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ARE ANY NON-STEREOSPECIFIC 1,3-DIPOLAR CYCLOADDITIONS KNOWN ? A REVISION

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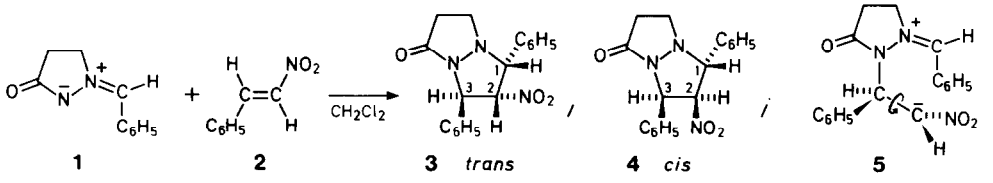
Summary The cycloaddition of 1-benzylidenepyrazolid-3-one betaine to *(E)*-β-nitrostyrene, which has been claimed to furnish 15-30% non-stereospecific product, revealed stereospecificity up to 99.92% in a renewed study; *(Z)*-β-nitrostyrene stereoisomerizes under the influence of the 1,3-dipole.

Diels-Alder reactions and 1,3-dipolar cycloadditions are $[_{\pi}4_{s}+_{\pi}2_{s}]$ processes which are allowed to be concerted by orbital symmetry and owe their wide scope and synthetic potential to the lack of high-energy intermediates. The configuration of the reactants must be retained in the concerted cycloaddition. Retention has been abundantly observed and substantially contributes to the great synthetic value. Rare exceptions suggest a change in mechanism.

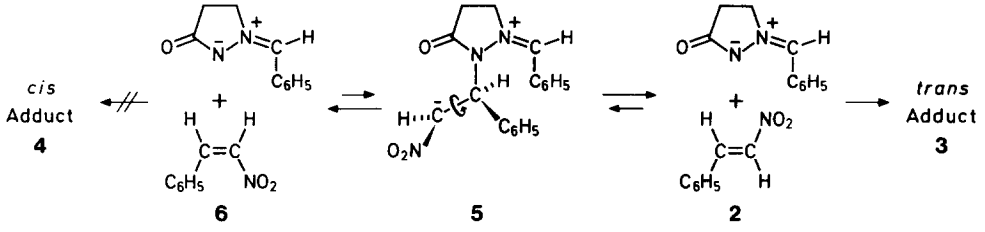


1 **2** **3** *trans* **4** *cis* **5**

Dorn, Ozegowski, and Gründemann [2] found the cycloadditions of 1-benzylidene-pyrazolid-3-one betaine (1),[3] an azomethine imine, to fumaric and maleic ester to be stereospecific. In contrast, the addition of 1 to *trans*-β-nitrostyrene (2) in refluxing dichloromethane yielded 15 - 30% of the *cis*-adduct 4 beside the normal *trans*-adduct 3. A two-step process *via* the zwitterion 5 was made responsible for the steric course. "For the first time products of a non-cisoid 1,3-dipolar cycloaddition were isolated",[2] and the authors were fully justified in claiming fundamental theoretical interest. The adducts 3 and 4 formed identical sodium salts and a subsequent isomerization 3 → 4 had to be considered; nitroalkanes are *stronger acids* than phenol. Dorn *et al.*[2] excluded this possibility: No trans → cis isomerization was noticed when 3 was refluxed in dichloromethane with and without water or with and without 1,3-dipole 1.

We repeated the cycloaddition without special precautions using 1 and 2 in a 1:1 ratio in chloroform, dichloromethane or acetonitrile at 20-60°C. When the adduct composition was monitored by ^{1}H NMR analysis of the ring protons - as Dorn *et al.*[2] did - the content of the *cis*-adduct 4 either stayed below the analytical limit of 1.2% or a little bit above; in 1 out of 10 experiments the cis

percentage reached 6%. In all experiments *at 20°C* (CH_2Cl_2 or CH_3CN) the cis portion remained below 1.2%. The mechanism *via* an intermediate like 5 rigorously requires a *constant trans,cis adduct ratio* under identical experimental conditions. The vacillation of the ratio between <1.2% and 30% suggested the non-stereospecificity to be an artefact.



It is a well-tried custom to use *both geometrical isomers* of the dipolarophile for the stereochemical test. When we reacted *cis*-β-nitrostyrene (6) with 30 mol% of the azomethine imine 1 in $CDCl_3$ in the ^1H NMR tube, surprisingly, 6 was slowly converted to *trans*-β-nitrostyrene (2) under catalysis by the 1,3-dipole 1. In a subsequent reaction, 2 entered the cycloaddition forming 3, and the cis,trans isomerization 6 → 2 came to a halt when 1 was consumed; no *cis*-adduct 4 was observed. Cis disubstituted ethylenes are less active dipolarophiles - and dienophiles - than the trans isomers as a result of steric hindrance of resonance.[4-6a] The catalysis by the 1,3-dipole 1 can be explained by a reversible nucleophilic addition to the α-position of nitrostyrene and rotation in the intermediate; 1 could become attached by the *N* atom as shown in 5 or, alternatively, by the oxygen function.

In *each* of the cycloadducts 3 and 4 the nitro group is flanked by a *cis-vic and a trans-vic* phenyl substituent. It would have to be the influence of the distant carbonyl function if the equilibrium constant were to deviate from value 1. In a $CDCl_3$ solution, 0.62 M in *trans*-adduct 3 and 0.15 M in triethylenediamine as a basic catalyst, the trans,cis equilibrium 3:4 = 64:36 was established within 11 min *at 34°C*. A rather dilute solution was required to measure the rate of stereoisomerization *at 0°C* starting from 3 and from 4 (Fig.1). The solid curves are calculated for first order reactions with the constants: $k_{1\psi}$(trans → cis) = 5.9 10^{-5} s^{-1} and $k_{1\psi}$(cis → trans) = 1.2 10^{-4} s^{-1}. The highest yield of *cis*-adduct 4 which Dorn *et al.*[2] observed in their *cycloaddition* experiments was 30%, close to the equilibrium concentration.

For a renewed study of the *stereospecificity of the cycloaddition* a more sensitive analytical method was required. HPLC with cyclohexane/THF (75:25) on Zorbax Sil (an acidic silica gel, 70 bar, UV detector 254 nm) allowed the analysis of even 0.02% *cis*-adduct 4 after calibration with artificial trans,cis mixtures (3 and 4). In new experiments with pure materials and carefully cleaned glassware, 0.75 mmol of 2 and 0.47 mmol of 1 in 1.5 ml $CHCl_3$ were stirred for 48 h at room temperature. After removal of the solvent, the residue was

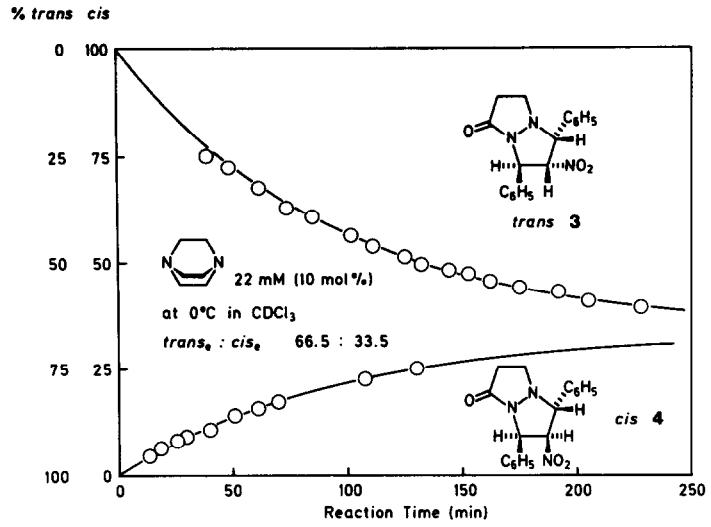


Fig. 1. Kinetics of equilibration of *cis*-and *trans*-adducts 3 and 4 (0.22 M) catalyzed by triethylenediamine (0.022 M); ^{1}H NMR analysis.

triturated with the HPLC solvent, filtered and analyzed. Independent runs in $CHCl_3$ (0.21, 0.29, 0.24%) or CH_2Cl_2 (0.28, 0.23%) converged at 0.25% cis content in the adduct mixture 3 + 4.[1] In more recent experiments a teflon vessel was used; the cycloaddition in CH_2Cl_2 in the presence of a trace of trifluoroacetic acid reached 30% conversion after 3 h and the cis,trans adduct mixture contained 0.08% cis.

In the framework of the two-step mechanism proposed by Dorn *et al.*,[2] a 99.92% stereospecificity would be in accord with $\Delta\Delta G^{\ddagger}$ = 4.2 kcal mol^{-1}, representing the difference between the rotational barrier and the activation free energy for cyclization of the intermediate 5. However, stray-shots of higher cis content disclosed that we are still not in full control of the reaction conditions and adventitious base catalysis cannot be ruled out. A catalysis of the equilibration of 3 and 4 by the 1,3-dipole 1 was not noticeable by ^{1}H NMR analysis; tests by HPLC are still required.

If the azomethine imine 1 catalyzes the cis,trans equilibration of β-nitrostyrenes, is it possible that ∿0.08% *cis*-adduct 4 is the result of a concomitant and likewise concerted addition of 1 to *cis*-β-nitrostyrene ? We observed by HPLC analysis that the thermal equilibrium, established from both sides by 0.2 mM triethylenediamine in CH_2Cl_2 in the dark, contains only 0.012 ± 0.004% *cis*-β-nitrostyrene (6). To reach 0.08% *cis*-adduct 4 in the adduct mixture, *cis*-nitrostyrene should combine with 1 faster than *trans*-nitrostyrene, at variance with expectation and the experiments reported above.

We cannot fully reconstruct the reasons for the occurrence of 15 - 30 % *cis*-adduct 4 which Dorn *et al.*[2] observed for 1 + 2. They reported removal of the unconsumed 1 on work-up by chromatography on silica gel. We noticed some

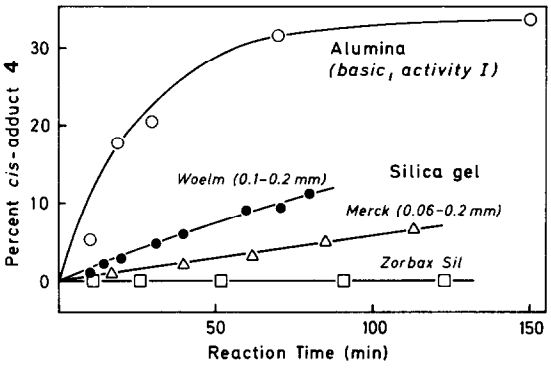


Fig.2. Stereoisomerization of *trans*-adduct 3 (5 ml 0.1 M in $CHCl_3$) by various adsorbents (200 mg) at 20°C; HPLC analysis of *cis*-adduct 4

trans → cis isomerization of 3 on passing a silica gel (Merck 0.06-0.2 mm) column. The catalytic activities of various adsorbents were compared by stirring with a solution of 3 (Fig.2). The commercial silica gels tested triggered the trans,cis isomerization - with one exception (Zorbax Sil of Du Pont de Nemours). It is no surprise that alumina is a more active catalyst than silica gel; the equilibrium concentration of 4 is nearly reached after 1 h.

The quintessence: No 1,3-dipolar cycloaddition is known which violates the principle of configurational retention. Orbital control allows concertedness, but does not forbid a two-step reaction course. The borderline between concerted and stepwise mechanism has not been transgressed as far as 1,3-dipolar cycloadditions are concerned. For Diels-Alder reactions this borderline is better explored (Reviews [6b,7]).

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Dedicated to Professor Hans Musso on the occasion of his 60th birthday

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