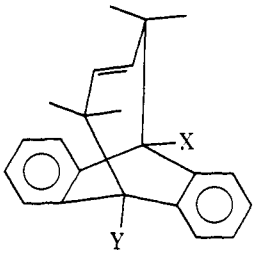
Chemistry of Exciplexes. IV. Orientation of Photocycloaddition of 1,3-Dienes to Anthracenes

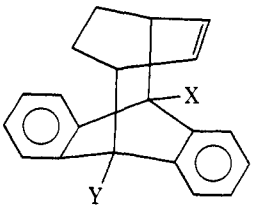
Sir:

The conservation of orbital symmetry plays an important role in the orientation of cycloadditions between unsaturated systems. The Woodward–Hoffmann rule of conservation of orbital symmetry predicts that suprafacial photocycloadditions involving $4n$ π-electrons are allowed processes while those involving $4n + 2$ π-electrons are forbidden.[1] Anthracene reacts photochemically with either 2,5-dimethyl-2,4-hexadiene (DMHD), an acyclic *s*-transoid 1,3-diene, or 1,3-cyclohexadiene (CHD), an alicyclic *s*-cisoid 1,3-diene, to give $4\pi_s + 4\pi_s$ adducts 1a and 2a, respectively, while 9-cyanoanthracene under similar conditions reacts with CHD to give the $4\pi_s + 4\pi_s$ adduct **2e** but with acyclic s-transoid 1,3-dienes to give $4\pi_s + 2\pi_s$ adducts such as **3e**.[2,3] The photocycloadditions of DMHD and other s-transoid 1,3-dienes to 9-cyanoanthracene constitute an "apparent forbidden" process according to the Woodward–Hoffmann rule, yet they proceed stereospecifically and regiospecifically in both high chemical and quantum yields.[3] Several explanations have been proposed for the orientation of these photocycloadditions,[3-5] but no systematic correlations have been presented so far. In our investigation on the nature and behavior of [arene*:1,3-diene] exciplexes, we studied simultaneously the exciplex fluorescence[6] and photochemistry of substituted anthracenes with 1,3-dienes. In this communication, we wish to report the relationship between the nature of exciplex and the orientation of photocycloaddition in arene:1,3-diene systems.

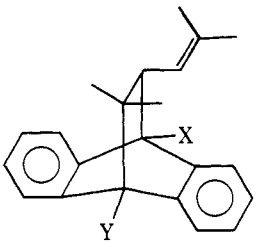
The photocycloadditions were usually carried out in 0.5% solutions of the arene in reagent grade benzene containing 1 *M* of the diene unless otherwise specified. The light source used was a Hanovia 450-W medium pressure Hg lamp with a cylindrical uranyl glass filter to cut off the light emission below 330 nm from the Hg lamp. The progress of the reaction was monitored by the uv spectrum of the irradiation mixture, and the products were isolated by column chromatography on activated alumina. The photochemical additions of DMHD and CHD to 9,10-difluoroanthracene (DFA), 9,10-dichloroanthracene (DCA), 9,10-dibromoanthracene (DBA), 9,10-dicyanoanthracene (DCNA), and acridine were investigated. The quantum yields of the disappearance of various arenes in the presence of 1,3-dienes were determined with degassed samples and a conventional merry-go-round apparatus at 365 nm and ambient temperature (21 ± 1°).[7] The results obtained are summarized in Table I together with the available spectroscopic data of the corresponding exciplexes and compared with those from published results of anthracene, 9-cyanoanthracene (CNA), and naphthalene.[2,3,8]



1a. X = Y = H
b. X = Y = F



2a. X = Y = H
c. X = Y = Cl
d. X = Y = Br
e. X = CN, Y = H
f. X = Y = CN



3b. X = Y = F
c. X = Y = Cl
e. X = CN, Y = H
f. X = Y = CN

Since all the reactions in this study except that of DFA were carried out under conditions such that 87.5–99+% of the anthracene fluorescence was quenched by the diene, i.e., most of the singlet excited anthracene was intercepted by the diene as the exciplex, most of the photocycloaddition must proceed via exciplex as the intermediate.

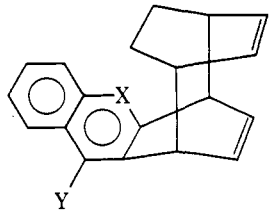
Judging from the results in Table I, we have found that a

Table I: Correlation of Orientation of Photocycloaddition of Arenes to 1,3-Dienes and [Arene*:1,3-diene] Exciplex Fluorescence

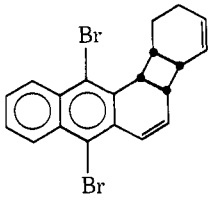
	Photocycloaddition[a]					Exciplex fluorescence (cm^{-1})[b]		
	CHD		DMHD		IP[b]	Methylcyclohexane		Solvent
Arenes	Orientation (%)[c]	ϕ-ArH	Orientation (%)[c]	ϕ-ArH	(eV)	or cyclohexane	EtOAc	shift
Naphthalene	$4\pi + 4\pi$ (7, 70%)	0.23	$4\pi + 4\pi$ (**6**)[d]	0.41	8.12	—[e]	—[e]	—
Anthracene	$4\pi + 4\pi$ (2a, 96%)	0.28	$4\pi + 4\pi$ (1a, 90%)	0.46	7.43	23,300 (DMHD)	23,300 (DMHD)	<600[f]
DFA	—[g]	—[g]	$4\pi + 4\pi$ (1b)[h] $4\pi + 2\pi$ (3b)	—[g]	7.49	23,000 (DMHD)	22,200 (DMHD)	800
DCA	$4\pi + 4\pi$ (2c, 60%) $4\pi + 4\pi$ (4c, 8%)	0.32	$4\pi + 2\pi$ (3c, 60%)	0.01	7.56	22,200 (DMHD)	21,100 (DMHD)	1100
DBA	$4\pi + 4\pi$ (2d, 29%) $2\pi + 2\pi$ (5d, 45%)	0.59	—[g]	—[g]	7.59	22,200 (DMHD)	20,700 (DMHD)	1500
CNA	$4\pi + 4\pi$ (2e, 87%)	0.65	$4\pi + 2\pi$ (3e, 84%)	0.56	7.95	21,500 (DMHD)	19,400 (DMHD)	2100
DCNA[i]	$4\pi + 4\pi$ (2f, 67%) $4\pi + 2\pi$ (8f, 9%)	0.005	$4\pi + 2\pi$ (3f, 85%)	0.016	—	18,700 (DMHD) 19,800 (CHD)	—[e]	—
Acridine	$4\pi + 2\pi$ (8g, 20%) Biacridan, 35% dihydroacridine, 20% $4\pi + 4\pi$ (4g, 4%)	0.40	Compound 10 (40%) biacridan (30%)	0.37	7.78	—[e]	—[e]	—

[a] All new products have been characterized by elemental analysis, uv, ir, and high resolution NMR spectroscopy. [b] Reference 6. [c] All yields given are for crystalline products, but the limit of detection of isomeric orientation adducts is 1%. [d] **6** undergoes Cope rearrangement rapidly at 20°, ref 8. [e] Not detected. [f] 600 cm^{-1} is the limit of experimental uncertainty in this case. [g] Not measured. [h] Photodimer of DFA is also formed. The relative proportions of 1b and 3b formed depend on the concentration of DFA used. [i] DCNA concentration, 0.2%.

majority of arenes react photochemically with CHD to give the corresponding $4\pi_s + 4\pi_s$ adduct **2**, only anthracene and naphthalene react with DMHD to give the respective $4\pi_s + 4\pi_s$ adducts **1a** and **6**, and most substituted anthracenes react with DMHD to give the corresponding $4\pi_s + 2\pi_s$ adduct **3**. Therefore, CHD is more reactive than DMHD in the $4\pi_s + 4\pi_s$ cycloaddition to excited arenes. The higher reactivity of CHD may be attributed to two factors. First there is a more favorable overlap between the π-systems of the reactants in the transition state of the photocycloaddition of CHD to anthracenes, i.e., carbon atoms 9, 11, 12, and 10 of anthracene and the π-system of CHD have identical geometrical arrangements. Second, adducts **1** from DMHD and other transoid 1,3-dienes which contain a *trans,cis*-1,5-cyclooctadiene system are considerably more strained than adducts **2** from CHD, and a part of this strain must have existed in the transition state of the cycloaddition. When substituents such as halogens are introduced into the meso positions of anthracene which influence the relative rates of photocycloaddition vs. competing decay processes from the exciplexes, the adduct **1** formation will be more easily overcome that of the adduct **2** formation. Another interesting effect caused by halogen substitutions at the meso positions of anthracene is that the end ring becomes reactive for the photocycloaddition with CHD. Both DCA and DBA react with CHD to give adducts in the end ring in variable amounts (**4c, 5d**). A small amount of $4\pi_s + 4\pi_s$ adduct (**4g**) to the end ring is also obtained in the acridine-CHD reaction.



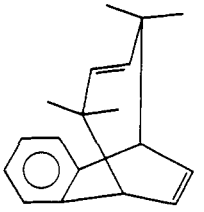
4c. X = C-Cl; Y = Cl
g. X = N; Y = H



5d

Cycloadditions among ground state molecules may proceed via an allowed $4\pi_s + 2\pi_s$ concerted pathway or an "apparent forbidden" $2\pi_s + 2\pi_s$ pathway involving polar intermediates.[9] In the accompanying communication,[6] we have characterized a number of [arene*:1,3-diene] exciplexes and demonstrated that these exciplexes may be the intermediate in the photocycloadditions. Exciplexes may be represented as a resonance hybrid with polar character derived from the contribution of ion-pair structures (eq 1).[10] The polarity of these exciplexes from a given diene may be determined by the red-shift of their fluorescence maxima in solvents of increasing dielectric constants.[6] The shifts of fluorescence maxima of these exciplexes from methylcyclohexane to ethyl acetate as a measure of their polarity are listed in Table I in increasing order. The shifts range from a nonmeasurable shift for [A*:DMHD] fluorescence to the disappearance of fluorescence in ethyl acetate for [DCNA*:DMHD] and [DCNA*:CHD] systems. *There is an excellent correlation between the polarity of [arene*:1,3-diene] exciplexes with the orientation of photocycloaddition of 1,3-dienes to arenes.* For DMHD, only the relatively nonpolar exciplex from excited anthracene undergoes the concerted $4\pi_s + 4\pi_s$ addition,[11] the polar exciplexes from substituted anthracenes undergo the "apparent forbidden" stepwise $4\pi_s + 2\pi_s$ additions, and the exciplex from DFA undergoes both processes which represents the intermediate case. Since the polarity of arene exciplexes with a given diene depends not only on the IP of the arene (a measure of the LUMO level of the excited arene) but also on the polarizability of the substituents,[6] naphthalene, in spite of its higher IP than most substituted anthracenes, reacts photochemically with DMHD to give the $4\pi_s + 4\pi_s$ adduct **6**, which may be derived from a relatively nonpolar exciplex. Since CHD is more reactive than DMHD in the concerted $4\pi_s + 4\pi_s$ photocycloaddition to arenes, it is expected to undergo the stepwise $4\pi_s + 2\pi_s$ addition only via highly polar exciplexes. Variable amounts of $4\pi_s + 2\pi_s$ adducts **8** are indeed formed from DCNA and acridine, and highly polar exciplexes are detected from DCNA. Acridine appears to be a limiting case, since the major adduct formed is **8g** and no $4\pi_s + 4\pi_s$ adduct similar to **2** is detected in the reaction mixture. The result may be justified by the stabilization of polar contributing structure of its exciplex by the electronegative nitrogen (**9**), but we have not been able to detect any exciplex emission from [acridine*:diene] systems as yet. Compound **10** was isolated as a major product in the [acridine*:DMHD] reaction which may be derived from **9** via proton transfer.

$$[\mathrm{ArH}^*:\mathrm{donor}] \longleftrightarrow [\mathrm{ArH}^{\cdot-}:\mathrm{donor}^{\cdot+}] \qquad (1)$$



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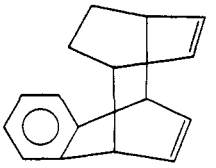

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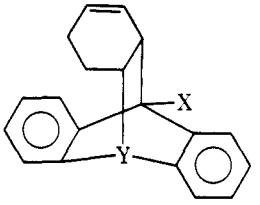
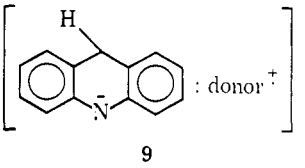
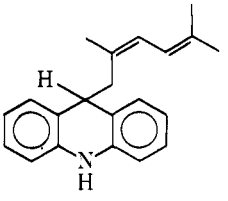


8f. X = CN; Y = C-CN
g. X = H; Y = N



9



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References and Notes

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relationship of his theory and our results will be treated in a future publication.

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(9) For a review of polar cycloadditions, see R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(10) D. A. Labianca, G. N. Taylor, and G. S. Hammond, *J. Am. Chem. Soc.*, **94**, 3679 (1972).
(11) Since [anthracene*:DMHD] exciplex still exhibits some polar character (ref 5), the results suggest that stepwise $4\pi_s + 2\pi_s$ photocycloadditions of 1,3-dienes to anthracene may occur concurrently with $4\pi_s + 4\pi_s$ additions under certain conditions. These have been found in photocycloadditions of highly unsymmetrical dienes and polar 1,3-dienes, J. Libman and T. Hamada, unpublished results.
(12) Guggenheim Fellow, 1974–1975.

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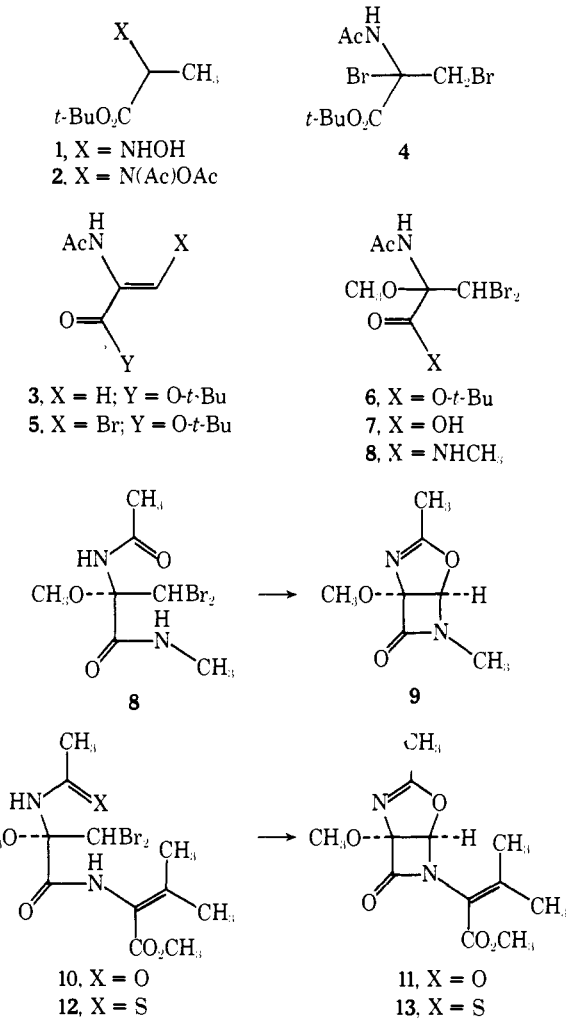
Biogenetic-Type Synthesis of Penicillin–Cephalosporin Antibiotics. I. A Stereocontrolled Synthesis of the Penam- and Cephem-Ring Systems from an Acyclic Tripeptide Equivalent

Sir:

Several magnificent total syntheses of penicillin–cephalosporin antibiotics have been completed,[1] but to our best knowledge none of them was achieved on the basis of the biosynthetic pathways[2] of the antibiotics. This series of papers is concerned with a biogenetic-type synthesis[3] of the bicyclic penicillin–cephalosporin antibiotics from an acyclic tripeptide[2a] equivalent. Our synthetic scheme is mainly based on the biosynthetic pathways suggested by Cooper[2d] in 1972.

2-Bromopropionyl bromide was converted to the hydroxylamine[5] **1** (mp 74–5°) in 85% yield by two steps (i.e., (1) *t*-BuOH–Py,[4] (2) $NH_2OH{\cdot}HCl$–$NaOCH_3$ in CH_3OH). Acetic anhydride treatment of **1** at 100° for 30 min yielded the diacetate[5] **2** (oil), which was converted to *N*-acetyldehydroalanine *tert*-butyl ester[5] (**3**) (oil) by triethylamine treatment in 72% overall yield from **1**. Bromine reacted smoothly with **3** in methylene chloride at room temperature, to give the dibromide **4** which was not isolable but clearly detectable by NMR analysis. Triethylamine treatment of **4** gave *N*-acetylbromodehydroalanine *tert*-butyl ester[5,6] (**5**) (mp 106–107°) in 90% overall yield from **3**. **5** reacts with bromine in a mixture of methylene chloride and methanol at room temperature, to yield the methoxydibromide *tert*-butyl ester[5] **6** (mp 115–116°) in 82%. Removal of the carboxylic acid blocking group of **6** under acidic conditions gave the methoxy dibromo acid[5] **7** (mp 143–144°) in 80% yield. A standard DCC procedure on **7** and methylamine in dioxane at room temperature afforded the methoxydibromodiamide[5] **8** (mp 114–115°) in 74% yield.[7]

On treatment with 2 equiv of sodium or potassium hydride in THF at room temperature, the methoxydibromodiamide **8** was cleanly converted to the β-lactam oxazoline **9**.[8]



The yield of the substance homogeneous on TLC was about 70%. The crystalline substance[5] (mp 84–85°) was isolated in about 40% yield. Structure **9** was assigned to the product on the basis of the spectroscopic data ($\delta_{ppm}^{CDCl_3}$ 2.13 (3 H, s), 2.91 (3 H, s), 3.58 (3 H, s), and 5.56 (1 H, s); $\nu_{max}^{CH_2Cl_2}$ 1785 and 1650 cm^{-1}) and the elemental analysis data. The double cyclization reaction (KH or NaH, THF, room temperature) worked cleanly on the dehydrovaline derivative **10**[5,9] (mp 150–151°), to afford the β-lactam oxazoline derivative **11**[5] (oil; $\delta_{ppm}^{CDCl_3}$ 1.86 (3 H, s), 2.14 (3 H, s), 2.28 (3 H, s), 3.63 (3 H, s), 3.79 (3 H, s), and 5.88 (1 H, s); $\nu_{max}^{CH_2Cl_2}$ 1785, 1728, and 1650 cm^{-1}) in 40% yield.[10]

To extend the new double cyclization reaction to a biogenetic-type synthesis of the antibiotics, cyclization was examined on the monothioamide **12**. Thus, the dehydrovaline derivative **10**, was treated with phosphorus pentasulfide in THF at 50° for 2 hr and the unpurified[11] monothioamide **12** was subjected to the double cyclization reaction under sodium hydride conditions. A preparative TLC separation of the products on aluminum oxide plates gave the β-lactam thiazoline derivative[5] **13** (oil) in 12% overall yield from **10**. The synthetic substance was identified with an authentic sample, synthesized from 6-aminopenicillanic acid[12] by following Koppel's[13] and then Cooper's[14] procedures, by comparison of NMR, ir, TLC (aluminum oxide and silica gel plates), and HLC (Corasil I).

NBS bromination of **13** in the presence of a small amount of α,α′-azobisisobutyronitrile in carbon tetrachloride (1.5 hr, 75°), followed by a preparative TLC separation on aluminum oxide plates, gave the monobromides **14** and **15** (70% yield), the dibromide **16** (10% yield), and the