at the time where the absorption at $\lambda = 400$ nm is recorded the diene and dienophile have already reacted.

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Figure 1. UV/VIS spectrum of the intermediate **4** formed from **1**

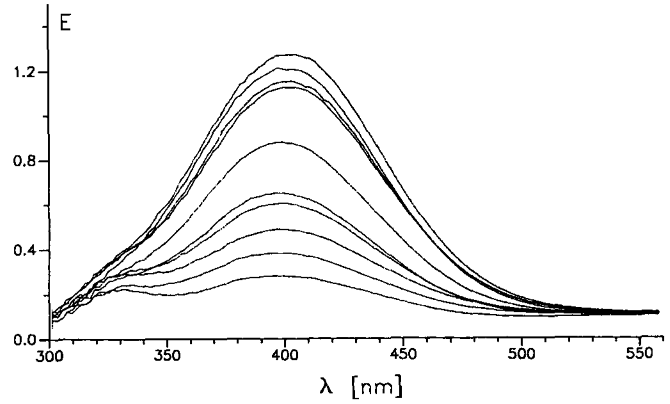
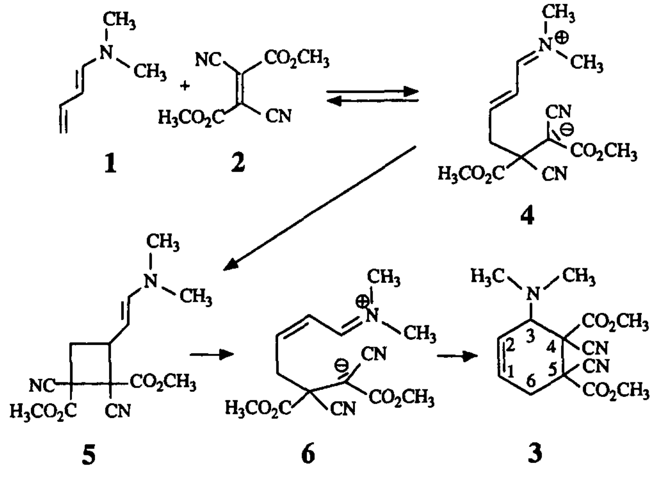


Figure 1. UV/VIS spectrum of the intermediate **4** formed from **1** and **2** in acetonitrile at −40°C. Dead times (seconds) after which the spectra were taken with the rapid-scan unit: 0.006, 0.009, 0.018, 0.023, 0.048, 0.076, 0.086, 0.123, 0.138, 0.176

The activation parameters for the disappearance of the intermediate were evaluated from measurements between −40°C and −16.6°C in acetonitrile. The Arrhenius activation energy is 14.5 ± 0.1 kcal mol^{-1}, lg$A$ corresponds to 14.71 ± 0.05 and is in agreement with a merely first-order reaction. The Eyring parameters are $\Delta H^{+} = 14.1 \pm 0.1$ kcal mol^{-1}, $\Delta S^{+} = 7.2 \pm 0.2$ cal mol^{-1} K^{-1} and $\Delta G^{+} = 11.95 \pm 0.01$ kcal mol^{-1}.

Concerted (4 + 2) cycloadditions display high negative activation entropies[1,2] (ca. −30 to −40 cal mol^{-1} K^{-1}). The decay of CT complexes is also connected with high negative activation entropies[14]. Therefore, the positive value of the activation entropy in this case is of particular interest. It can be interpreted on the basis that the new absorption in acetonitrile is due to the zwitterion **4**. The formation of the zwitterion goes along with build-up of charges which will induce strong solvation by acetonitrile molecules. Disappearance of such an intermediate on the other hand requires destruction of charges and consequently desolvation. This latter process should have a positive activation entropy. The experimental observation of $\Delta S^{+} = +7.2 \pm 0.2$ cal mol^{-1} K^{-1} is thus in agreement with the zwitterion hypothesis.



The stereochemical studies on the cycloaddition of dimethyl dicyanomaleate and dimethyl dicyanofumarate[12] also suggest that the reaction takes place stepwise with a zwitterion as the most plausible intermediate.

Diene **1** exists mainly in the antiperiplanar conformation[12]. The intermediate should be formed, therefore, in conformation **4** where a *trans*-substituted double bond is present between the atoms C-2 and C-3 of the former diene. Such structures have been established for zwitterions formed from 1,1-bis(dimethylamino)-1,3-butadiene and electron-deficient olefins[9,10]. A direct formation of the (4 + 2) cycloadduct from this structure is not possible without rotation about the C-2/C-3 bond of the zwitterion. The substructure corresponds to a substituted allylic cation. Even though rotational barriers to this type of substituted allylic cation are not known it can be anticipated from rotational barriers in other such cations[15] that under our conditions a rotation should be slow. The formation of a vinylcyclobutane structure **5** with subsequent ring opening to **6** presents the simplest way to the cycloadduct. As we do not observe **5** by ^{1}H NMR, even not at low temperature, its ring opening to **6** and ring closure must occur at such a rate that no detectable concentration of **5** accumulates. The activation parameters thus describe the formation of the vinylcyclobutane **5**.

It is interesting that in dichloromethane as solvent the situation is different. The transient absorption cannot be recorded, indicating that the intermediate does not build up to detectable concentrations. At the same time the rate constant for the disappearance of reactants is even slightly higher than in acetonitrile [ca. (1−2) × 10^{8} l mol^{-1} s^{-1}]. Such rate increases in going from acetonitrile to dichloromethane have been observed in other studies where zwitterions are involved in (4 + 2) cycloadditions[4]. These findings are interpreted as follows: In dichloromethane the zwitterion is less stabilized by solvation, with the consequence that ring closure to **5** is faster, thus not building up in high enough a concentration for detection. The other explanation would be a concerted cycloaddition in dichloromethane. This, however, would contradict the stereochemical observations which were obtained in dichloromethane[12].

It was attempted to determine the activation parameters for the disappearance of the reactants. In the range from −40°C to +20°C no systematic variation of the rate constans could be found in acetonitrile. The value was ca. (4 ± 1) × 10^{7} l mol^{-1} s^{-1}. This value approaches diffusion control, pointing out that almost each encounter of reactants leads to a molecule of the intermediate and that the activation parameters will be mainly determined by the solvent viscosity.

Conclusion

The experimental results described in this study allow for the first time to follow kinetically the disappearance of a zwitterionic intermediate in a stepwise (4 + 2) cycloaddition. The formation of the intermediate takes place almost diffusion-controlled. It remains to be seen whether zwitterions can be identified kinetically in other cases. Work in this area is in progress.

This work was supported by the *Deutsche Forschungsgemeinschaft.*

Experimental

Reagents and Cycloaddition: Preparation of reagents and the cycloaddition of **1** to **2** are described in ref.[12].

Stopped-Flow Measurements: The kinetic experiments were carried out with a cryostopped-flow spectrofluorimeter from HI-TECH Scientific[16]. The spectrometer was equipped with a Spectrascan MG 3000 unit which allowed scans from 200–800 nm within ca. 7 ms. The apparatus could be thermostated from -100°C to $+60$°C with an accuracy of ± 0.1 °C. The spectrometer was connected to a Hewlett-Packard 300 desktop computer and used the DataPro software suite of HI-TECH Scientific for acquisition, presentation and analysis of kinetic data.

Kinetic Measurements: Equimolar solutions of **1** and **2** in acetonitrile and dichloromethane which had been purified by standard procedures and were kept under argon were used for the kinetic measurements. The new absorption ($\lambda_{max} = 400$ nm in acetonitrile) was recorded with 8.3×10^{-3} M solutions of the reactants. The molar extinction coefficient ($\varepsilon_{400} = 327$ M^{-1} cm^{-1}) was determined from time-resolved measurements. The initial extinction was obtained by extrapolating the values to $t = 0$. The activation parameters for the decay of the absorption were evaluated from measurements at $\lambda = 400$ nm in the temperature range of -40.0°C to -16.6°C. Measurements were carried out at temperature intervals of 3–4°C, a total of 9 rate constants was used for the regression analysis ($R^2 = 99.99\%$). The disappearance of reactants was measured at 276 nm, the λ_{max} value of the dienophile ($\lg\varepsilon = 4.353$). The molar extinction of the dienophile at this wavelength was $\lg\varepsilon = 2.876$. Due to the rapid decay of the absorption only part of the curve could be analyzed. The kinetic data were evaluated according to a second-order rate law with consideration of both the absorption of diene and dienophile.

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CAS Registry Numbers

1: 139943-10-5 / **2**: 35234-87-8 / **4**: 140201-50-9