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Further Studies on the Velocity of Diels-Alder Reaction

It has generally been accepted that, in the Diels–Alder reaction, a *trans*-dienophile adds to a diene faster than the corresponding *cis*-dienophile.[1a–g] On the other hand, our previous finding indicates that the reactivity of maleonitrile is higher than that of fumaronitrile in the addition reaction to 4-carboxymethyl-5-ethoxyoxazole.[2]

Present report deals with some findings together with considerations on the velocity of the Diels–Alder reaction.

We took three pairs of dienophiles *viz cis*- and *trans*-dibenzoylethylenes, dimethyl maleate and dimethyl fumarate, maleonitrile and fumaronitrile as the large, middle and small size dienophiles. The dienes included four oxazole derivatives and tetrachlorofuran.

Table shows that most of *trans*-dienophiles react faster than the *cis*-isomer, and that maleonitrile (*cis*-dienophile) adds faster than fumaronitrile (*trans*-dienophile) to the dienes.[3]

TABLE. Reaction Rate Constant at 74° in Dioxane [$10^6 \cdot k_2$(liter mole^{-1} sec^{-1})][a]

Diene / Dienophile	5-Ethoxy-4-methyl-oxazole	5-Ethoxy-2,4-dimethyl-oxazole	4-Benzyl-5-ethoxy-oxazole	5-Ethoxy-4-methyl-2-phenyloxazole	Tetra-chloro-furan
cis-Dibenzoylethylene	120	—	—	—	—
trans-Dibenzoylethylene	820	—	—	—	—
Dimethyl maleate	37.3	2.70	27.0	—	—
Dimethyl fumarate	83.3	57.0	44.7	—	—
Maleonitrile	742	255	172	26.7	13.3
Fumaronitrile	700	157	140	11.3	12.0

a) The progress of the reaction was followed by the change of the amplitude in the vinyl proton signals of the dienophile using Varian 60 NMR spectrometer.

Sauer and co-workers[1c,d] proposed two factors in order to explain the higher reactivity of *trans*-dienophiles over *cis*-dienophiles. First, the steric hindrance in the *cis*-isomer weakens the activating effect of the substituents on the double bond which comes in contact with diene. Secondly, the compression of the eclipsed *cis*-substituents increases during the cycloaddition when the 120° bond angle is reduced to 109°. These two factors, resulting only from the configuration of dienophiles, positively fail to expailn our experimental result, namely, the higher reactivity of maleonitrile over fumaronitrile. Another factor mentioned for discussion by them is the interaction of the π-electron system between diene and dienophile in the transition complex. Little attention, however, has been paid to this factor. In view of our results, the factor seems to give most reasonable explanation of our results.

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1) *a*) R. Huisgen, H. J. Strum, and H. Wagenhofer, *Z. Naturforsch.*, **17b**, 202 (1962); *b*) J. Sauer, H. Wiest, and A. Mielert, *ibid.*, **17b**, 203 (1962); *c*) J. Sauer, D. Lang, and H. Wiest, *ibid.*, **17b**, 206 (1962); *d*) J. Sauer, D. Lang, and H. Wiest, *Chem. Ber.*, 97, 3208 (1964); *e*) J. Sauer, H. Wiest, and A. Mielert, *ibid.*, **97**, 3183 (1964); *f*) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem. Intern. Ed. Engl.*, **1**, 268 (1962); *g*) J. Sauer, *ibid.*, **6**, 16 (1967).
2) T. Miki and T. Matsuo, *J. Pharm. Soc. Japan*, **87**, 323 (1967).
3) R. Huisgen, R. Grashey, and J. Sauer described that the reaction rate constant in the addition of fumaronitrile and maleonitrile to cyclopentadiene were 81 and 91×10^{-5} liter/mole sec at 20° in dioxane (R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, 1964, p. 519) and 3280 and 3180×10^{-6} liter/mole sec at 40° in dioxane.[1b] They stated that the difference is lost in the case of the above 1,2-dicyanoethylenes. We have already examined the reaction at 74° in dioxane and found that the addition of fumaronitrile proceeds much faster than that of maleonitrile.

It is known that *cis*-dienophiles form exclusively endo-adducts. This suggests that the interaction of the π-electrons with the mobilization of two substituents may decrease the activation energy in the transition state. When the dienophiles are small in size like maleonitrile, the difference of the activation energy between *cis*- and *trans*-dienophile complexes may be small. When the diene is less reactive and when the substituents of the dienophile are small in size, the decrease of the activation energy by the longer overlapping of π-electron may be a dominant factor to accelerate the reaction. In our case, less reactivity of dienes resulted into faster addition of maleonitrile over fumaronitrile to these dienes.

We may, therefore, conclude that the interaction of the π-electron system between diene and dienophile is a significant factor that governs the velocity of the Diels–Alder reaction.

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Products from Reaction of Cholesteryl Acetate with Nitrous Acid[1]

It is generally known that a double bond reacts with nitrous acid to form an adduct. During our studies on steroids, the double bond in steroids was found to be fairly sensitive to nitrous acid to form interesting products.

Cholesteryl acetate reacted readily with sodium nitrite in acetic acid solution in the presence of conc. sulfuric acid to afford several products. Fractional recrystallization of the products gave I, colorless needles, mp 233—236°, $C_{29}H_{48}O_4$,[2] in 10% yield and II,[3] colorless needles, mp 168.5—170.5°, $C_{31}H_{50}O_6N_2$, in *ca.* 50% yield. The infrared (IR) spectrum (KBr) of I exhibits absorptions at 3410 (OH), 1735 (AcO), and 1710 cm^{-1} ($>$C=O), and its nuclear magnetic resonance (NMR) spectrum (100 Mc, $CDCl_3$) shows absorptions at δ 5.02 (1H, m) and 1.98 (3H, s). These data suggest that I possesses, in its molecule, a hydroxyl and a carbonyl group in addition to an acetoxyl group at C-3β. Finally, I was identified with an authentic sample of 3β-acetoxy-5α-hydroxycholestan-6-one through mixed melting point, and IR and NMR spectral comparison.

When II was allowed to stand in methanolic potassium hydroxide solution at room temperature, a potassium salt was formed. On treatment with acetic acid, the latter gave an oxime (III), mp 174—175°, $C_{27}H_{46}O_4N_2$. Refluxing of III in methanolic potassium hydroxide gave a hydroxy-ketone (IV), mp 232—235°, $C_{27}H_{46}O_3$, whose IR spectrum (KBr) exhibited absorptions at 3360 (OH) and 1705 cm^{-1} ($>$C=O). IV was identified as 3β,5α-dihydroxycholestan-6-one. From these evidences, the presence of AcO- at C-3β, ONO- at C-5α, and

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1) Steroids. I.
2) Satisfactory analytical data have been obtained for all compounds reported.
3) During the preparation of this communication, this compound has been presented by Narayanan and others in *Tetrahedron Letters*, **1970**, 4703.