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FURTHER CONTRIBUTIONS TO THE STEREOSPECIFICITY OF 1,3-DIPOLAR CYCLOADDITIONS OF THIOCARBONYL YLIDES [1]

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Summary The stereospecific cycloadditions of thiobenzophenone S-methylide (4) to dimethyl 2,3-dicyanofumarate and of thiocarbonyl ylide 1 to maleonitrile contribute to the separation of electronic (HO-LU energy distances) and steric effects in the borderline region of competing concerted and two-step processes.

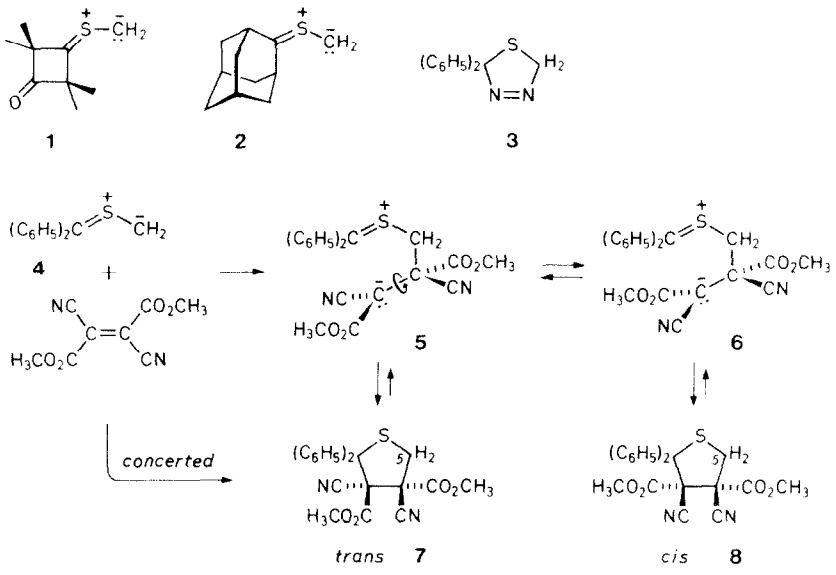
Stereospecificity is a necessary, but not conclusive criterion for *concerted bond formation* in cycloadditions. The retention of dipolarophile configuration amounted to >99.997% for methyl tiglate + diazomethane [2] and >99.92% for 1-benzylidenepyrazolid-3-one betaine + *trans*-β-nitrostyrene.[3] In the framework of a two-step process, these data correspond to >6.2 or >4.2 kcal mol^{-1} for $\Delta G_{rot}^{-}-\Delta G^{\neq}_{cycl}$; such rotational barriers of an intermediate appear excessive.[4a]

In accordance with PMO arguments, we observed *non-stereospecific cycloadditions* of the thiocarbonyl ylides 1 and 2 (high π-MO energies) with dimethyl 2,3-dicyanofumarate (low π-MO energies).[5] The results pointed to a *complete reaction via a zwitterionic intermediate*, capable of rotation. It was supposed that *steric encumbrance* at one terminus of 1 and 2 hindered the concerted addition to a higher extent than the two-step process. We report here on further experiments which help to distinguish between electronic and steric influences on the balance of one-step (concerted) *vs.* two step cycloadditions.

Thiobenzophenone *S*-methylide (4), liberated from 3 in 8 h at -45°C in THF,[6] added *in situ* to dimethyl dicyanofumarate to give 82% of 7.[7] Before searching for a *cis*-isomer, we studied the stability of *trans*-adduct 7. Stereoequilibration, 7 ⇌ 8, took place in refluxing acetonitrile; ratios of 32:68 and 29:71 were reached after 48 h, starting from 7 or 8, respectively.

The *trans*-adduct 7, mp 191-192°C, crystallized from chloroform; the mother liquor provided the more soluble *cis*-isomer 8,[8] mp 160.5-161.5°C. The ^1H NMR spectra show AB patterns of 5-H_2 at δ 3.78 and 4.03 for 7, and at 3.55, 4.18 for 8. ^{13}C NMR data were consistent with the structures, but did not allow configurational assignments. The preponderance of the *cis*-adduct 8 in the equilibrium was astounding, because *trans:cis* = 56:44 was found for the adducts of 2 to dimethyl dicyanofumarate.[5] Therefore, 8 was chosen for structural confirmation by X-ray analysis (Fig. 1).[9]

With a dihedral angle C3-C4-C5-S1 of 9.4°, the 5-membered ring corresponds



to an envelope conformation with C2 as the "flap". C2 is located 75.6 pm below the best plane of the other ring atoms, whereas the puckering displacement of cyclopentane amounts to 43.8°.[10] The dihedral angles of *a*-C_6H_5 and *e*-C_6H_5 with 3-CO_2CH_3 are 49.1° and 173.5°; those of the two ester and the two nitrile groups are 41.1° and 39.0°, respectively. The 3-CO_2CH_3 occupies a pseudo-axial position and the phenyl planes are arranged to minimize interference.

Equilibration of the cycloadducts of 2 and dimethyl dicyanofumarate required 139°C in benzonitrile and was not observable in refluxing acetonitrile.[5] The higher isomerization rate 7 ⇌ 8 is in harmony with the superior stabilization of the benzhydryl-type zwitterions 5 and 6.

To test the stereospecificity of the cycloaddition, 30.3 mmol thiobenzophenone in 15 ml THF at -78°C were titrated with diazomethane in 45 ml THF for decolorization. The solution of 3 lost N_2 when stirred in the presence of 34 mmol dimethyl dicyanofumarate in 45 ml THF for 15 h at -49°C. After removal of

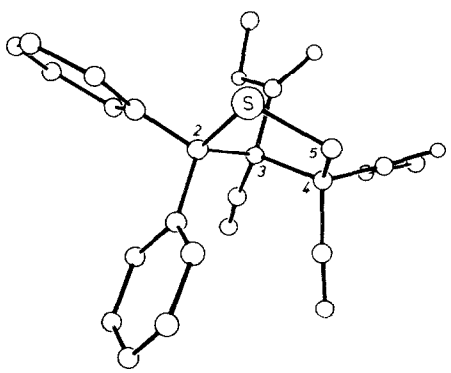
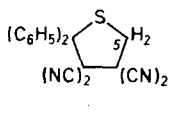


Figure 1. Structure of dimethyl *cis*-3,4-dicyano-2,2-diphenyltetrahydrothiophene-3,4-dicarboxylate (8). Selected bond lengths: S1-C2 184.1(3), C2-C3 159.6(5), C3-C4 158.4(5), C4-C5 154.4(5), C5-S1 180.7(4) pm; cyclopentane [10] 154.6 pm. Bond angles in ring at S1 94.4(2)°, C2 100.6(2)°, C3 105.5(2)°, C4 108.2(3)°, C5 109.0(2)°.

the THF at 20°C, the residue was ultrasonically triturated with 100 ml ether; 12.5 g of colorless undissolved material contained 29.5 mmol 7 (97%) and 2.6 mmol dicyanofumaric ester (^{1}H NMR analysis). The ethereal phase revealed the presence of 0.103 mmol 8 (0.34%) by a singlet at δ 3.31. We are reluctant to diagnose a minor violation of stereospecificity because the small percentage of 8 could be the result of subsequent isomerization. Test: Pure 7, 77 mM in THF, contained after 3 h at 30°C (work-up as above) 0.6% 8.

The zwitterionic intermediate from 1 and tetracyanoethylene (TCNE) is interceptible by water and methanol.[11] Thiobenzophenone *S*-methylide (4) combines with TCNE to yield 89% 9.[6] We repeated the reaction of 3 with 1.1 equiv of TCNE in THF: *a*. absolute, *b*. with 2 vol% H_2O, *c*. with 2 vol% CH_3OH. ^{1}H NMR analysis (s, δ 3.95 for 5-H_2) indicated 89%, 92%, and 94% of cycloadduct 9.[12]

Why does thiocarbonyl ylide 4 in reactions with electron-deficient ethylene derivatives still follow the orthodox concerted pathway ? Phenyl substitution creates a compression of the HO-LU energy distance which is typical for conjugated systems; *i.e.*, the interaction LU(1,3-dipole) - HO(dipolarophile) is *no longer negligible*.



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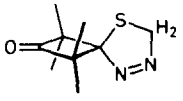

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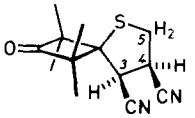

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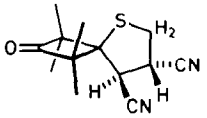

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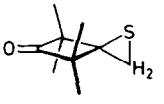

13

Whereas thiocarbonyl ylide 1 adds to dimethyl fumarate with >99.97% retention, a small stereochemical leakage was observed for dimethyl maleate: 81% maleic + 0.92% fumaric ester adduct;[5] the rest was spirothiirane 13, the electrocyclization product of 1. The cycloadducts of 1 to fumaronitrile (11) and maleonitrile (12) were previously described.[13] We checked the stereospecificity of the addition to *maleonitrile*; the specimen contained after repeated crystallization still 0.058% fumaronitrile (^{1}H NMR in CD_3OD, 500 MHz, comparison with ^{13}C satellites of maleonitrile). Extrusion of N_2 from 10 in C_6D_6 (16 h 40°C) in the presence of 2 equiv of maleonitrile furnished 89% 11 + 12 in the ratio 99.87 : 0.13 (^{1}H NMR in C_6D_6, 500 MHz, 2 s δ 1.134 and 1.144 for 12). Competition experiments of fumaronitrile and maleonitrile for 1 in benzene at 40°C furnished κ = 2.5. One calculates that the 0.058% content of fumaronitrile gives rise to 0.080% 12. This reduces the *non-stereospecific* portion for the reaction of 1 + maleonitrile to *0.05%*, so close to the analytical limit that we don't dare to assume existence of a competing two-step cycloaddition.

Fumaric ester is a better dipolarophile [4b] and dienophile [14] than maleic ester; IP values, 10.70 *vs.* 10.47 eV, support steric hindrance of resonance in maleic ester. This difference is lost in the fumaronitrile/maleonitrile pair (both IP 11.15 eV). The competition constants of dimethyl fumarate *vs.* maleate

(κ = 53)[5] and fumaronitrile *vs.* maleonitrile (κ = 2.5) for thiocarbonyl ylide 1 reflect the diminishing steric effects in the dinitrile series. No violation of configurational retention was detected for maleonitrile.

ACKNOWLEDGMENT

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8. Satisfactory elemental analyses (CH, N, S) and spectra were obtained for all new compounds.
9. Syntex P3 four circle automated diffractometer with graphite monochromatized MoK_α radiation at ambient temperature; SHELXTL structure solution package (Version 4.1). $C_{22}H_{18}N_2O_4S$, M_r 406.46, monoclinic $P2_1/n$, a = 10.060(4), b = 14.357(8), c = 14.158(8) Å, β = 100.74(8)°, V = 2012.2(8) Å^3, Z = 4, D_r = 1.342 g/cm^3, μ = 1.79 cm^{-1}. Crystal size: 0.30 x 0.42 x 0.5 mm. - Data collection using learned profile fit method; 2θ range 2 - 50°, scan speed 2 - 29.3°/min for <150 - >2500 counts/s; scan range 0.8°. 3902 data recorded including 176 check reflections. 308 reflections were rejected (spikes); no absorption correction, 2544 unique data with $I \geq 3\sigma(I)$. - Structure solved by direct methods, anisotropic refinement of all nonhydrogen atoms. H atoms included with fixed U_i adjusted to $\sim$1.2 U_{eq} of the respective carbon atom, 316 parameters refined. Final R = 0.051. Highest residual peak in difference map 0.4 e/Å^3. - Lists of atomic coordinates etc. are deposited at the Cambridge Crystallographic Data Center.
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