Syn Selectivity in Diels-Alder Reactions of Isodicyclopentadiene

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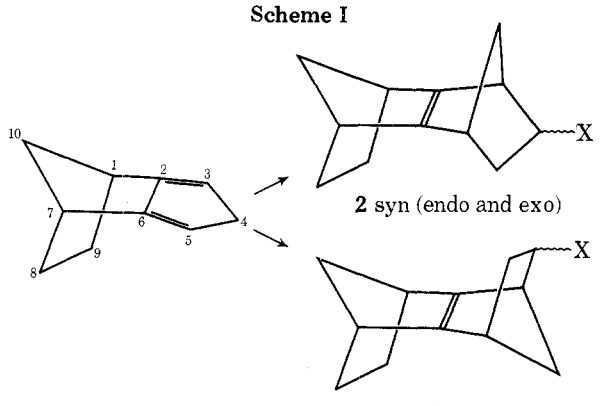
We have studied the stereochemistry of the Diels–Alder reactions of tricyclo[5.2.1.$0^{2,6}$]deca-2,5-diene (isodicyclopentadiene, 1)[1] with methyl acrylate and propiolate. Conceivable for these reactions are the two stereochemical courses, syn and anti, which may be so termed according to the modes of attack from the ethano and methano sides of the norbornane framework, leading to the formation of **2** and **3**, respectively (Scheme I). These should be differentiated from the endo–exo isomerism possible for the stereochemical arrangement of dienophile substituents with respect to the cyclopentadiene moiety. (Note that the syn–anti isomerism corresponds exactly to the endo–exo terminology which is usually adopted for the stereochemistry of norbornenes.) Investigation of the syn–anti stereochemistry for **1** would also be interesting in connection with that for norbornenes.[2]

Scheme I

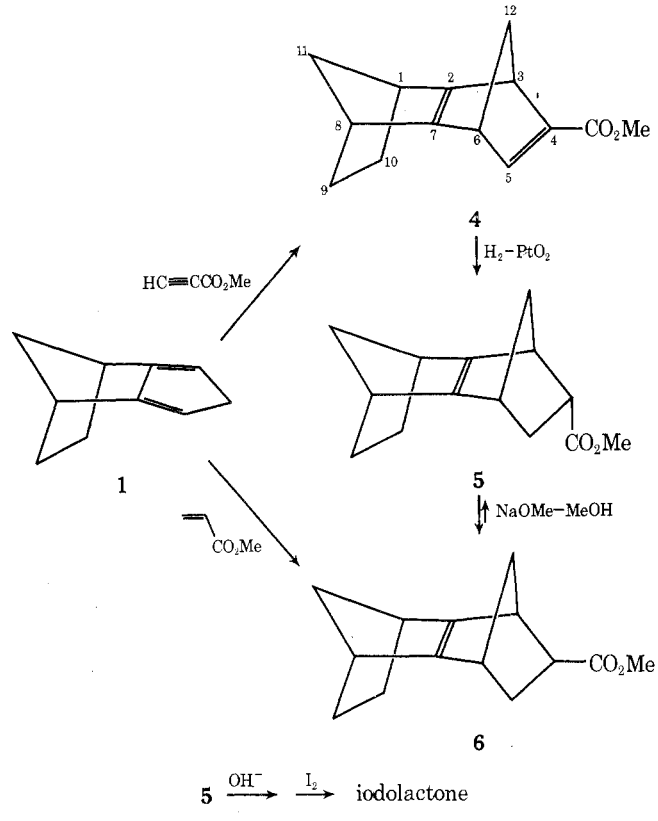


NMR spectroscopy, epimerization experiments, and chemical transformations of the adducts to a known compound have shown that the Diels–Alder adducts are exclusively of syn structure. The stereochemistry observed exhibits a sharp contrast to the preferential exo selection of norbornenes and seems to illuminate a potential importance of stereoelectronic effect and/or steric attraction in determining stereochemical courses of Diels–Alder reactions.

Diels–Alder reactions of **1** with methyl propiolate and acrylate were conducted in *n*-hexane at 40–50 °C. The products were isolated in a relatively high yield of 84 and 77%, respectively, after purification through column chromatography. Both adducts were homogeneous; no isomeric products were discernible on TLC and NMR spectra.

The product **4** from methyl propiolate was hydrogenated over platinum oxide at room temperature until an equimolar amount of hydrogen gas was absorbed. The central double bond remained unchanged under this condition. Since the hydrogenation of norbornene is established to occur exclusively from the exo side, the present hydrogenation

Scheme II



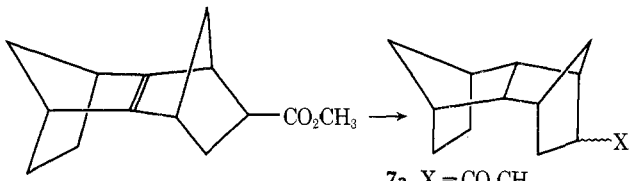
product **5** is expected to have the endo configuration. This was supported by the coupling pattern of the exo proton at C_4 α to the carbomethoxy substituent[3] and ascertained by the successful transformation to a lactone via carboxylic acid. Isomerization of this *endo*-carbomethoxy derivative **5** in the presence of sodium methoxide in methanol at 100 °C gave an equilibrium mixture which contained more than 95% exo isomer **6** (Scheme II). NMR, ir, and VPC analyses identified this exo isomer with the original kinetic adduct **6** which resulted from methyl acrylate.

The above-described results clearly indicate that the syn–anti stereochemical selections of the propiolate and acrylate are identical. In order to determine the syn–anti configuration, we have first examined the NMR spectra of **4–6**. Although no signal was observed in the range higher than 0.5 ppm in the spectra of **5** or **6**, there were recorded multiplets at 0.26 ppm in the spectrum of compound **4**. These multiplets were assigned unequivocally to the endo protons of the ethano bridge (C_9–C_{10}) of **4** through decoupling as well as comparison with the spectrum of 9,10-*exo,exo*-dideuterio-**4**.[4] Thus it might be said that these endo protons suffer appreciable higher field shift in **4**. This might be best explained by the assumption that the endo protons of the ethano bridge in **4** face to the olefinic double bond (C_4–C_5) in the opposite norbornene skeleton. The situation is possible only when the syn addition is involved.

If the adducts have the syn structure, it would be possible to lead them to known cage compounds **7** by exo hydrogenation of the central double bond. Although this double bond is resistant to the catalytic hydrogenation as has been described above, it was found to be readily hydrogenated by diimide generated from potassium azodicarboxylate in

methanol.[5] The adduct **6** was transformed to a known bird cage alcohol **7e** by the sequential route via **7a** to **7d** as shown in Scheme III. Alkaline hydrolysis of **7a** followed by

Scheme III



6

7a, X = CO_2CH_3
b, X = CO_2H
c, X = COCl
d, X = *m*-ClC_6H_4COOCO
e, X = OH

the treatment with thionyl chloride gave an acid chloride **7c**. Treatment of **7c** with *m*-chloroperbenzoic acid in *n*-hexane at 0 °C for a few hours followed by reflux resulted in the formation of the acyl carbonate **7d** via carboxy inversion. Without isolation of **7d**, hydrolysis and chromatography gave rise to the hydroxy derivative **7e** in an overall yield of 17%. **7e** thus obtained was identified with the authentic cage alcohol.[6] During these reactions, no contamination by epimeric products was observed. These transformations firmly establish the syn configuration of the original kinetic adducts **4** and **6**. An alternative pathway to **7e** starting from the anti isomer **3** is no doubt a highly hedged possibility.[7]

The high stereoselectivity of isodicyclopentadiene (**1**) in favor of syn addition of dienophiles is rather surprising in comparison with the preferential exo addition of a wide variety of reagents to norbornene and its homologues.[2] Accordingly, the stereochemistry here observed can hardly be compromised with the ideas such as steric repulsion by the ethano bridge[2b] and torsional strain,[8] which have been invoked to explain the exo preference in the additions to norbornenes.

A similar syn preference in Diels–Alder reactions was observed for pentachlorocyclopentadiene and was interpreted in terms of the dipolar stabilizations.[9] However, such an interaction does not seem to be responsible for the syn selection here observed; the diene **1** is essentially nonpolar in nature.

Two explanations seem to be possible for the observed selectivity. One is a greater steric attraction by the ethano bridge which should stabilize the syn transition state. In previous papers we suggested the importance of steric attraction as well as dispersion forces in determining the endo–exo selectivity in Diels–Alder reactions of cyclopentadiene and norbornadiene.[10] The role of such a steric attraction has been stressed for several other types of reactions exhibiting contrathermodynamic stereoselectivities.[11] In the diene **1**, the reaction center is apart by one more carbon unit from the norbornane framework. This would allow steric attraction to outweigh steric repulsion which should diminish more sharply with the increase in distance.

The other explanation is a recourse to stereoelectronic effect. A greater development of π orbitals toward the exo side has been suggested to account for the exo preference of norbornene.[12] The relatively unstable filled σ orbitals of the norbornane skeleton would be so high lying as to permit its mixing with the π orbital. The mixing may well bias the spread of the π orbital in space above and below the cyclopentadiene plane of **1**. It is probable that such a spatial asymmetry of the π orbital should in effect favor the syn orientation of an attacking dienophile.

At present, it is not possible for us to decide which will be the more dominant factor to control the stereochemistry. Perhaps, the two factors combine to lead to the observed syn stereoselectivity. All that we can state at the present stage is that the syn predominance is not due to the steric repulsion.

Experimental Section

General. NMR spectra were measured on $CDCl_3$ solutions with Varian HA-100, T-60, and EM-360 spectrometers using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Hitachi EPI-G spectrophotometer. Vapor phase chromatography was performed on a Perkin-Elmer F6-D instrument equipped with a capillary column, 45 m × 0.25 mm coated with Carbowax 20M. Tricyclo[5.2.1.$0^{2,6}$]deca-2,5-diene (**1**) was prepared according to the method of Alder et al.[1]

Diels–Alder Reaction of 1 with Methyl Acrylate. A solution of 1.00 g (7.58 mmol) of **1**, 2.00 g (23.3 mmol) of freshly distilled methyl acrylate, and a small amount of hydroquinone (ca. 10 mg) in 10 ml of *n*-hexane was maintained at 50 °C until **1** was consumed. The reaction was monitored by TLC (silica gel), and 1 day of heating was required. After evaporation of solvent and excess dienophile, the crude reaction mixture was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. Evaporation of intermediate fractions gave 1.28 g (5.87 mmol) of 4-*exo*-carbomethoxy-*syn*-tetracyclo[6.2.1.1.^{3,6}.$0^{2,7}$]dodec-2-ene (**6**) (77% based on **1**): NMR 0.73–2.4 (10 H), 2.7–3.02 (br s, 1 H), 3.02 (br s, 3 H), 3.12 (br s, 1 H), 3.73 ppm (s, 3 H); ir (neat) 2950, 2875, 1733 (C=O), 1424, 1356, 1195, and 1043 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1, M^+), 190 (1), 132 (18), 117 (12), 104 (75), 91 (10), 78 (9), and 55 (42).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66. Found: C, 77.27; H, 8.27; O, 14.86.

Diels–Alder Reaction of 1 with Methyl Propiolate. A similar procedure as described above was employed. A mixture of 2.00 g (15.2 mmol) of **1** and 1.00 g (11.9 mmol) of methyl propiolate in *n*-hexane was maintained at 40 °C for 24 h. There was isolated 2.16 g (10.0 mmol) of 4-carbomethoxy-*syn*-tetracyclo[6.2.1.$1^{3,6}$.$0^{2,7}$]dodeca-2,5-diene (**4**) (84%) after chromatography on silica gel using ether–petroleum ether (1:10) eluent: NMR 0.26 (ddd, 2 H, J = 8, 3.5, 2 Hz), 1.10 (dt, 1 H, J = 8, 1.5 Hz), 1.42 (m, 3 H), 2.25 (dd, 1 H, J = 6.5 Hz), 2.99 (br d, 2 H), 3.45 (br s, 1 H), 3.70 (s, 3 H, and br, 1 H), 7.40 ppm (d, 1 H, J = 3 Hz); ir (neat) 2960, 2875, 1720, 1595, 1570, 1435, 1320 cm^{-1}; mass spectrum *m/e* (rel intensity) 216 (1, M^+), 200 (1), 198 (2), 173 (2.5), 172 (3).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46; O, 14.79. Found: C, 77.35; H, 7.77; O, 15.22.

Catalytic Hydrogenation of 4. A solution of 0.553 g (2.54 mmol) of **4** and 15 mg of PtO_2 in 15 ml of ethyl acetate was pressured in a microbomb with hydrogen to 140 atm at room temperature and the mixture was shaken overnight. After removal of catalyst by filtration and of solvent under reduced pressure, the crude product was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. By collecting early fractions, 0.465 g (2.13 mmol) of 4-*endo*-carbomethoxy-*syn*-tetracyclo[6.2.1.1.^{3,6}.$0^{2,7}$]dodec-2-ene (**5**) was obtained (84%): NMR 0.65 (m, 2 H), 0.85–2.2 (m, 8 H), 2.97 (br s, 4 H), 3.45 (dd, 1 H, J = 3, 5.5 Hz), 3.65 ppm (s, 3 H); ir (neat) 2960, 2865, 1740 (C=O), 1600, 1420, 1350, 1278, 1200, 793, and 770 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1, M^+), 190 (0.7), 159 (1.1), 150 (1.1), 132 (5), 117 (4), 115 (3), 104 (15.4), 95 (5), 55 (7).

Iodolactonization of 5. A solution of 0.160 g (0.73 mmol) of **5** in 10 ml of 10% methanolic sodium hydroxide was maintained overnight at 50 °C. The reaction mixture was poured into 30 ml of water and the solution was acidified with dilute hydrochloric acid. The oily mixture was extracted with ether (30 ml × 2) and dried (Na_2SO_4). After evaporation of ether, 0.155 g of crude product was obtained. The crude product and 0.05 g of sodium hydroxide were dissolved in 30 ml of water, and 0.250 g (0.98 mmol) of iodine and 0.150 g (1.0 mmol) of sodium iodide were added and stirred at room temperature for 2 h. The solution turned to a dark brown slurry, and the reaction mixture was extracted twice with 30 ml each of chloroform. The combined chloroform solution was washed with aqueous sodium thiosulfate in order to remove excess iodine, and washed with water and dried (Na_2SO_4). After evaporation of solvent, the crude product where slight contamination was observed on TLC (silica gel) was chromatographed on silica gel using chloroform eluent. By totaling early fractions 0.110 g (0.33 mmol) of white solid was obtained (46% from **5**): NMR 1.0–3.0 ppm (br m); ir (KBr) 3055, 2950, 2875, 1775 (C=O), 1460, 1228, 1023, and

735 cm^{-1}; mass spectrum *m/e* (rel intensity) 203 (1, M − 1), 175 (1), 149 (2.5).

Isomerization of 5 to 6. Into 2.0 ml of methanol containing 0.20 g of sodium 0.07 g of **5** was dissolved and the solution was maintained at 100 °C in a sealed tube for 20 h. The solution was poured into 20 ml of water and acidified with dilute hydrochloric acid, and the oily mixture was extracted with ether (20 ml × 2). The combined extracts were washed with water (30 ml) and dried ($CaCl_2$). To this solution was added ethereal diazomethane solution generated from *N*-nitrosomethylurea until the solution remains yellow colored and the evolution of nitrogen ceases. After standing for 0.5 h at room temperature, a few drops of acetic acid were added to remove excess diazomethane and the solution was washed with saturated aqueous sodium bicarbonate, then with water and dried (Na_2SO_4). After evaporation the crude product was subjected to VPC analysis (Carbowax 20M, capillary tube 45 m × 0.25 mm, 140 °C), which exhibited the presence of **6** as a main component and the ratio over **5** to be 20.

Diimide Reduction of 6. To a stirred suspension of 4.05 g (20.9 mmol) of potassium azodicarboxylate in 20 ml of methanol containing 2.05 g (9.4 mmol) of **6** was added a solution of 3.15 g (52.5 mmol) of acetic acid in 5 ml of methanol during 0.5 h. After stirring was continued for an additional 0.5 h, 30 ml of water was added and the product was extracted with ether (30 ml × 2). The combined extracts were washed with water (30 ml) and dried (Na_2SO_4). After evaporation of solvent, the crude product (1.85 g) was chromatographed on silica gel using ether–petroleum ether (1:20) eluent. By collecting intermediate fractions, 1.433 g (6.51 mmol) of 4-*exo*-carbomethoxy-*endo,endo*-tetracyclo-[6.2.1.1^{3,6}.0^{2,3}]dodecane (**7a**) was isolated (69%): NMR 1.2–1.8 (m), 2.00 (br s), 2.36 (br s) (these signals were not separately recorded and total signal intensity in this region corresponds to 15 protons), 2.60 (br s, 1 H), 3.30 (ddd, 1 H, *J* = 1.5, 5.5, 9.0 Hz), 3.66 ppm (s, 3 H); ir (neat) 3020, 2950, 2885, 1738, 1420, 1355, 1303, 1195, 1173, and 1050 cm^{-1}; mass spectrum *m/e* (rel intensity) 220 (1, M^+), 193 (1.5), 180 (8), 161 (5), 134 (4), 121 (515), 119 (8), 104 (6), 93 (7.5), 91 (7.5), 87 (7.5).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.05; H, 9.28; O, 14.29.

Transformation of 6 to 4-*exo*-Hydroxy-*endo,endo*-tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodecane (7e). To 10 ml of 10% methanolic potassium hydroxide, 1.205 g (5.48 mmol) of **7a** was dissolved and the solution was stirred overnight at room temperature. The reaction mixture was poured into 50 ml of water and acidified with dilute hydrochloric acid, and the product mixture was extracted with ether (30 ml × 3). The combined extracts were washed with water (30 ml) and dried (Na_2SO_4). Evaporation of ether afforded 1.08 g of crude carboxylic acid **7b**. The crude **7b** was heated under reflux with 10 ml of thionyl chloride and 0.50 ml of pyridine for 3 h. Excess thionyl chloride was removed by distillation, and the residue was further distilled under reduced pressure at 100–130 °C (0.1–0.5 mm) by using a Kugelrohr micro distilling apparatus to obtain 1.750 g of pale brown solid. This crude **7c** was used directly without further purification. A chilled stirred mixture of 1.750 g of crude **7c** and 1.583 g (7.78 mmol) of 85% *m*-chloroperbenzoic acid in 20 ml of *n*-hexane (dried over sodium) was treated dropwise with 0.615 g (7.78 mmol) of pyridine in 5 ml of *n*-hexane (5 min). The mixture was allowed to warm to room temperature with stirring and was left stand overnight. The solution was decanted from pyridine hydrochloride and the residue was washed with 5 ml of ether. The combined washings were evaporated and replaced with 30 ml of 10% methanolic potassium hydroxide. The solution was stirred at room temperature for 2 h followed by heating under reflux for 1 h. After cooling to room temperature, the solution was concentrated under reduced pressure, and the residue was treated with 30 ml of ether. The combined extracts were evaporated and the crude mixture was chromatographed on silica gel using ether–petroleum ether (1:5) eluent to isolate 0.165 g (0.93 mmol) of 4-*exo*-hydroxytetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodecane (**7e**) (17% from **7a**). This material was confirmed to be identical with the authentic sample of **7e** by means of NMR, ir, and VPC.

Acknowledgment. We wish to thank Professor T. Fueno for helpful discussions.

Registry No.—**1**, 6675-72-5; **4**, 58240-70-3; **5**, 58240-71-4; **6**, 58267-54-2; **7a**, 58240-72-5; **7b**, 58240-73-6; **7c**, 58240-74-7; **7d**, 58240-75-8; **7e**, 7273-98-5; methyl acrylate, 96-33-3; methyl propiolate, 922-67-8.

References and Notes

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(2) For a summary see (a) R. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968); (b) H. C. Brown, *Acc. Chem. Res.*, **6**, 377 (1973), and references cited therein.

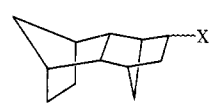
(3) P. Laszlo and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964).

(4) The deuterated adduct 9,10-*exo,exo*-d_2-**4** was obtained by the Diels–Alder reaction of methyl propiolate with 8,9-*exo,exo*-d_2-**1**, where exo deuteriums were introduced by catalytic D_2 reduction of dicyclopentadiene at the first step of the preparation of **1**. The multiplets around 1.40 ppm disappeared while the signals at 0.26 ppm became sharp considerably owing to the decrease of geminal coupling and were assignable to endo protons at C_9 and C_{10}.

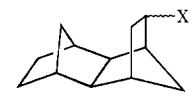
(5) J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).

(6) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

(7) Diimide reduction of **3** inevitably involves the reduction of a norbornene fragment from its endo side, a situation which is known to be seriously disfavored: W. C. Baird, Jr., B. Franzus, and J. H. Surrige, *J. Chem. Soc.*, **89**, 410 (1967). Even if the situation is overcome to produce **8**, some skeletal rearrangement is required in order for **8** to form **7e** during the transformation procedure. However, it has been calculated that



8a



8b

the parent hydrocarbon **7** is thermochemically less stable by 9.05 kcal/mol than its isomer **8** (X = H): E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *ibid.*, **95**, 8005 (1973).

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Propellanes. XI. On the Mechanism of Oxygenation of Cyclopropyllithiums

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Some time ago, Longone[1] reported that the oxygenation of cyclopropyllithiums to give cyclopropanols was a synthetically useful reaction. However, the stereochemistry, and hence mechanism, of the oxygenation step was not elucidated. We now report results which strongly implicate an electron transfer process to give a superoxide intermediate.

Propellanes **1** and **5** were initially chosen as substrates, owing in part to our need to obtain the corresponding alcohols for another study.[2] We took advantage of the previously demonstrated[3,4] stereoretention of the *n*-BuLi exchange reaction in order to generate **2** and **6**. After cooling to −78 °C, O_2 was bubbled through the solution for ≥1 h. The resultant mixture of cyclopropanol(s) and 1-butanol (a tenfold excess of *n*-BuLi was normally used) was usually acetylated directly, followed by purification and separation of the epimeric acetates; **3** and **4** could then be regenerated by reaction with KOH in aqueous MeOH. A particularly distinguishing feature of **3**, not found for **4**, was an intramolecularly hydrogen-bound hydroxyl absorption in the ir spectrum.

While the exclusive formation of **4** from **5** might lead one to consider direct collapse of **6** with O_2, the epimeric mix-