THE STEREOSPECIFICITY OF DIAZOMETHANE CYCLOADDITIONS

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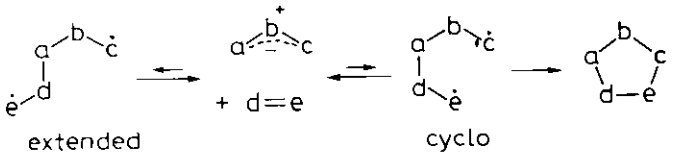
Dedicated to Adolf Butenandt on the Occasion of His Seventy-fifth Birthday

The 1,3-dipolar cycloadditions of diazomethane to methyl angelate and methyl tiglate proceed with >99.94 % and >99.997 % retention of dipolarophile configuration. The unconsumed dipolarophiles show <0.008 and <0.0006 % cis,trans isomerization. The mechanistic implications are discussed.

The Problem

Any report of a stereospecific reaction should be specified by yields as well as the analytical limits for the "wrong" isomer. Retention of dipolarophile configuration was observed for numerous 1,3-dipolar cycloadditions [1] - without exception. The experiments were carried out with pairs of cis,trans isomeric olefins ; the nmr analytical limit for the "nonstereospecific" product in artificial mixtures usually was found in the range of 1 - 2 %, corresponding to $\Delta\Delta G^{\ddagger} \sim 2.3 - 2.7$ kcal mol^{-1} for reactions with retention and inversion. Retention of 1,3-dipole configuration within the same analytical limits was established for cycloadditions of azomethine ylides [2] and carbonyl ylides ; [3] these are the only 1,3-dipoles in which the terminal centers become chiral and offer a probe.

Stereospecificity is an indispensable, but not a conclusive criterion for concertedness in cycloadditions. Two-step processes may also appear stereospecific, if the ratio of cyclization vs. rotation of the intermediate is sufficiently large for the nonstereospecific adduct to escape detection.

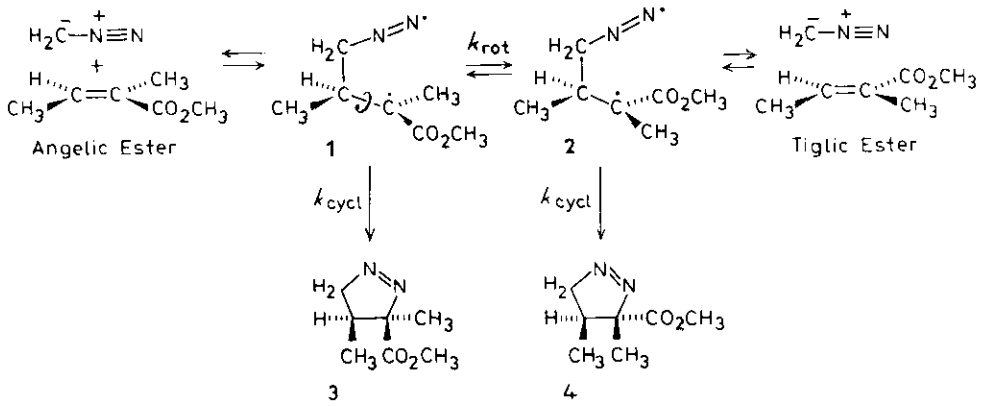


We have discussed and dismissed alternative mechanisms with zwitterionic or diradical intermediates [4] in favor of the concerted pathway of 1,3-dipolar cycloaddition on the basis of various mechanistic criteria. A recent revival of the diradical hypothesis for Diels-Alder reaction and 1,3-dipolar cycloaddition [5] tries to cope with retention of dipolarophile configuration in a highly artificial way : neither extended nor cyclo conformations of the alleged diradical will undergo rotation about the single bond d-ė, but rather dissociate to reactants or cyclize, respectively. Otherwise, the stereospecificity of adduct formation would be violated and the dipolarophile d=e cis,trans isomerized. Which ratios of cyclization and dissociation vs. rotation are still reasonable and defendable ?

The Experimental Solution

We searched for an example in which gas chromatography (GC) allowed the analysis of very small amounts of the nonstereospecific adduct. The diazomethane cycloadditions to the cis,trans isomeric 2,3-dimethyl-acrylic esters, methyl angelate and methyl tiglate, have been described. [6] The two dipolarophiles and their diazomethane adducts, the 1-pyrazolines 3 and 4, were sufficiently volatile to pass a 50 m capillary column with silicon rubber SE 30 at 92°C (Perkin Elmer FD 20, injection block 141°C, N_2); retention times (min) : ether 9, methyl angelate 12.3, methyl tiglate 13.3, adduct 3 26.5, adduct 4 27.5. The two dipolarophiles were purified by preparative GC (APG 402 of Hupe and Busch, injector block 127°C, 2 m apiezon L on siliceous earth at 89°C, N_2, retention times 26.5 and 36 min for angelic and tiglic ester).

Methyl angelate which contained 0.023 % methyl tiglate reacted with 1 eq diazomethane in ether at 21°C. Evaporation after 63 % conversion (photometry of diazomethane) and GC analysis indicated that the methyl tiglate content was reduced to 0.015 %; in kinetic runs (DMF, 25°C) it was shown that methyl tiglate adds diazomethane 2.6 ti-



mes faster than methyl angelate. In an analogous experiment with methyl tiglate, the methyl angelate content went up from 0.039 % to 0.085 %.

After double preparative GC, methyl tiglate showed no signal for angelate in the capillary GC, whereas an admixture of 4.6 ppm of methyl angelate produced a clearly discernible signal. The pure methyl tiglate combined with 1 eq ethereal diazomethane at 25°C in the dark, until 26 % were consumed. The residual tiglate did not exhibit an angelate peak in the GC at highest attenuation; the peak was unequivocal after addition of 6.0 ppm methyl angelate.

Methyl angelate and methyl tiglate, respectively, interacted with an excess of 0.5 M ethereal diazomethane at 21° until the unsaturated ester was virtually consumed (~ 20 d). GC analysis with nonane as standard revealed 94 ± 3 % formation of the cycloadducts 3 and 4, respectively. The yield probably approaches a quantitative one. Separate experiments disclosed that the decomposition of the 1-pyrazolines 3 and 4 commences at 141°C (injection block), in a mixture of 3 and 4 without much discrimination, however.

The adduct 3 from pure methyl angelate + diazomethane did not show the peak of the tiglic ester adduct 4 which became visible after adding 0.059 % 4; thus, the reaction product must contain < 0.059 % 4. It diminishes the analytical precision that the small peak of 4 is located on the tail of the 3 peak.

The analysis of 3 in 4 is expected to be more sensitive due to the lower retention time of 3. In the crucial experiment 14.4 mmol of methyl tiglate (containing $<$ 4.6 ppm angelic ester) was mixed with 13.8 ml 0.46 M diazomethane (6.3 mmol) in ether and kept in the dark at 25°C; after 2.5 h the extinction at 418 nm indicated 60 % consumption. GC analysis of the residue brought to light several impurities in the ppm range, most of them originating from the pyrazoline thermolysis. The big 4 peak is preceded by an unknown peak (Fig. 1), but the one of 3 is missing. Admixing of 4.9 µg of pure 3 in ether to 496 mg of reaction product (164 mg of unconsumed 4) produced a noticeable 3 peak which grew after further 3 addition (Fig. 1). Thus the amount of 3 in the reaction product must be smaller than 0.0049/164 = 30 ppm.

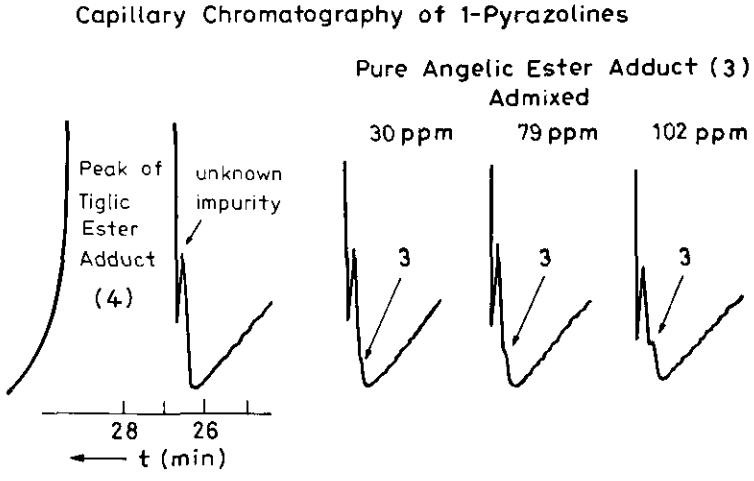


Figure 1

Conclusions

Neither a nonstereospecific cycloaddition nor a cis,trans isomerization of the dipolarophile during the diazomethane reaction has been ascertained. If addition of 30 ppm of 3 to the cycloadduct 4 from diazomethane + methyl tiglate generated the first visible 3 peak, then the stereospecificity of the reaction must be

$$> (100 \text{ minus } 0.0030\ \%) = > 99.997\ \%$$

The ratio of products corresponds to the ratio of rate constants for 3 and 4 formation; it can be defined in the framework of a mechanism with diradical intermediate:

$$k_{cycl} / k_{rot} = k_4 / k_3 = > 33\,000$$

$$\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{rot} - \Delta G^{\ddagger}_{cycl} = > RT \ln 33\,000 = > 6.2 \text{ kcal mol}^{-1}.$$

Analogously, the other figures of Table 1 were evaluated. The value given for $\Delta G^{\ddagger}_{rot} - \Delta G^{\ddagger}_{diss}$ is based on the arbitrary assumption that dissociation of the zwitterion is 3 times faster than its cyclization.

Table 1. Reaction of Diazomethane with cis,trans Isomeric Methyl 2,3-Dimethylacrylates in Ether at 25°C

	Experiments with	
	Methyl tiglate	Methyl angelate
% Nonstereospecific Cycloadduct	< 0.0030	< 0.059
Stereospecificity (%)	> 99.997	> 99.94
k_{cycl} / k_{rot}	> 33 000	> 1 700
$\Delta G^{\ddagger}_{rot} - \Delta G^{\ddagger}_{cycl}$ (kcal mol^{-1})	> 6.2	> 4.4
% Isomerization of Unconsumed Dipolarophile	< 0.00055	< 0.007
$\Delta G^{\ddagger}_{rot} - \Delta G^{\ddagger}_{diss}$ (kcal mol^{-1})	> 7.2	> 6.3

The data of Table 1 are based on a reaction model with intermediate. Is this model reasonable? We don't think so. Even if $\Delta G^{\ddagger}_{cycl} \approx 0$ is assumed for the intermediate 2, a rotational barrier of > 6.2 kcal mol^{-1} appears to be excessive. The steric requirements at the single bond of the diradical 2 may be similar to the ones in the tetramethylethyl radical, $(CH_3)_2CH-\dot{C}(CH_3)_2$, for which a barrier to rotation of 1.2 kcal mol^{-1} has been measured.[7] Moreover, the assumption of $\Delta G^{\ddagger}_{cycl} \approx 0$ for the intermediates 1 and 2 is no longer meaningful, because such a mechanism would become indistinguishable from a concerted pathway.

In addition, another feature makes the assumed intermediates 1 and 2 highly unlikely. Diazo radicals eliminate N_2 very fast.[8] No nitrogen is evolved during the cycloadditions here described. Whenever nitrogen evolution was observed in the interaction of diazomethane and unsaturated compounds, it was traced back to the decomposition of an initially formed pyrazoline, as described, e.g., for diazomethane + benzylidenemalodinitrile and other electrophilic double bonds.[9]

As long as not a single violation of stereospecificity has been observed, it may be a safe assumption that the extent of stereospecificity here established is a general characteristic of 1,3-dipolar cycloadditions. This is in harmony with the concertedness ascribed to such orbital symmetry-allowed processes.

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