Regioselective Diels-Alder Reaction of 2-Substituted Acrylonitriles with Cyclic Dienones and Hydrolytic Ring Cleavage of the Adducts

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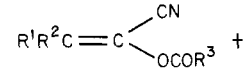
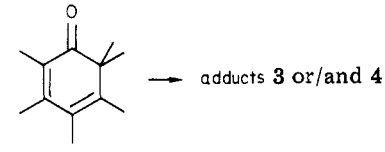
The reactions of 2-substituted acrylonitriles $R^1R^2C{=}C(X)CN$ (1, where $R^1 = R^2 = H$, X = $OCOCH_2Cl$, OCOPh, OCOOEt, $OCOCH_3$; or 8, where X = Cl) with hexamethylcyclohexa-2,4-dienone (2) proceeded with a high regioselectivity to afford solely head-to-tail-type adducts 3 (80–92%, anti/syn ratio of 1.3–5.7). The anti isomers are thermodynamically more stable. The reaction of 1 ($R^1 = R^2 = H$, X = $OCOCH_3$) with tetracyclone (10) gave adduct 11 in fair yields (35%, endo/exo ratio of 1–1.7). On being heated the adducts yielded 2,3,4,5-tetraphenylbenzonitrile (12, 55%). The reaction of 8 with 10 also gave adduct 14 (92%, endo/exo ratio of 1.27). The alkaline hydrolysis of 3 gave the corresponding bicyclic diketone 5 (98%): the anti isomer hydrolyzed 2 times faster than the syn. Under severe conditions 3 straightly afforded (1,3,3,4,5,6-hexamethyl-2-oxocyclohex-4-en-1-yl)acetic acid (15, 94%). The alkaline hydrolysis of 11 afforded 12 (36%), whereas 11 was unreactive toward acid hydrolysis.

The commonly accepted empirical rule that the Diels–Alder reaction of an electron-deficient dienophile takes place efficiently only in combination with an electron-rich diene cannot be regarded as valid any longer as argued in a number of exceptional reactions.[1] Ketene, in this category, can be used as an electron-deficient dienophile and utilized in two-carbon annelation reactions though its laboratory handling meets with difficulties. The recently developed method for the facile synthesis of 2-(acyloxy)acrylonitriles (1-cyano-1-alkenyl esters, 1)[2] enabled us to use them as the synthetic equivalent of ketenes in a number of Diels–Alder reactions. Although there have been reported several reactions of 2-acetoxyacrylonitrile,[3] they were limited to combination with electron-rich dienes. Our first subject, therefore, is the Diels–Alder reaction of 2-(acyloxy)acrylonitriles with electron-deficient cyclic dienones. In this type of reaction it is important to clarify the regioselectivity as well as the stereoselectivity of the reaction because, with cyclohexadienone, two regioisomers are possibly formed, and most synthetic methods demand a high selectivity. The reaction of 1 with cyclopentadienones, on the other hand, has no regioisomerism but end–exo isomerism.

The adducts obtained in these reactions seem to become the potential precursors of some polyfunctional compounds such as bicyclic cyanohydrins, diketones, and (oxocycloalkenyl)acetic acids. In the present study we have also investigated the hydrolytic ring-opening reaction of these adducts to clarify how the two-carbon elongation is included in product structures.



1a, $R^1 = R^2 = H$; $R^3 = CH_2Cl$
b, $R^1 = R^2 = H$; $R^3 = Ph$
c, $R^1 = R^2 = H$; $R^3 = OEt$
d, $R^1 = R^2 = H$; $R^3 = Me$
e, $R^1 = H$; $R^2 = Me$; $R^3 = Me$
f, $R^1 = R^2 = Me$; $R^3 = Me$



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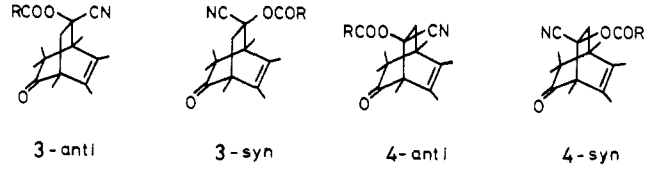
Results and Discussion

Reaction of Hexamethylcyclohexa-2,4-dienone (2) with 2-(Acyloxy)acrylonitriles (1). The reactions of 2-(acyloxy)acrylonitriles **1a–f** with hexamethylcyclohexa-2,4-dienone (2) were carried out in sealed tubes at 100 °C without solvent. Products were obtained in relatively high yields (80–92%) from unsubstituted esters **1a–d**, and the yields are apparently higher than those of the reported reactions with electron-rich dienes.[4] However, the reaction was unfavorable for methyl-substituted dienophiles; thus 2-acetoxy-3,3-dimethylacrylonitrile (**1f**) was unreactive under various conditions. Results are shown in Table I.

The reaction of unsubstituted dienophiles **1a–d** yielded a mixture of two isomeric adducts which can be ascribed to two of the following four possible bicyclo[2.2.2]octenecarbonitrile structures: *anti*-**3**, *syn*-**3**, *anti*-**4**, and *syn*-**4**.



Structure **3** is the head-to-tail and **4** is the head-to-head structure (here, the anti and syn nomenclature is defined according to the IUPAC rule for nitrile derivatives).[5] In order to elucidate the adduct structures, we analyzed their ^1H NMR spectra (vide infra).

(a) Regioselectivity. First of all, it should be noted that the reaction proceeded with a high regioselectivity because the adduct consisted solely of two isomers,[6] and the alkaline hydrolysis of any isomer couple afforded an identical bicyclic diketone **5** under mild conditions (Table IV). Therefore, the adduct couple should be the anti and

(1) Sauer, J.; Sustman, R. *Angew Chem.* **1980**, *92*, 773.
(2) (a) Oku, A.; Arita, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3337. (b) Oku, A.; Nakaoji, S.; Kadono, T.; Imai, H. *Ibid.* **1979**, *52*, 2966.
(3) (a) Little, J. C. *J. Am. Chem. Soc.* **1965**, *87*, 4020. (b) Dilling, W. L.; Kroening, R. D.; Little, J. C. *Ibid.* **1970**, *92*, 928. (c) Birch, A. J.; Hutchinson, E. G. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1757.
(4) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, 121.
(5) Fletcher, J. H., Dermer, O. C., Fox, R. B., Eds. "Nomenclature of Organic Compounds. Principles and Practice"; American Chemical Society: Washington, DC, 1974; pp 74, 114.
(6) On the basis of the analysis of the amplified NMR spectrum, the regioselectivity of the addition is almost 99 ± 1% since no methylene protons other than those of two major components were observed. Also in the spectral analysis of diketone **5**, by noticing bridgehead methyls as well as ring methylene protons, the concomitant formation of the alternative isomer **6** could not be detected.

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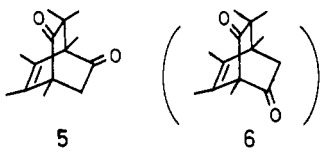


5 6

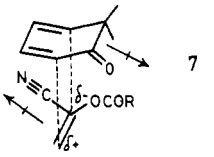
syn stereoisomers with a single regioisomerism. This is to be contrasted with the somewhat lower selectivity exhibited in the reaction with electron-rich dienes.[4] The most characteristic feature of the diketone in its ^1H NMR spectra is that the chemical shifts of two bridge-head methyl groups are identical (δ 1.25) in contrast to a 0.3–0.4-ppm difference in the adducts as shown in Table II. This provides the evidence for the head-to-tail structure **5** in which each bridgehead methyl is influenced almost equally by its surroundings while in structure **6** only one methyl sandwitched between two carbonyls.

Additional evidence for the structure **5** is available not only from the observation that the chemical shift difference ($\Delta\delta$ = 0.18 ppm, Table II) between two *gem*-methyl groups of the diketone is larger than that of the corresponding adduct (0.06–0.11 ppm) but also from the study of lanthanide-induced shift (LIS) with Eu(fod)$_3$.[7]

(b) Anti–Syn Isomerism. The noticeable feature in the NMR spectra of the adducts is that in any isomer couple the methylene protons of the bicyclo[2.2.2]octene ring appear as a pair of doublets in one isomer ($\Delta\delta$ ca. 1.3 ppm) whereas in the other isomer they almost coalesce or appear as a slightly split pair of doublets ($\Delta\delta$ ca. 0.1–0.2 ppm). This significant difference is then assessed as follows. (1) In bicyclo[2.2.2]octanes,[8] the acetoxyl group causes a ca. 0.6–0.9-ppm upfield shift of the vicinal cis methylene proton relative to the trans proton, whereas the cyano group acts similarly but only to a small extent (ca. 0.1 ppm).[9] (2) The long-range shielding effects of both the carbonyl and carbon–carbon double bond for the C-7 methylene protons of bicyclo[2.2.2]oct-5-en-2-one are found to be trivial (ca. 0.05 ppm) by the framework examination of the shielding field diagram.[10] Several examples support this estimation.[11] However, the shielding effect of the double bond is strengthened by the methyl substitution whereas, for the carbonyl group, it is counteracted by the electrostatic effect. Therefore, the proton endo to the carbonyl should be deshielded relative to the exo proton. As a consequence of overlapping of effects 1 and 2, they are cancelled in the anti isomer of **3** to give a small $\Delta\delta$ value, whereas they are multiplied in the syn isomer to give an amplified value.

(c) Stereochemistry of the Addition Reaction. The exclusive formation of the head-to-tail regioisomers **3** (selectivity 99 ± 1%) must be noted in comparison with the results reported by Evans[4] where two isomers were formed from unsymmetrically substituted cyclohexadienes. The high regioselectivity is attributed mainly to a polar interaction between the diene **2** and the dienophile **1**. The extent of this effect apparently surpasses the steric effect which may arise between the *gem*-dimethyl groups of **2** and the substituents of **1** although the latter type of effect was observed, for example, in the reaction of **2** with substituted benzynes.[12]

The predominant formation of the anti isomer of **3** tells us that its formation is at least thermodynamically favored because, in any reaction of **1a–d**, the syn isomer always isomerized to the anti whereas the anti did not isomerize to the syn isomer. For example, the adduct mixture with an initial isomer ratio of *anti*:*syn*-**3a** of 0.83 changed its ratio into 1.10 after heating at 200 °C for 1 h; similarly the anti/syn ratio for **3b** of 3.0 changed to 6.1, and that for **3d** changed from 1.5 to 2.0. This aptitude of stereoselectivity can be interpreted in terms of a dipole–dipole interaction[13] which is exerted not only in a thermodynamically equilibrated adduct mixture but also in the transition state as illustrated in **7**.



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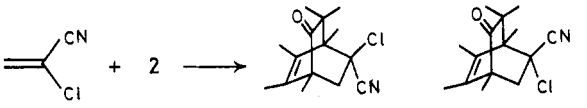
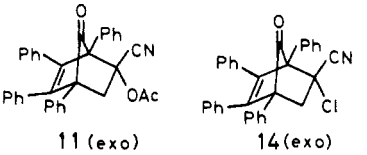
(d) Reaction of 2 with 2-Chloroacrylonitrile (8). In the Diels–Alder reactions, 2-chloroacrylonitrile (**8**)[14] has been used mostly in combination with electron-rich dienes,[15] and it seemed necessary to compare the reactivity of **8** with that of **1** in the present study. The reaction of **8** with **2** was carried out under conditions analogous to



8 9 (anti) 9 (syn)

those of **1**. The adduct also consisted of two nitrile stereoisomers, *anti*-**9** and *syn*-**9**, with the same regioselectivity as that of **3**. The isomer ratio (anti/syn = 0.21) was determined on the assumption that the chlorine substituent can be regarded as equivalent to acyloxy functions, and the ratio was found to be converse to the result of **1a** where the ratio was 2.1.

Reaction of 2-(Acyloxy)acrylonitriles (1) with Tetraphenylcyclopentadienone (10). The reaction of tetraphenylcyclopentadienone (**10**) with **1d** in benzene solution afforded the endo–exo mixture of bicyclic carbonitrile **11** in fair yields (see Table III; notice that in this



11 (exo) 14 (exo)

system the definition of endo and exo nomenclature corresponds to the anti and syn of **3**, respectively). Both isomers were separated, and their structural assignment was performed by ^1H NMR on the same bases as were applied to the adducts **3**: one isomer (mp 265 °C) showed methylene protons at δ 2.90 and 3.90 (J = 14.4 Hz) whereas the other isomer showed these protons at δ 3.90 and 3.5 (J = 14.5 Hz). The former adduct with a larger $\Delta\delta$ value between the methylene protons was assigned to the exo and the latter to the endo isomer.

(7) The LIS slope of the syn methylene proton of *anti*-**3a** was found to be as large as 3.75 and 2.7 for *syn*-**3a**. Such large values of LIS slope indicate that the keto carbonyl moiety is located near the methylene group.

(8) Jackman, L. M.; Sternhell, S. "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press: Elmsford, NY, 1969; p 232.

(9) Applying these observations to 2-acetoxy-2-cyanobicyclo[2.2.2]octane, the chemical shift difference ($\Delta\delta$) between two methylene protons at the C-3 position will be as large as 0.5–0.8 ppm.

(10) Tillieu, J. *Ann. Phys.* (*NY*) **1957**, *2*, 471. See also ref 8, p 83.

(11) Davis, J. C.; van Auken, T. *J. Am. Chem. Soc.* **1965**, *87*, 3900.

(12) Oku, A.; Matsui, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3338.

(13) Sasaki, T.; Kanematsu, K.; Iizuka, K. *J. Org. Chem.* **1976**, *41*, 1105.

(14) Corey, E. J.; Weinshenker, M. M.; Schaaf, T. F.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

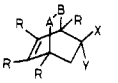
(15) (a) Gregson, R. P.; Mirrington, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 598. (b) See also ref 4.

Table I. Reaction of 2-(Acyloxy)acrylonitriles 1a-f [$R^1R^2C=C(CN)OCOR^3$] or 2-Chloroacrylonitrile (8) with Hexamethylcyclohexa-2,4-dienone (2)

compd	substituent R^1	R^2	R^3	time, h	yield of adduct,[a] %	isomer ratio,[b] anti/syn
1a	H	H	CH_2Cl	6	90	2.1
1b	H	H	Ph	6	77	5.7
1b	H	H	Ph	16	90	5.7
1c	H	H	OEt	16	80	1.2
1d	H	H	Me	16	92	1.9
1e[c]	Me	H	CH_2Cl	192	15	*d*
1f	Me	Me	Me	168	0	
8	H	H	Cl	48	72	0.21

[a] Isolated yields. [b] Determined by ^1H NMR before product isolation. [c] The starting ester consisted of *Z* and *E* isomers (*Z*/*E* ratio of 5.0). [d] Unable to be determined.

Table II. ^1H NMR Data (δ) of the Diels-Alder Adducts and Diketone 5



compd[a]	substituent X	Y	bridgehead methyls δ_a	δ_b	$\Delta\delta_{a,b}$	*gem*-dimethyls[b] exo	endo	$\Delta\delta$	bridge methylenes[b] anti (endo)	syn (exo)	$\Delta\delta$
anti-3a	$OCOCH_2Cl$	CN	1.14	1.45	0.31	0.96	1.02	0.06	2.20	2.40	0.20
syn-3a	CN	$OCOCH_2Cl$	1.16	1.42	0.26	1.02	1.10	0.08	1.60	2.90	1.30
anti-3b	OCOPh	CN	1.15	1.56	0.41	0.94	1.04	0.10	2.37	2.37	0
syn-3b	CN	OCOPh	1.15	1.60	0.45	1.04	1.15	0.11	1.77	3.04	1.27
anti-3d	$OCOCH_3$	CN	1.14	1.46	0.32	0.95	1.02	0.07	2.20	2.30	0.10
syn-3d	CN	$OCOCH_3$	1.15	1.45	0.30	1.00	1.08	0.08	1.60	2.87	1.27
5	-O-		1.25	1.25	0	0.97	1.15	0.18	2.19	2.34	0.15
anti-9	Cl	CN	1.20	1.50	0.30	1.08	1.12	0.04	2.44	2.60	0.16
syn-9	CN	Cl	1.17	1.53	0.36	1.03	1.08	0.05	2.12	2.92	0.80
exo-11	CN	$OCOCH_3$							3.90	2.90	1.00
endo-11	$OCOCH_3$	CN							3.51	3.09	0.42
exo-14	CN	Cl							3.78	3.12	0.66
endo-14	Cl	CN							3.57	3.57	0

[a] In compounds 3, 5, and 9, the A-B bridging is $CO-C(CH_3)_2$, and R is Me. In compounds 11 and 14, the A-B is -CO-, and R is Ph. [b] The exo-endo and anti-syn nomenclatures are based on the IUPAC rule.

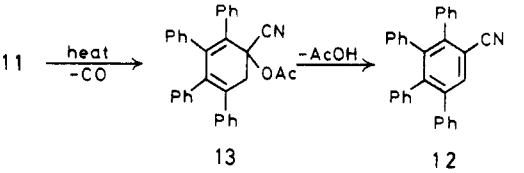
Table III. Reaction of 2-Substituted Acrylonitriles 1d and 8 [$CH_2=C(X)CN$] with Tetraphenylcyclopentadienone (10)[a]

X in dienophile	reagent ratio of 1d(or 8)/10	additive[b] (mol %)	time, h	adduct yield %[c]	adduct isomer ratio,[d] endo/exo
$OCOCH_3$	3	DBP (1)	24	18	
$OCOCH_3$	3	DBP (1)	48	35	1.4
$OCOCH_3$	1	DBP (1)	700	23[e]	0.59
$OCOCH_3$	3	DBP (1), BF_3Et_2O (5)	48	26	1.3
$OCOCH_3$	1	DBP (1), BF_3Et_2O (5)	170	24[e]	1.0
Cl	1		48	90	0.72
Cl	3		48	92	0.77

[a] At 100 °C in benzene. [b] DBP/di-*tert*-butylphenol. [c] Based on the amount of dienophile. [d] Determined by NMR. [e] 2,3,4,5-Tetraphenylbenzonitrile (12) was also formed.

The rate of this reaction was slow, and the product yield was not as high as expected (Table III) probably due to the facile retro reaction.[16] It has been reported that cyclopentadienone reacted more easily with electron-rich dienophiles rather than electron-deficient ones.[17] In the present study, phenyl-substituted cyclopentadienone **10** reacted easily with electron-deficient dienophiles **1** or **8**, probably because the HOMO level of **10** which is raised by phenyl substitution can interact, with a small energy gap, with the low-lying LUMO of **1d**.[1]

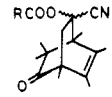
In this reaction, tetraphenylbenzonitrile **12** was also



formed after prolonged heating. This may have been formed through decarbonylation followed by aromatization, in which the elimination of AcOH rather than HCN takes place preferentially. In addition, when the endo–exo mixture of **11** was heated at 190 °C for 2 h, **10** (30%) was formed besides **12** (55%). Thus, a relatively large equilibrium constant of this reversible addition reaction seems

(16) (a) Kakushima, M.; Espinosa, J.; Valenta, Z. *Can. J. Chem.* **1976**, *54*, 3304. (b) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.
(17) (a) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (b) Paquette, L. E.; Moerck, R. E.; Harirchian, B.; Magnus, P. D. *Ibid* **1978**, *100*, 1597. (c) Harrison, E. A. Jr. *J. Org. Chem.* **1979**, *44*, 1807.
(18) Oku, A.; Fuse, T.; Mashio, F. *Nippon Kagaku Kaishi* **1972**, 1199.

Table IV. Alkaline Hydrolysis of the Diels-Alder Adducts 3a-d[a]



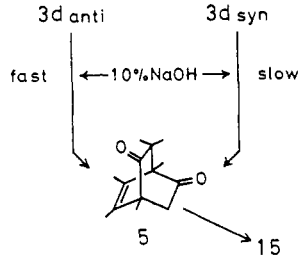
entry	compd	R	time, min	product(s)	yield of 5 (or 15a)[b]
1	*anti*-3d	Me	1.0	3, 5	12
2	*anti*-3d	Me	2.5	3, 5	45
3	*syn*-3d	Me	2.5	3, 5	15
4	*anti*-3d	Me	5.0	3, 5	56
5	*syn*-3d	Me	5.0	3, 5	30
6	*anti*-3d	Me	10	5	98
7	*syn*-3d	Me	10	3, 5	68
8	*anti*-3b	Ph	10	3	0
9	*anti*-3b	Ph	60	15a	66
10	*anti*-3a	CH_2Cl	20	15a	71
11	*anti*- + *syn*-3c	OEt	30	15a	70
12	5		5.0	5, 15a	22
13	5		20	15a	94

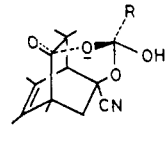
[a] The hydrolyses were carried out in dioxane-aqueous 10% NaOH solutions: entries 1-7, NaOH/3 ratio of 2.43, temperature 50 °C; entry 8, 2.63 and 60 °C; entry 9, 17.6 and 95 °C; entry 10-13, 2.8 and 80 °C. [b] Isolated yields; products were isolated as a single component or as a mixture of products and unreacted starting compound.

to be responsible for the low yield of the adduct.

The addition of **10** with **8** was also carried out to compare **1** with **8** in the reaction of **10**. The endo–exo mixture of the adduct **14** was obtained in a respectable yield (92%). Apparently the reactivity of **8** with **10** is higher than that of **1d**. The exo/endo isomer ratio of 1.30 was determined on the basis of the NMR assignment of the isomer with a larger $\Delta\delta$ value (0.66) between methylene protons as exo and the other isomer ($\Delta\delta$ = 0) as endo (see Table II) in analogy to the assignment applied for **3**.

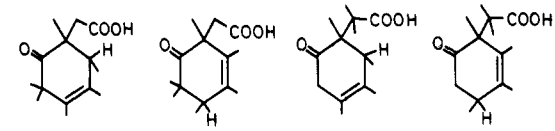
Hydrolysis of Adducts 3. The alkaline hydrolysis of the Diels–Alder adducts **3a–d** with aqueous NaOH under mild conditions afforded bicyclic diketone **5** in high yields (Table IV). Further hydrolysis of the diketone under relatively severe conditions induced the hydrolytic ring opening of **5** to produce (2-oxocyclohexen-1-yl)acetic acid **15** or **16** (94%). As shown in Table IV, the anti isomer of **3d** apparently underwent the hydrolysis somewhat faster





than the syn isomer. Though small, this difference in hydrolytic reactivities between these two stereoisomers is interesting from a mechanistic point of view: a possible rationalization seems to be the dipole effect in the anti isomer which stabilizes the hydroxide-addition intermediate **17**. It is clearly demonstrated that, under controlled conditions, the hydrolysis of **3d** takes place stepwise to form the diketone **5** first and then the ring-opened monocyclic carboxylic acid. Benzoyloxy derivative **3b**, however, did not afford **5** but only the acid because its rate of hydrolysis is slower than that of **5**.

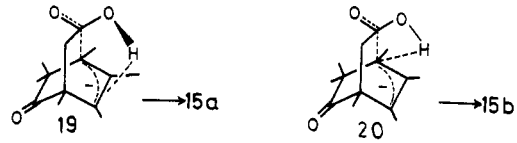
For the structure of the hydrolysis product acid, four isomeric structures are possible, **15a**, **15b**, **16a**, and **16b**,



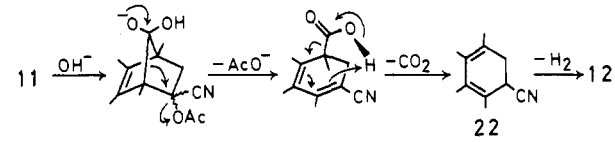
15a 15b 16a 16b

each consisting of two stereoisomers, *Z* and *E*, with regard to the disposition of carboxymethylene and the methyl group on the secondary carbon. However, the unity of the hydrolysis product was confirmed by VPC analysis after treatment with diazomethane as well as by TLC and NMR. The structural determination was performed by NMR.

Since both the methylene and the *gem*-dimethyl proton signals appeared as a sharp singlet, structures **16a** and **16b** were ruled out. The choice out of the remaining **15a** and **15b** by ^1H NMR analysis seems difficult to perform. In ^{13}C NMR analysis, it was noticed that the $\Delta\delta$ value between the double bond carbons was found to be as large as 20–25 ppm. Additive substituent parameters[19] suggest that the estimated value is larger than 15 ppm for **15a** but as small as 10 ppm for **15b**; thus **15a** seems favorable. The structure is also accessible from the stereochemistry of the hydroxide-induced ring-cleavage process of cyclic ketones.[20] That only one product was formed in the present reaction indicates the intervention of a highly chemo- and stereoselective cleavage–protonation process most plausibly via the intramolecular protonation, as depicted in **19**, in preference to the four-membered way as in **20**. Consequently, this survey also supports structure **15a** and its *E* configuration although no spectral analysis seems able to ensure this.



Hydrolysis of Adduct 11. The alkaline hydrolysis of the Diels–Alder adduct **11** afforded 2,3,4,5-tetraphenylbenzonitrile **12**, but other anticipated products were not formed.[21] Thus, the hydrolytic behavior of **11** is different from that of **3**, being specific with regard to the formation of nitrile **12**. Although compound **11** undergoes pyrolytic decarbonylation to produce **12** (vide ante), the hydrolysis temperature is too low to induce the same reaction, and, therefore, a different mechanism must be involved here. On the basis of the work by Sasaki and co-workers,[13] who reported the formation of 1,4-diphenyl-3-cyano-1,2-dihydrotriphenylene (**21**) from the adduct of phencyclone with **1a**, we assume that the mechanism outlined below is



a reasonable path. The difference that **22** aromatized

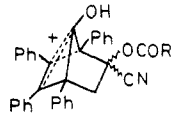
(19) Levy, G. C.; Nelson, G. L. "Carbon-13 NMR for Organic Chemists"; Wiley: New York, 1972. Translated by: Tanaka, S. *Tokyo Kagaku Dojin* **1973**, 40–60.

(20) Erman, W. F.; Kretschnar, H. C. *J. Am. Chem. Soc.* **1967**, *89*, 3842.

(21) The hydrolysis of **11** by aqueous NaOH gave a relatively clear result among several of the reagents examined such as MeONa/MeOH, KOH/MeOH, *t*-BuOK/0.5 equiv of H_2O/Me_2SO (or Et_2O), and Na_2S/H_2O–EtOH.

whereas **21** did not can presumably be explained in terms of the difference in resonance energy: it is much larger between **22** and **12** than between **21** and its dehydrogenated triphenylene.

Some attempted acid hydrolysis of **11** proved that **11** is surprisingly stable under such drastic conditions as heating at 80 °C for 1.5 h with 30% sulfuric acid, in contrast to the facile hydrolysis of ordinary cyanohydrin acetates.[22] A distinct difference in structure **11** is that it has a strained ketocarbonyl group which undergoes protonation to produce a degenerated carbocation **23**. This may hardly undergo further acid hydrolysis of the acyloxy function.



23

In conclusion, the Diels–Alder reaction between electron-deficient cyclic dienones and such electron-deficient dienophiles as 2-(acyloxy)acrylonitriles (**1**) or 2-chloroacrylonitrile (**8**) can be registered as a member of ordinary diene synthesis.

Experimental Section

^{1}H NMR chemical shifts are given in δ units in $CDCl_3$ solution. Melting points are uncorrected, and combustion analysis was performed by the Microanalytical Laboratory of Kyoto University.

Reagents. 2-Acyloxyacrylonitriles **1a–f** were synthesized from the corresponding acyl cyanides and acyl chlorides according to our previous study.[2] Hexamethylcyclohexa-2,4-dienone (**2**) was prepared from hexamethylbenzene.[18]

1,4,6,6,7,8-Hexamethyl-2-(chloroacetoxy)-5-oxobicyclo[2.2.2]oct-5-ene-2-carbonitrile (3a). General Procedures for the Reaction of 1 with 2. Stoichiometrically equal amounts of **1a** (1.33 g, 12 mmol) and **2** (2.14 g, 12 mmol) were mixed at ambient temperature. The mixture was equally divided into four portions, and each fraction was placed in a sealed tube followed by flushing with purified nitrogen stream. The tubes were immersed in a bath controlled at 100 ± 0.5 °C. After every 6.5, 13, 26, and 48 h, a tube was taken out for the ^{1}H NMR measurement. The mixture in the last tube was chromatographed on a silica gel column ($CHCl_3$) to give a mixture of *anti*-**3a** and *syn*-**3a** (anti/syn ratio of 68:32 based on the NMR integration of the ring methylene protons).[6] The total yield was 92%. The mixture was recrystallized from CCl_4 to give the anti isomer first and the syn isomer after repeated recrystallizations. *anti*-**3a**: mp 145–147 °C; mass spectrum, m/e 323 (M^+); ^{1}H NMR 0.96, 1.02, 1.14, 1.45 (3 H each, s), 1.77, 1.83 (3 H each, q, J = 1 Hz), 2.20, 2.40 (1 H each, 2 d, J = 16 Hz), 4.40 (2 H, s). Anal. Calcd for $C_{17}H_{22}NO_3Cl$: C, 63.06; H, 6.85; N, 4.33. Found: C, 63.15; H, 7.02; N, 4.17. *syn*-**3a**: mp 100–101 °C; mass spectrum, m/e 323 (M^+); ^{1}H NMR 1.02, 1.10, 1.16, 1.42 (3 H each, s), 1.73, 1.80 (3 H each, q, J = 1 Hz), 1.60, 2.90 (1 H each, 2 d, J = 15 Hz), 4.07 (2 H, s). Similar procedures were applied to the reactions of **2** with other 2-(acyloxy)acrylonitriles.

2-Benzoyloxy Derivative of 3 (3b). The adduct yield was over 90% (anti/syn ratio of 85:15). The anti isomer was isolated in pure state. *anti*-**3b**: mp 200–201 °C; mass spectrum, m/e 351 (M^+); ^{1}H NMR 0.94, 1.04, 1.15, 1.56 (3 H each, s), 1.84 (6 H, br s), 2.37 (2 H, s) 7.3–8.05 (5 H, m). *syn*-**3b**: ^{1}H NMR 1.04, 1.60 (3 H each, s), 1.15 (6 H, s), 1.80 (6 H, br s), 1.77, 3.04 (1 H each, 2 d, J = 16 Hz).

2-(Ethoxyformyl)oxy Derivative of 3 (3c). The yield of the adduct (viscous oil) was 80% after column chromatography (anti/syn ratio of 55:45); mass spectrum, m/e 319 (M^+). The isomers were not separated in pure states. However, the isomer ratio was determined by comparing the ^{1}H NMR spectral intensities of ethoxy and ring methylene protons.

2-Acetoxy Derivative of 3 (3d). After column chromatography the yield of the adduct was 92% (anti/syn ratio of 65:35). Only the anti isomer was separated by recrystallization (ethanol). *anti*-**3d**: mp 152–154 °C; mass spectrum, m/e 289 (M^+); ^{1}H NMR 0.95, 1.02, 1.14, 1.46 (3 H each, s), 1.78, 1.83 (3 H each, q, J = 1 Hz), 2.05 (3 H, s), 2.20, 2.30 (1 H each, 2 d, J = 17 Hz). *syn*-**3d**: ^{1}H NMR 1.00, 1.08, 1.15, 1.45 (3 H each, s), 1.70, 1.80 (3 H each, q, J = 1 Hz), 2.07 (3 H, s), 1.60, 2.87 (1 H each, 2 d, J = 15.5 Hz).

1,3,4,6,6,7,8-Heptamethyl-2-(chloroacetoxy)-5-oxobicyclo[2.2.2]oct-5-ene-2-carbonitrile (3e). The rate of reaction of **1e** (a mixture of 80% *Z* and 20% *E*) with **2** was slow, and the product yield reached to only 15% after 8 days when **1e** was almost consumed. The reaction mixture was chromatographed (silica gel) to give a fraction of the mixture of four possible isomeric adducts, *anti*-*Z* and -*E* and *syn*-*Z* and -E. The NMR assignment of each isomer was unsuccessful. However, the mass spectra of the mixture as well as the elemental analysis proved the identity of the fraction: mass spectrum, m/e 337 (M^+); Anal. Calcd for $C_{18}H_{24}NO_3Cl$: C, 63.98; H, 7.16; N, 4.15. Found: C, 63.81; H, 7.28; N, 4.12.

Thermal Isomerization of the Adducts. The isolated anti isomer of **3b** or **3d** (200 mg) was placed in a sealed tube under a nitrogen atmosphere, and the tube was heated at 200 °C for 10 min. The solid melted. After the mixture cooled, NMR spectra showed no evidence for the formation of the corresponding syn isomer. A mixture of the anti and syn isomers of each adduct, **3a**, **3b**, or **3d**, was analogously heated at 200 °C for 1 h. The ratio changed after this treatment: **3a**, anti/syn ratio of 0.83 to 1.10; **3b**, anti/syn ratio of 3.0 to 6.1; **3d**, anti/syn ratio of 1.5 to 2.0.

2-Chloro Derivative of 3 (9). A mixture of **8** (1.0 g, 11.2 mmol), **2** (2.03 g, 11.2 mmol), and 2,6-di-*tert*-butylphenol (DBP; 0.024 g, 0.11 mmol) was heated in a sealed tube for 48 h at 100 °C. Three spots were detected on a TLC plate, but **8** disappeared. After chromatography ($CHCl_3$, silica gel; total yield 72%), fractions were recrystallized from cyclohexane to give the syn isomer of **9**: mp 93–95 °C; ^{1}H NMR 1.03, 1.08, 1.17, 1.53 (3 H each, s), 1.73, 1.83 (3 H each, q, J = 1 Hz), 2.12, 2.92 (1 H each, 2 d, J = 15.5 Hz). The anti isomer was obtained only as a mixture with syn isomer: ^{1}H NMR 1.08, 1.12, 1.20, 1.50 (3 H each, s), 1.78, 2.22 (3 H each, q, J = 1 Hz), 2.44, 2.60 (1 H each, d, J = 16 Hz); isomer ratio of syn/anti of 4.6.

Reaction of 1d with Tetraphenylcyclopentadienone (10). In a sealed tube, **1d** (1.00 g, 9 mmol), **10** (1.15 g, 3 mmol), and DBP (20 mg, 0.1 mmol) in 3 mL of dry benzene were heated at 100 °C for 30 days. Unreacted **10** was removed by recrystallization from benzene, and the residue was chromatographed into four fractions. The second fraction was recrystallized from benzene to give tetraphenylbenzonitrile **12** (12%). The third consisted of the exo and endo isomers of the adduct **11**. The fourth afforded pure *exo*-**11**: total yield 23%; endo/exo ratio of 0.59. For **12**: mp 217–218 °C; IR (KBr) 2230, 3000–3060 cm^{-1}; mass spectrum, m/e 467 (M^+); ^{1}H NMR 6.6–7.3 (20 H, m), 7.80 (1 H, s). Anal. Calcd for $C_{31}H_{21}N$: C, 91.37; H, 5.19; N, 3.44. Found: C, 91.12; H, 5.01; N, 3.26. For *exo*-**11**: mp 262–270 °C; mass spectrum, m/e 564 (M^+); IR (KBr) 1755, 1720, no absorption around 2200 cm^{-1}; ^{1}H NMR 2.18 (3 H, s), 2.90, 3.90 (1 H each, d, J = 14.4 Hz), 6.6–7.4 (20 H, m). Anal. Calcd for $C_{34}H_{25}NO_3$: C, 82.40; H, 5.08; N, 2.83. Found: C, 82.18; H, 4.95; N, 2.83. For *endo*-**11**: ^{1}H NMR 1.98 (3 H, s), 3.09, 3.51 (1 H each, 2 d, J = 14.5 Hz), 6.6–8.0 (20 H, m).

Reaction of 8 with 10. A mixture of **8** (1.00 g, 11.2 mmol), **10** (1.46 g, 3.8 mmol), and DBP (24 mg) was heated in a sealed tube under a nitrogen atmosphere at 100 °C for 48 h. After the product mixture was chromatographed ($CHCl_3$, silica gel), a colorless mixture of the exo and endo isomers of 1,4,5,6-tetraphenyl-2-chloro-7-oxobicyclo[2.2.1]hept-5-ene-2-carbonitrile (**14**) was obtained: 1.64 g (92%); mp 174–177 °C dec. For *exo*-**14**: ^{1}H NMR 3.12, 3.78 (1 H each, 2 d, J = 13.2 Hz), 6.6–7.8 (20 H, m). For *endo*-**14**: ^{1}H NMR 3.57 (2 H, s), 6.6–7.8 (20 H, m). The isomer endo/exo ratio was 0.77. Anal. Calcd for $C_{32}H_{22}NOCl$ (isomeric mixture): C, 81.43; H, 4.70; N, 2.97. Found: C, 81.41; H, 4.82; N, 2.86.

Alkaline Hydrolysis of 3. Method A. Preparation of 1,3,3,4,7,8-Hexamethylbicyclo[2.2.2]oct-7-ene-2,5-dione (5). The anti isomer of **3d** (80 mg, 0.16 mmol) dissolved in 2 mL of

(22) For example, acid hydrolysis of 2,2-diphenyl-1-cyanocyclopropyl acetate in 35% HCl/dioxane at 90 °C for 1.5 h afforded the corresponding cyanohydrin in 92%.

dioxane was mixed with 0.24 mL of 10% aqueous NaOH, and the mixture was warmed at 50 °C for 10 min.[23] After the solvents were removed, the residue was washed with diethyl ether and then water. From the ethereal solution was obtained diketone **5** (98%) as a viscous oil: mass spectrum, *m/e* 220 (M^+); IR (film) 1700, 1720 cm^{-1}; ^1H NMR 0.97, 1.15 (3 H each, s), 1.25 (6 H, s), 1.65, 1.83 (3 H each, q, J = 1 Hz), 2.19, 2.34 (1 H each, 2 d, J = 19 Hz).[6] Under the same conditions, the syn isomer of **3d** afforded the same diketone **5** in a 68% yield (see also Table IV). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 75.40; H, 9.29.

Method B. Preparation of (1,3,3,4,5,6-Hexamethyl-2-oxocyclohex-4-en-1-yl)acetic Acid (15a). When the hydrolysis by method A was performed under prolonged conditions (e.g., more than 30 min), ring-opened acid **15a** was produced. After evaporation of the solvents, the residue was washed with a mixture of water and ether, and the aqueous layer was slightly acidified with acetic acid and extracted several times with ether to give solid **15a**: 60%; mp 128–130 °C (recrystallized from 60% EtOH); mass spectrum, *m/e* 238 (M^+); ^1H NMR 1.04, 1.08, 1.17 (3 H each, s), 1.23 (3 H, d, J = 7.5 Hz), 1.77, 1.91 (3 H each, q, J = 1 Hz), 2.38 (2 H, s), 2.83 (1 H, br q, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) 11.9, 15.0, 18.0, 19.8, 21.0, 22.3, 41.7, 42.5, 42.7, 49.2, 133.7, 153.8, 178.7, 203.7. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.30; H, 9.39.

Hydrolysis of Diketone 5. Diketone **5** (43 mg, 0.2 mmol) dissolved in 2 mL of dioxane was mixed with 0.2 mL of 10% aqueous NaOH, and the mixture was shaken at 75 °C for 20 min. After removal of the solvents, the residue was extracted with ether (no extract), the aqueous layer was acidified with AcOH, and the separated cloudy material was extracted with ether to give the acid **15a** (94%; see also Table IV).

(23) This procedure seems to convert cyanohydrin esters into the corresponding ketones better than the one reported by: DePuy, C. H.; Story, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 627.

Methyl Ester of 15a. After the treatment of compound **15a** (240 mg) with an equivalent amount of ethereal diazomethane, the methyl ester formed was analyzed by VPC (Apiezon grease and PEG-20M, 2 m, 180 °C). Only a single sharp fraction peak was observed at ca. 8–10 min on both columns. No splitting or shouldering of the peak was observed: mass spectrum, *m/e* 252 (M^+); IR (film) 1730 cm^{-1}.

Alkaline Hydrolysis of 11. Adduct **11** (50 mg, 0.1 mmol) dissolved in 3 mL of $CHCl_3$ was mixed with 6 mL of 5% NaOH (7.5 mmol), and the total solution was warmed at 50 °C for 90 min. After cooling, the solution was diluted with water (20 mL), neutralized with AcOH, and extracted with ether to afford a mixture of 2,3,4,5-tetraphenylbenzonitrile (**12**, 36%) and **11** (58%). Both compounds were separated by a column chromatography (silica gel, $CHCl_3$).

Attempted Acid Hydrolysis of 11. Adduct **11** (100 mg, 0.2 mmol) dissolved in 10 mL of benzene was mixed with 2.8 mL of 30% H_2SO_4 (2.02×10^{-2} mol), and the mixture was warmed for 1.5 h under solvent reflux. After cooling, the solution was neutralized by aqueous 10% NaOH to a slightly acidic state (pH 3) and was extracted with ether three times. The extracted material (92 mg) proved to be identical with **11** by IR and NMR.

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Registry No. 1a, 72876-47-2; **1b**, 72876-48-3; **1c**, 13427-72-0; **1d**, 3061-65-2; *Z*-**1e**, 78672-72-7; *E*-**1e**, 78672-73-8; **1f**, 72603-94-2; **2**, 3854-96-4; *anti*-**3a**, 78672-74-9; *syn*-**3a**, 78737-56-1; *anti*-**3b**, 78672-75-0; *syn*-**3b**, 78737-57-2; *anti*-**3c**, 78672-76-1; *syn*-**3c**, 78737-58-3; *anti*-**3d**, 78672-77-2; *syn*-**3d**, 78737-59-4; **3a**, 78672-78-3; **5**, 34327-63-4; **8**, 920-37-6; *anti*-**9**, 78672-79-4; *syn*-**9**, 78737-60-7; **10**, 479-33-4; *exo*-**11**, 78672-80-7; *endo*-**11**, 78672-81-8; **12**, 78672-82-9; *exo*-**14**, 78672-83-0; *endo*-**14**, 78672-84-1; **15a**, 78672-85-2; **15a** methyl ester, 78672-86-3.

Tetrabutylammonium Hydroxide: A Reagent for the Base-Catalyzed Dehydration of Vicinal Dihydro Diols of Aromatic Hydrocarbons. Implications to Ion-Pair Chromatography

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Vicinal dihydro diols of benzo[*a*]pyrene and benz[*a*]anthracene are dehydrated to their phenolic derivatives by the methanol eluate of reverse-phase (octadecylsilane) columns previously treated with tetrabutylammonium phosphate. Phenols are also produced by treating the dihydro diols with methanolic tetrabutylammonium hydroxide on removal of solvent. In most cases the regioselectivity is markedly different from the acid-catalyzed dehydration. The in situ generated tetrabutylammonium phenoxides are converted to the butyl ethers at high temperatures (150 °C) but not under the conditions of dehydration (60 °C). Tetraethylammonium and tetramethylammonium hydroxides also dehydrate dihydro diols, whereas potassium and sodium hydroxides do not. Dehydration does occur by treatment of dihydro diols with potassium hydroxide in the presence of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) and with sodium methoxide in the presence of tetrabutylammonium chloride. A mechanism is suggested.

Reverse-phase ion-pair chromatography was developed to allow for separation of ionic compounds. The technique typically involves the use of tetraalkylammonium phosphate and alkyl sulfonate buffers for the analysis of weak organic acids and bases, respectively.[2]

During our studies on the analysis of vicinal dihydro diols of polycyclic aromatic hydrocarbons by reverse-phase liquid chromatography, an ODS (octadecylsilane) column previously treated with tetrabutylammonium phosphate was used. We found that the collected dihydro diol frac-

(1) Present Address: Waters Associates, Inc., 34 Maple Street, Milford, MA 01757.

(2) For an excellent review of ion-pair chromatography see: E. Tomlinson, T. M. Jefferies, and C. M. Riley, *J. Chromatogr.*, **159**, 315 (1978).

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