

DIELS-ALDER CYCLOADDITION OF 1,3-DISUBSTITUTED BUTADIENES TO
 ISOQUINOLINOPYRROLINEDIONES: SOLVENT AND TEMPERATURE EFFECT
 ON cis-endo TO cis-exo ISOMERIZATION OF THE ADDUCT¹.

Yoshisuke Tsuda* and Takeshi Ohshima

Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa
 920, Japan

Takehiro Sano* and Jun Toda

Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo 154,
 Japan

Abstract— Diels-Alder cycloaddition of 1,3-disubstituted butadienes to isoquinolinopyrrolinediones gives two cycloadducts, the previously reported cis-endo (regarding the dioxopyrroline ring) adduct and the new cis-exo adduct, with a variable ratio largely depending on the solvent and temperature of the reaction. Determination of their stereochemistries and isomerization experiments proved that the former adduct is a kinetic and the latter adduct is a thermodynamic product. Acceleration of dissociation and recombination of the former to the latter adduct in polar solvents (such as CHCl_3) was also suggested.

Previously we showed that the Diels-Alder reaction of isoquinolinopyrrolinediones with activated butadienes provides a useful method for preparation of ring D functionalized erythrinans. The reaction proceeds in regio- and stereo-selective manner to give the cis-endo (regarding the dioxopyrroline ring) adduct exclusively². In this communication, we wish to show that this adduct (A) corresponds to the kinetic product and another cycloadduct (B), the thermodynamic product, is obtained by reactions under different conditions, and that the ratio of these two adducts is markedly affected by factors of solvent and temperature.

During repetitions of the above cycloaddition reaction, we found that a new cycloadduct (B), which is isomeric to A, is produced under some reaction conditions. For example, when the dioxopyrroline 1 and an excess of 1,3-bis(trimethylsilyloxy)-butadiene were heated in CH_2Cl_2 at 180°C for 15 min, a new cycloadduct 3(B), mp

136-139°C, was produced in 70% yield, whereas the reaction in dioxane at 130°C afforded an isomer $\underline{2(A)}$ ², mp 141-143°C, in 65% yield. Solvent and temperature effects on this reaction are shown in Table 1. Several other combinations of the diene and the dienophile showed more or less an analogous trend, two cycloadducts being always produced with variable ratios depending on the solvent and temperature used (see also Table 2).

The two isomers showed very close chromatographic behaviour and spectroscopic properties, but characteristically distinguished by ¹H-chemical shift of aromatic protons. The new isomer (B), which is assumed as cis-exo (regarding the dioxopyrroline ring) adduct, always showed wider spacing of two Ar-H compared to the previously reported cis-endo adduct (A) (see Table 3).

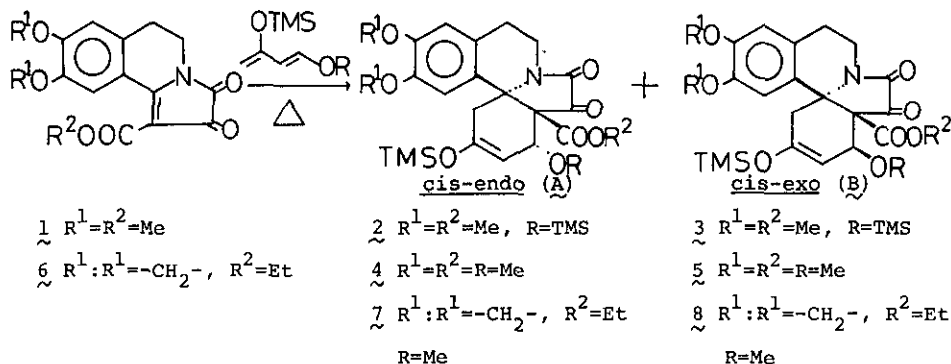


Chart 1

That the two isomers differ only in the stereochemistry at C_1 and the adduct \underline{A} corresponds to cis-endo and the adduct \underline{B} to cis-exo product were proved as follows. On treatment with KF in THF, $\underline{2(A)}$ and $\underline{3(B)}$ gave the ketone, $\underline{9}^3$, mp 207-209°C, and $\underline{10}^3$, mp 220-223°C, respectively, which are isomeric to each other. Reduction of $\underline{10}$ with $n-Bu_4NBH_4$ ⁴ in CH_2Cl_2 gave the ketol $\underline{11}$, mp 113-115°C; (60%), which on treatment 5% HCl-THF afforded the enone $\underline{12}$, mp 209-211°C. This was identical (TLC, IR, NMR) with the corresponding enone prepared from the adduct $\underline{2(A)}$ (i. $LiBH_4$, ii. 5% HCl-THF)⁵. Analogously, $\underline{7(A)}$ ⁶ afforded the ketone $\underline{13}^{2,3}$ mp 210-213°C, on treatment with KF. This was converted, by $NaBH_4$ reduction followed by acetylation, to the diacetate $\underline{14}$, mp 242-244°C, whose structure and configuration had been firmly established by X-ray analysis². On the other hand, treatment of the adduct $\underline{8(B)}$ with KF gave an isomeric ketone $\underline{15}^3$, mp 202-203°C, which on $NaBH_4$ reduction gave a mixture of diols. None of their diacetates was identical with $\underline{14}$.

Table 1. Solvent and temperature dependence in cycloaddition

of the dioxopyrroline 1 to 1,3-bis(trimethylsilyloxy)butadiene.

solvent	temp.(°C)	time(min.)	adduct ^a
dioxane	130	50	A>>B
dioxane	180	15	A< B
benzene	180	15	A> B
toluene	180	30	A> B
hexane	180	45	A< B
(neat)	180	15	A< B
CH ₂ Cl ₂	130	50	A<<B
CH ₂ Cl ₂	180	15	A<<B

A: cis-endo adductB: cis-exo adducta) The ratio was roughly estimated from ¹H-NMR spectra.Table 2. Formation of the cis-endo (A) or cis-exo (B) adduct by cycloaddition of dioxopyrrolines (1 and 6) to 1,3-disubstituted butadienes

dienophile	diene	solvent	temp.(°C)	time(min.)	isolable product,mp(°C)
<u>1</u>	<u>i</u>	dioxane	130	50	A(2) 141-143 ^a
		CH ₂ Cl ₂	180	15	B(3) 136-139
<u>1</u>	<u>ii</u>	dioxane	130	50	A(4) 142-144 ^a
		CH ₂ Cl ₂	180	50	B(5) gum
<u>6</u>	<u>ii</u>	toluene	130	60	A(7) gum ^{a,b}
		CHCl ₃	180	60	B(8) 176-179

i: 1,3-Bis(trimethylsilyloxy)butadiene ii: 1-Methoxy-3-trimethylsilyloxy-butadiene

a) see ref. 2

b) Mp of the isomer B is mis-listed for this compound in Table 3 of ref. 2. It must be changed as this.

Table 3. Characterization of the cis-endo(A) and the cis-exo(B) adduct.¹H-NMR aromatic protons of C₁₄-H and C₁₇-H in CDCl₃, δ ppm)

dienophile-diene	<u>cis-endo</u> (A)		<u>cis-exo</u> (B)	
<u>1-i</u>	6.72	6.58	7.14	6.58
<u>1-ii</u>	6.70	6.57	7.35	6.59
<u>6-ii</u>	6.72	6.60	7.35	6.54

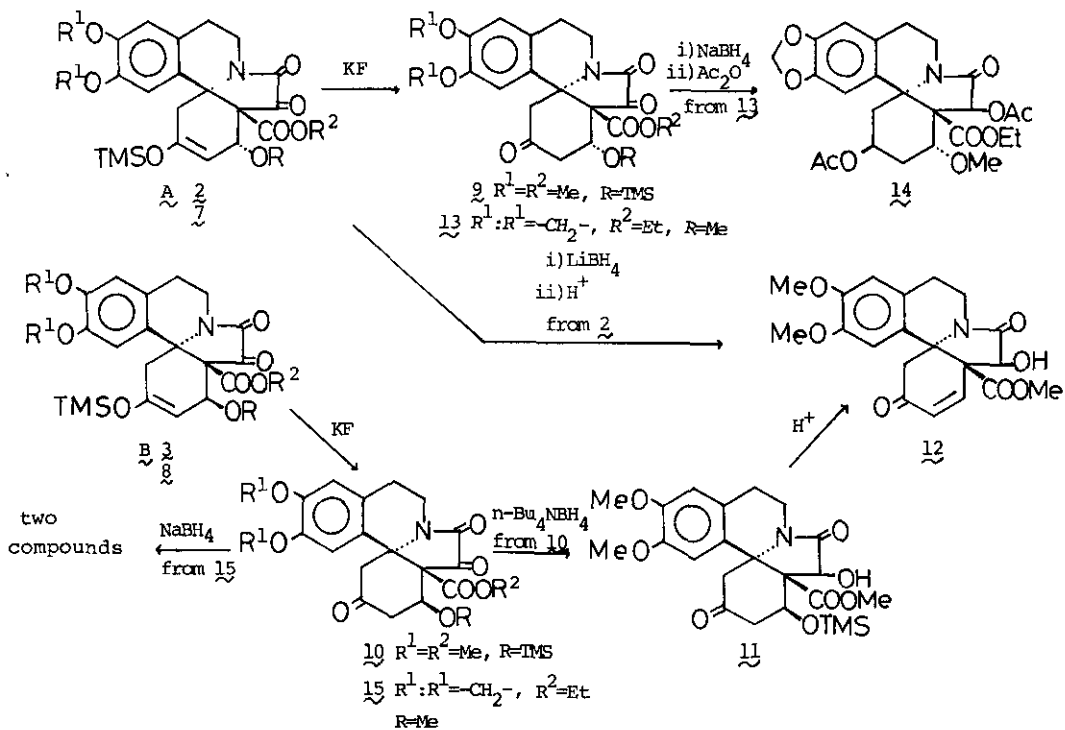
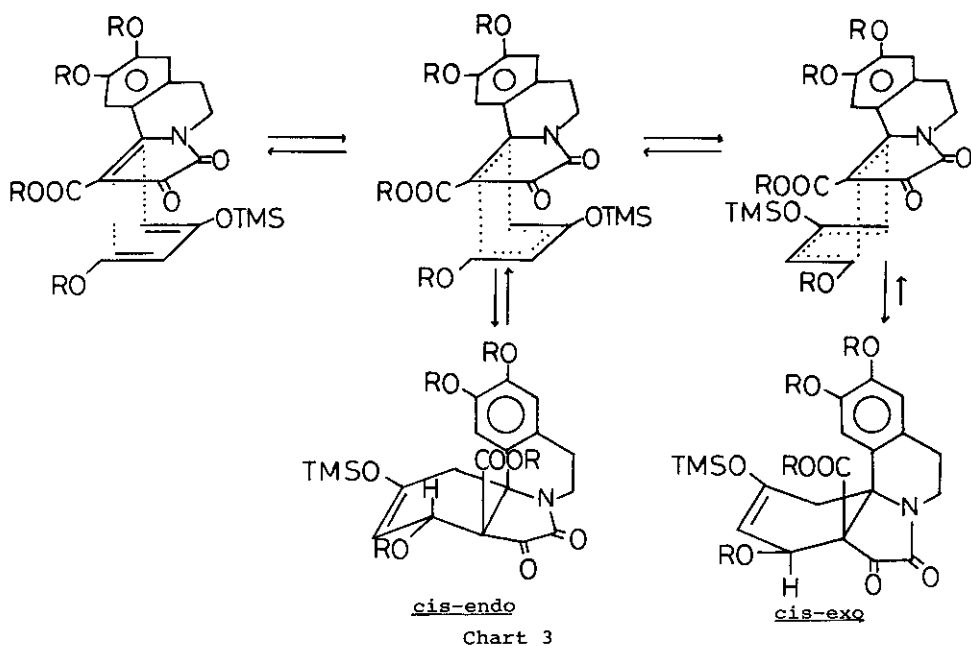


Chart 2

It has been sometimes demonstrated for simpler systems that an endo-exo ratio of the Diels-Alder adducts varies depending on the reaction temperature; that is, the proportion of exo-isomer generally increases on elevating temperature⁷. The same trend of temperature dependency was observed in our cycloaddition. Reaction of 1-methoxy-3-trimethylsilyloxybutadiene with the dioxopyrroline 1 in dioxane gave the cis-endo adduct 4 exclusively at 130°C (50 min), while the cis-endo (4) and the cis-exo (5) adduct were produced in ratio of 1 : 3.5 at 180°C (50 min). This can be explained by dissociation of the kinetic product (cis-endo) to the original components and recombination of them to the more stable thermodynamic product (cis-exo) (see Chart 3)⁸. This consideration was supported by the following evidence. On heating pure 4(A) in $CHCl_3$ at 180°C (1 h), it dissociated to the original dioxopyrroline 1 (42%). The 1H -NMR spectrum of the mother liquor from 1 was identical with that of 5(B). When this thermolysis (in $CHCl_3$, 180°C, 1 h) was carried in presence of excess diene, the isomerization of 4(A) into 5(B) occurred almost quantitatively.

There are very little reports on the solvent effect of Diels-Alder reaction. Berson et al.⁹ suggested that exo-selectivity increases with decrease of solvent polarity when the reaction is kinetically controlled. Apparently their suggestion is conflicting with our case, where the proportion of exo-product increases with increase of solvent polarity.¹⁰ Although we do not have any conclusive explanation for the role of solvent in our result, it may be safely assumed that a polar solvent such as CH₂Cl₂ or CHCl₃ facilitates dissociation of the kinetically produced cis-endo adduct.



REFERENCES AND NOTES

1. Dioxopyrrolines XXIV. Syntheses of Erythrina and Related Alkaloids (7). Part XXIII: T. Sano, J. Toda, and Y. Tsuda, Heterocycles, **18**, 229 (1982).
2. T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, and Y. Iitaka, Heterocycles, **15**, 1151 (1981).

3. 9: IR: 1770, 1750, 1715 cm^{-1} . $^1\text{H-NMR}$: 6.46(1H, s), 5.94(1H, s), 5.09(1H, t, $J=3$ Hz), 3.03(3H, s), 3.77, 3.64(each 3H, s), 0.13(9H, s).
- 10: IR: 1775, 1750, 1720 cm^{-1} . $^1\text{H-NMR}$: 6.83(1H, s), 6.44(1H, s), 4.99(1H, t, $J=3$ Hz), 3.02(3H, s).
- 13: IR: 1770, 1745, 1720, 1705 cm^{-1} . $^1\text{H-NMR}$: 6.58(1H, s), 6.08(1H, s), 5.89(2H, s), 4.55-4.73(2H, m), 3.31(3H, s), 0.70(3H, t, $J=7$ Hz), 3.78, 3.75(each 3H, s), 0.31(9H, s).
- 15: IR: 1765, 1740, 1725, 1705 cm^{-1} . $^1\text{H-NMR}$: 7.22(1H, s), 6.56(1H, s), 5.94(2H, s), 4.49-4.67(2H, m), 3.70(3H, s), 0.74(3H, t, $J=7$ Hz).
4. Reduction of 3 with LiBH_4 followed by acid treatment as described for 2 (ref. 5) gave an isomeric enone 16, mp 209-211°C, IR(KBr): 1730, 1677 cm^{-1} , $^1\text{H-NMR}$: $-\text{CH}=\text{CH}-$, 7.04 and 6.44 (each 1H, d, $J=11$ Hz).
- 16
5. T. Sano, J. Toda, and Y. Tsuda, see part XXIII (ref. 1).
6. See footnote b) of Table 2. Careful re-inspection of the $^1\text{H-NMR}$ spectra of the compounds in Table 3 of ref. 2 confirmed that the 11a-d and 12a-d given there had cis-endo configuration.
7. For review article of this subject, see J. G. Martin and R. K. Hill, Chem. Rev., 61, 537(1961).
8. Coupling patterns of $\text{C}_1\text{-H}$ in 9 and 10 suggested that both the isomers had similar orientation at C_1 . This can be interpreted by assuming that the ring D in the both isomers adopts a boat conformation as depicted in Chart 3.
9. J. A. Berson, Z. Hamlet and W. A. Mueller, J. Am. Chem. Soc., 84, 297(1962).
10. The solvent polarity may be expressed qualitatively by Kosower's Z [E. M. Kosower et al.: J. Am. Chem. Soc., 80, 3253, 3261, 3267(1958); 82, 2188, 2195(1960)] which is suggested to have linear relationship with a product distribution parameter Ω in Diels-Alder reaction (ref. 9).

Received, 22nd June, 1982