# DOMINO AND PINCER CYCLOADDITIONS WITH syn-o,o'-DIBENZENES PRESSURE DEPENDENCE AND MECHANISTIC IMPLICATIONS

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Summary: For additions of acetylenic dienophiles to various syn-o,o'-dibenzenes a two-step mechanism is inferred from relative rate enhancements and stereoselectivities in high-pressure vs. ambient-pressure reactions.

In the preceding letter,[1] the scope and preparative potential of multiple Diels-Alder reactions of the domino and pincer type with syn-o,o'-dibenzene derivatives (1) are addressed. The caged bis-dienes are valuable synthons for the rapid construction of highly condensed carbo- and hetero-polycyclic pagodane systems[2] which provide an opportunity for further structural elaboration.[3]
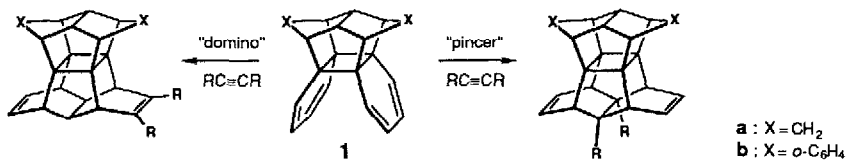
By conventional means, under no experimental conditions could a hypothetical primary product arising from an initial [4+2]-cycloaddition be detected or trapped before its intramolecular collapse.[4] Therefore, the mechanistically intriguing speculation about more or less concerted polyelectron-pericyclic processes[5] (**A** or **B**), as implied in the term "domino reaction", within the exceptionally favorable stereoelectronic situation given in 1 was probed by a series of high-pressure experiments.[6]
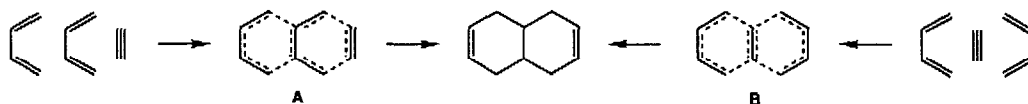

In case of a two-stage process, the first step - the bimolecular addition - should be strongly accelerated by pressure whereas the rate of the second, intramolecular addition step should be

almost pressure independent. While for the addition of maleic anhydride (MA) to **1a** at ambient pressure elevated temperatures (80 °C) are mandatory because of steric inhibition,[1] at 7 kbar reaction occurs readily at ambient temperature, again leading exclusively to the domino adduct. A summary of reaction conditions and further results is presented in Table I.

From reactions of **1a** with acetylenes such as dimethyl acetylenedicarboxylate (DMAD) and dicyanoacetylene (DCA) at 12/14 kbar and at ambient temperature, pincer and domino product mixtures[7] were obtained in ratios similar to those determined for uncompressed reactions[1] (Table I). The influence of *anti*-methoxy substitution at C-15 and C-19 (**2**[8]) on reactivity and stereoselectivity seems to be negligible. When the pressure is increased from 1 bar to 14 kbar, the pincer product with DCA (**6**) becomes slightly more favored by a factor of 1.6 while no pincer adduct (**4**) at all could be detected with DMAD. Methoxy groups placed at the termini of one diene unit (**7**[8]), however, exert the expected strong influence on the product ratio.[9] An outside dienophile capture is now preferred, which in turn is biased completely towards the electron-rich diene moiety.

In the pressurized reaction of dibenzotetraene **1b**[4,9] and DCA at ambient temperature the domino adduct[1] is formed exclusively. At ambient pressure, the selectivity proved to be temperature dependent with increasing amounts of the pincer product being formed at higher temperatures.

Again corroborative to speculations about cooperativity, in none of the cases investigated could a reaction intermediate or a bisadduct be detected.
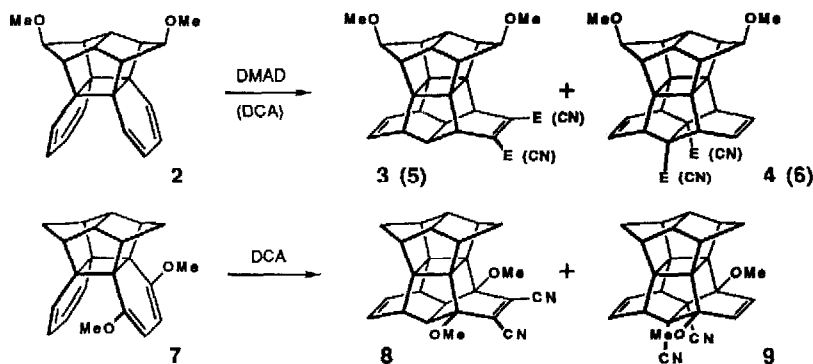
It follows from the pressure dependance that the rate controlling intermolecular cyclo-addition is highly accelerated by pressure. An increase of pressure from 1 bar to 14 kbar causes an enhancement of the reaction rate by a factor of >3000 indicating a highly negative activation volume as expected for a Diels-Alder cycloaddition.[10] High pressure only marginally promotes the formation of the pincer *vs.* domino adduct. The activation volumes of the competing intermolecular cycloadditions are obviously almost equal. For a higher concerted process, *e.g.* an "orthogonal" double $[\pi_4+\pi_2]$-pincer addition **B**, a distinct additional acceleration would have to be expected relative to a stepwise sequence. Hence, these arguments suggest a similar, simple mechanism for the initial product determining steps. This interpretation is in full agreement with earlier conclusions drawn from SCF-MO calculations.[4,11] Accordingly, the

pincer as well as the domino adducts seem to arise from a two-step process via an elusive primary Diels-Alder adduct which obviously subsequently undergoes a very rapid intramolecular cycloaddition.

The force-field geometry (MM2[12]) of an assumed intermediate (Fig. 1) reveals that the reaction centers indeed occupy an almost perfect orientation for a collapse into a consecutive [4+2]-bonding scheme with almost colinear σ-alignment of the π-lobes at a distance of less than 3.0 Å (2.94 Å for acetylene, 2.92 Å for ethylene as domino dienophile). This situation implies a considerable merging of the crucial frontier orbitals beyond the plain van-der-Waals π/π-distance (3.4 Å) towards the transition state. In light of the demand of the symmetry-allowed [4+2]-cycloaddition for a highly ordered approach of the reaction partners,[13] their rigid pre-positioning in the intermediate considerably lowers the activation barrier for the second step.[4,11]
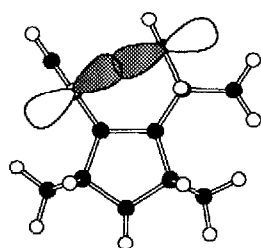
Table I. Reaction Conditions and Product Ratios[7] (Toluene)

Diene	Dienophile	Pressure	Temp.	Domino:pincer
1a	MA	7 kbar	r.t.	100 : 0
1a	DMAD	14 kbar	r.t.	97 : 3
1a	DCA	12 kbar	r.t.	15 : 85
2	DMAD	14 kbar	r.t.	100 : 0
2	DCA	14 kbar	r.t.	13 : 87
2	DCA	1 bar	r.t.	19 : 81
7	DCA	12 kbar	r.t.	63 : 37
1b	DCA	14 kbar	r.t.	100 : 0
1b	DCA	1 bar	r.t.	100 : 0
1b	DCA	1 bar	80 °C	96 : 4
1b	DCA	1 bar	100 °C	88 : 12

Fig. 1 MM2-calculated geometry of domino intermediate

The regioselectivities observed for different dienophiles and substituents as well as the temperature dependency of the reaction of DCA with **1b** allow the conclusion that the primary addition step may be controlled by (transient) complexation between the orthogonal π-bonds of the acetylenic dienophile and the inner π-faces of the electron-rich[14] diene units which are juxtaposed at an angle of 67.2°,[3] or alternatively by one outer π-face and a suitably oriented benzene ring.[1,15] In DCA, both acetylenic π-bonds are equally activated by the two cyano groups and therefore are ideally arranged to form a complex with both of the inner π-faces of the diene units. Starting from this orientation, the pincer adduct becomes the final product. The corresponding complex of this dienophile with the outer diene face and the benzene unit of **1b** is obviously sterically better accessible and likely responsible for the prevalence of domino capture. In contrast, in DMAD each carboxylate group can only interact with one of the acetylenic π-bonds. A complexation to both inner diene faces and hence a central approach are evidently not favorable. The reactive species can be envisioned as a coplanar ester rotamer where only one of the orthogonal π-bonds is doubly activated, and in this case the stereoselectivity may be mainly ruled by steric effects. Accordingly, methyl propiolate adds exclusively in domino manner (100 °C; 12 kbar; 80%). The observed stereoelectronic effects

from association of additional, non-reacting π-components may be related to those which control the well known *endo*-selectivity found in many Diels-Alder reactions.[16]

References and Notes

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7) Crude adduct mixtures were analyzed by ^{1}H NMR prior to separation either by recrystallization or LC. All major components are fully characterized by their spectra (^{1}H, ^{13}C NMR; IR; UV; MS) and elemental analysis; *e.g.* **8**: ^{1}H NMR (CDCl$_3$) δ 6.62 (s,2H), 6.38 (m,2H), 3.77 (m,2H), 3.73 (s,6H), 2.65 (m,2H), 2.55 (m,2H), 2.28 (m,2H), 1.55, 1.50, 1.45, 1.38 (2 AB,4H); ^{13}C NMR (CDCl$_3$) δ 129.9, 129.0, 116.4, 82.5, 64.4, 62.7, 59.4, 56.7, 54.6, 43.1, 41.5, 40.9, 40.7, 40.3. **9**: ^{1}H NMR (CDCl$_3$) δ 6.20 (m,2H), 3.52 (s,6H), 3.18 (m,2H), 2.65 (m,2H), 2.50 (m,2H), 2.35 (m,2H), 2.22 (m,2H), 1.58, 1.27, 1.49, 1.38 (2 AB,4H); ^{13}C NMR (CDCl$_3$) δ 131.5, 129.7, 112.5, 82.0, 66.6, 59.4, 58.4, 52.6, 51.4, 42.9, 41.1, 40.4, 39.7, 35.6.

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15) The primarily kinetic rather than thermodynamic origin of the stereoselectivities is also suggested by force-field calculations[12] which indicate only a marginal difference in stability between the initial outer and inner products of **1a/1b** with 2-butyne (as a model for substituted acetylenes; $\Delta\Delta H_f^\circ = 0.5/0.8$ kcal/mol).

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