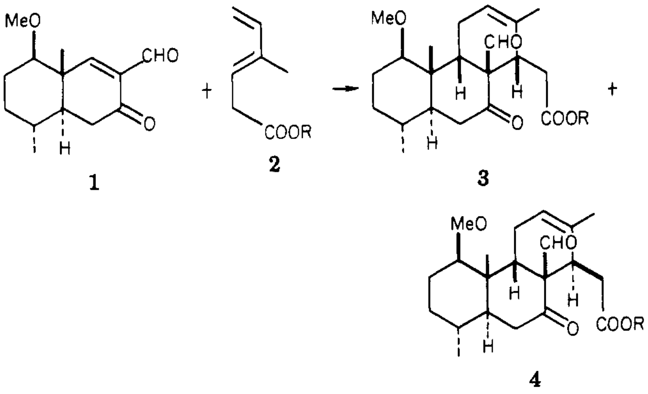
J. Org. Chem. **1983**, *48*, 3137-3139 **3137**

Communications

Aqueous Intermolecular Diels-Alder Chemistry: Reactions of Diene Carboxylates with Dienophiles in Water at Ambient Temperature

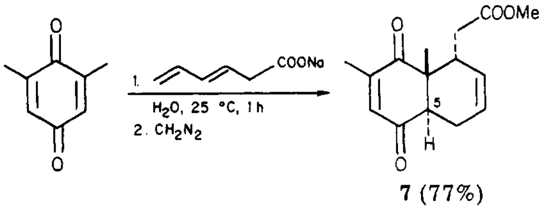
Summary: The aqueous intermolecular Diels-Alder reactions of sodium (*E*)-3,5-hexadienoate (**5**) and sodium (*E*)-4,6-heptadienoate (**6**) with a variety of dienophiles proceed rapidly at ambient temperature in good to excellent yields. The enhanced rates observed in aqueous medium stand in sharp contrast to the rates observed for the corresponding reactions in hydrocarbon solvents employing the methyl esters of **5** and **6**.

Sir: Our observation[1] that dienophile **1** reacts with diene carboxylate **2** (R = Na) in aqueous medium to give rise after 4 h at ambient temperature to a 3:1 ratio of Diels-Alder adducts **3** and **4**, respectively, in 99% yield, which stands in sharp contrast, in terms of rate and selectivity, to the results with **1** and **2** (R = Et) in benzene,[2] led us to further investigate the scope of this potentially useful synthetic process.

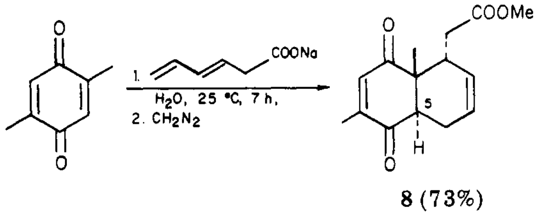


We detail below the results of an investigation into the Diels-Alder reaction of sodium (*E*)-3,5-hexadienoate (**5**)[3] and sodium (*E*)-4,6-heptadienoate (**6**)[3] with a variety of dienophiles in aqueous medium. Our preliminary studies focused on the reaction of sodium (*E*)-3,5-hexadienoate (**5**) with 2,6-dimethylbenzoquinone and 2,5-dimethylbenzoquinone.

In general, reactions were conducted, as illustrated in eq 1 and 2, at ambient temperature with vigorous stirring, employing 5.0 equiv of **5** in a 2 M aqueous solution. The transformation of 2,6-dimethylbenzoquinone and 2,5-dimethylbenzoquinone into Diels-Alder adducts **7** and **8**,[4] mp 77-80 °C, respectively, proceeds efficiently with excellent regiochemical control. Note that under the conditions of the aqueous intermolecular Diels-Alder reaction the initially formed cis adducts equilibrate to the more stable trans-fused systems.[5] In contrast, the corresponding reactions in hydrocarbon solvents (e.g., toluene, benzene) at room temperature employing methyl (*E*)-3,5-hexadienoate proceed at a negligible rate at room temperature even after several days. For example, in the case of 2,6-dimethylbenzoquinone, one finds after 1 week in toluene at room temperature only a trace of **7**.[6]



7 (77%) (1)



8 (73%) (2)

The rates of the aqueous Diels-Alder reactions depicted in eq 1 and 2 are dependent upon (1) the presence of excess diene carboxylate, (2) the concentration of diene, and (3) absence of cosolvents. Use of cosolvents such as methanol, dioxane, and tetrahydrofuran while maintaining the 1 M concentration of diene results in a rapid fall off in the rate of the reaction. Similar rate retardation is observed when the concentration of diene in water is decreased. As suggested previously,[1a] our results suggest some type of "micellar" catalysis, resulting in mutual binding of reactants in an aggregate.

The data obtained from the Diels-Alder reaction between sodium (*E*)-3,5-hexadienoate (**5**) with methyl (acetoxymethyl)acrylate (**9**) in water also stand in contrast to the results reported by Boeckman[7] for the corresponding reaction in hydrocarbon solvent employing methyl (*E*)-3,5-hexadienoate (Table I). It was reported[7] that reaction between **9** and methyl (*E*)-3,5-hexadienoate required 96 h in refluxing toluene in order to realize an 84% yield of Diels-Alder adducts **10** (R = Me) and **11** (R = Me) in a ratio of 1:2. The corresponding reaction in water employing **9** and sodium (*E*)-3,5-hexadienoate gave rise, after only 24 h at 60 °C, to a 67% yield of adducts **10** (R = H)[8] and **11** (R = H). Most significant, in the case of the aqueous reaction, was the predominance of the endo ad-

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(1) (a) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. Also see: (b) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901.

(2) Intermolecular Diels-Alder reaction between dienophile **1** and diene **2** (R = Et) proceeds in benzene at room temperature, giving rise, after 288 h, to only a 52% yield of **3** and **4** in a ratio of 1:1.2, along with 29% recovered dienophile.

(3) Sodium (*E*)-3,5-hexadienoate (**5**) and sodium (*E*)-4,6-heptadienoate (**6**) were prepared in situ by the addition of 0.95 equiv of solid sodium bicarbonate to a suspension of (*E*)-3,5-hexadienoic acid[7] and (*E*)-4,6-heptadienoic acid[9] in water.

(4) The structure of the Diels-Alder adduct was unambiguously established by single-crystal X-ray analysis.

(5) When the reaction of 2,6-dimethylbenzoquinone and ammonium (*E*)-3,5-hexadienoate was conducted in D_2O, the Diels-Alder adduct **7**, upon isolation, possessed 90% deuterium at C(5).

(6) When this reaction was carried out in toluene at 110 °C for 8 h, a 79% yield of **7** was obtained after chromatography on silica gel, along with 4% of the corresponding cis-fused regioisomer.

(7) (a) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789. (b) Private communication from Professor Boeckman.

(8) The structure of **10** (R = H) was unambiguously established by single-crystal X-ray analysis of its methyl ester, mp 52-53 °C.

(9) Jacobson, M. *J. Am. Chem. Soc.* **1955**, *77*, 2461.

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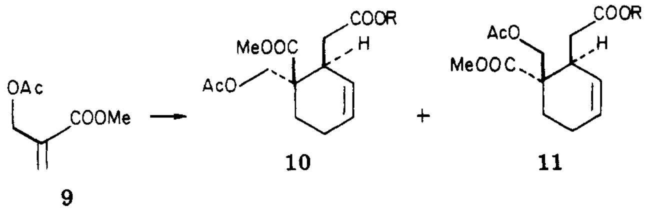
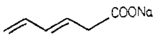
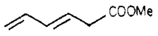
Table I

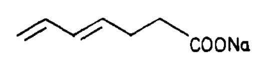


9 10 11

diene	solvent	temp	time, h	ratio 10:11	yield, %
	H_2O	60 °C	24	2:1	67
	$PhCH_3$	reflux	96	1:2	84[7b]

duct 10 over 11 by a ratio of 2:1. Careful analysis by HPLC and NMR of the crude reaction product revealed that ca. 2% of the corresponding regioisomers were present.

To gain further insight into the generality of the aqueous processes cited above, we have extended our study to include sodium (*E*)-4,6-heptadienoate (6). Table II reveals

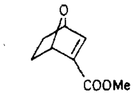
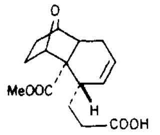
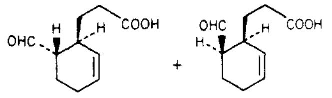
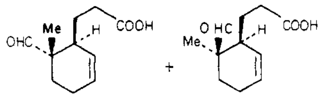
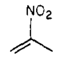
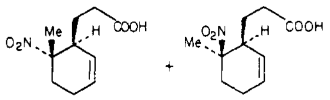
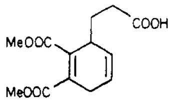
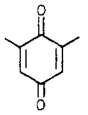
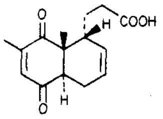
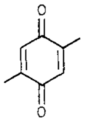
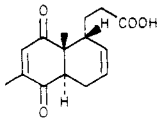
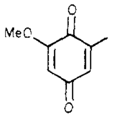
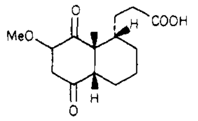
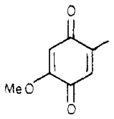
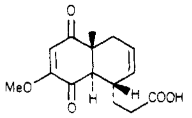


6

the results of an investigation employing 6 and a variety of dienophiles. In general, reactions proceed readily at ambient temperature in a few hours, giving rise to good to excellent yields of Diels–Alder adducts. The analogous nonaqueous Diels–Alder reactions employing ethyl (*E*)-4,6-heptadienoate do not proceed at any appreciable rate at ambient temperature. For example, reaction of 2,6-dimethylbenzoquinone with ethyl (*E*)-4,6-heptadienoate in toluene provides only a trace of the corresponding Diels–Alder adduct after 1 week. As can be seen from entries 2, 6, 7, and 9, the kinetically formed endo cis-fused adducts isomerize under the conditions of the reaction to the more stable trans-fused endo adducts.

Further studies are underway to define the scope and limitations of aqueous intermolecular Diels–Alder reaction

Table II. Reactions of Sodium (*E*)-4,6-Heptadienoate (6) with a Variety of Dienophiles in Aqueous Medium

entry[a]	substrate	temp, °C	time[b]	product[c]	yield,[d] %
1		25	2 h		94
2	acrolein	25	3 h	 10:1	70
3	methacrolein	25	5 h	 1:18	67
4[e]		0	9 h	 1:15	51
5	MeOOCC≡CCOOMe	25	24 h		60
6		25	1.5 h		86
7[f]		25	4 h		78
8[4]		25	24 min		79
9[g]		25	25 h		53

[a] All reactions employed a fivefold excess of diene, and the concentration of diene in water was 2.0 M. [b] Reactions were judged to be complete by TLC analysis. [c] Ratios were determined by NMR and/or HPLC. [d] All compounds were characterized, with the exception of entry 1, as their methyl esters. Yields reported are for chromatographically pure materials. [e] Lithium (*E*)-4,6-heptadienoate was employed. [f] Approximately 13% of the regioisomer was present. [g] Approximately 11% of the regioisomer was present.

employing diene carboxylates.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (AI 17410) from the National Institute of Allergy and Infectious Diseases. We thank Professor Robert K. Boeckman, Jr., for providing information and data on the thermal Diels–Alder reaction between **9** and methyl (*E*)-3,5-hexadienoate. We thank Dr. John C. Huffman for carrying out all of the single-crystal X-ray analysis work. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant No. CHE-81-05004).

Registry No. 1, 86669-09-2; 2 (R = Et), 76200-27-6; 3 (R = Et), 86688-50-8; 4 (R = Et), 86709-23-1; 5, 86668-91-9; 5 methyl ester, 32775-94-3; 5 free acid, 32775-95-4; 5·NH$_3$, 86669-10-5; 6, 86668-96-4; 6 free acid, 75283-35-1; 6·Li, 86669-12-7; 7, 86668-92-0; 7-d_5, 86669-11-6; *cis*-7, 86708-66-9; 8, 86668-93-1; 9, 30982-08-2; 10 (R = Me), 86668-94-2; 11 (R = Me), 86668-95-3; H$_2$, 1333-74-0; MeOCOC≡CCOOMe, 762-42-5; 2,6-dimethylbenzoquinone, 527-61-7; 2,5-dimethylbenzoquinone, 137-18-8; methyl 7-oxabicyclo[2.2.1]hept-2-ene-3-carboxalate, 86708-65-8; acrolein, 107-02-8; methacrolein, 78-85-3; 2-nitropropene, 4749-28-4; 2-methoxy-6-methylbenzoquinone, 611-68-7; 2-methoxy-5-methylbenzoquinone, 614-13-1; (1α,4α,4aβ,5β,8aβ)-1,2,3,4,4a,5,8,8a-octahydro-4a-(methoxycarbonyl)-1,4-epoxynaphthalene-5-propanoic acid, 86668-97-5; *trans*-6-formyl-2-cyclohexene-1-propanoic acid methyl ester, 86668-98-6; *cis*-6-formyl-2-cyclohexene-1-propanoic acid methyl ester, 86668-99-7; *trans*-6-formyl-6-methyl-2-cyclohexene-1-propanoic acid methyl ester, 86669-00-3; *cis*-6-formyl-6-methyl-2-cyclohexene-1-propanoic acid methyl ester, 86669-01-4; *trans*-6-methyl-6-nitro-2-cyclohexene-1-propanoic acid methyl ester, 86669-02-5; *cis*-6-methyl-6-nitro-2-cyclohexene-1-propanoic acid methyl ester, 86669-03-6; 3-(3-methoxy-3-oxopropyl)-1,4-cyclohexadiene-1,2-dicarboxylic acid dimethyl ester, 86669-04-7; (1α,4aα,8aβ)-7,8a-dimethyl-5,8-dioxo-1,4,4a,8a-tetrahydronaphthalene-1-propanoic acid methyl ester, 86669-05-8; (1α,4aα,8aβ)-6,8a-dimethyl-5,8-dioxo-1,4,4a,8a-tetrahydronaphthalene-1-propanoic acid methyl ester, 86669-06-9; (1α,4aβ,8aβ)-7-methoxy-8a-methyl-5,8-dioxo-1,4,4a,8a-tetrahydronaphthalene-1-propanoic acid methyl ester, 86669-07-0; (1α,4aβ,8aα)-7-methoxy-4a-methyl-5,8-dioxo-1,4,4a,8a-tetrahydronaphthalene-1-propanoic acid methyl ester, 86669-08-1.

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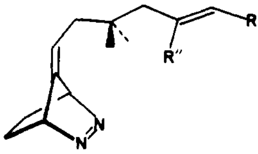
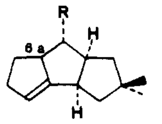
Consequences of Intramolecular Diyl Trapping Reactions Using Unactivated Diylophiles. A Short, Convergent Synthesis of Hirsutene

Summary: The consequences of utilizing an unactivated diylophile in an intramolecular diyl trapping reaction were examined. While the diyls derived from diazenes **6** and **7** both have unactivated diylophile π bonds, their chemistries differ substantially. Thus, while diyl dimerization and a reverse regiochemical mode of trapping are observed when starting with **7**, no dimer and only the normal mode of trapping leading to the linearly fused tricyclopentanoids **8** and **9** in a 5:1 ratio are observed when starting with **6**. The major product, **8**, was converted to ketone **5**, thereby completing a short, efficient, and convergent synthesis of the mold metabolite hirsutene.

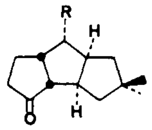
Sir: The diyl trapping reaction can be characterized as one that involves a cycloaddition, either inter- or intramolecular, between a 2-alkylidenecyclopentane-1,3-diyl and a diylophile.[1-3] In general, those olefins that are reactive Diels–Alder dienophiles are also reactive diylophiles.[1] For the intermolecular process, diyl dimerization and diyl trapping are competitive. It was for this reason that our published route to racemic hirsutene was a deliberately cautious one that utilized a diylophile activated by an electron-withdrawing group, despite the fact that the trapping reaction was to be intra- rather than intermolecular.[2] Thus, starting with diazene **1**, the cis,anti and cis,syn tricyclopentanoids **2** and **3** were isolated in high yield (>85%) in a ratio of 9:1. The ring-fusion stereoselectivity was attributed to the lower energy of the extended pseudochair transition-state representation leading to the cis,anti product in comparison with that of the folded pseudochair representation leading to the cis,syn product. Two factors of unequal importance were suggested to contribute to the energy difference: namely, a dominant conformational factor favoring the extended conformation in preference to the folded and the existence of two weakly bonding secondary orbital interactions that can exist in the extended but not in the folded formulation.[1b,2] A natural consequence of the cautious approach outlined above was the requirement that the carbomethoxy activating group be removed at a later stage in the hirsutene synthesis. Thus, after functional group manipulation, a (Ph$_3$P)$_3$RhCl-induced decarbonylation of keto aldehyde **4** was utilized to achieve this objective. Obviously, the synthesis could have been shortened considerably and the costly decarbonylation step avoided if an unactivated diylophile would have been utilized.



1, R′ = CO_2CH_3, R″ = H
6, R′ = R″ = H



2, R = CO_2CH_3, C_{6a} β-H
3, R = CO_2CH_3, C_{6a} α-H
8, R = H, C_{6a} β-H
9, R = H, C_{6a} α-H



4, R = CHO
5, R = H

Objectives. With the factors outlined above in mind, diazene **6** was selected for study (1) to determine whether diyl dimerization is competitive with the intramolecular diyl trapping reaction when an unactivated diylophile is present; (2) to determine the cis,anti to cis,syn product ratio for a system wherein the bonding secondary orbital interactions referred to above cannot be operable; (3) to devise a short, efficient synthesis of hirsutene that does not require the removal of the diylophile activating group; and, finally, (4) to compare the regiochemical outcome of the trapping reaction of the diyl derived from diazene **6** with that observed beginning with diazene **7**, which is also devoid of diylophile activation.[3]

Results and Discussion. Compound **6** was conveniently and simply prepared starting with 3,3-dimethylglutaric anhydride.[2] Analysis of the reaction mixture that resulted from simply refluxing a 0.1 M solution of diazene **6** in THF clearly indicated the presence of the cis,anti and

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(1) (a) Berson, J. A. In "Diradicals"; Borden, W. T., Ed.; Ch. 4, pp. 151-ff, Wiley-Interscience: New York, 1982; Chapter 4, pp 151 ff, and references therein. (b) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* 1981, *37*, 4371–4383.

(2) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* 1981, *103*, 2744–2749.

(3) (a) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* 1981, *22*, 4389–4392. (b) Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Chem. Soc.* 1983, *105*, 928–932.