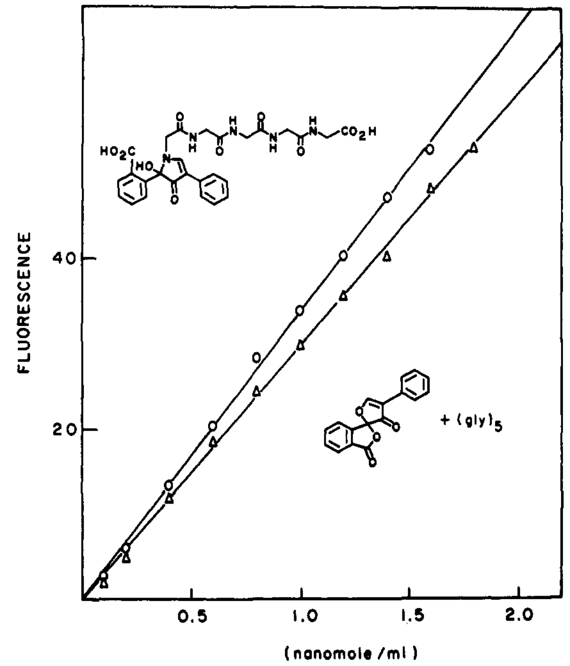


Figure 1. Relative fluorescence of **1** [R = $CH_2(CONHCH_2)_4CO_2H$] (O) and of the reaction of pentaglycine with **10** (Δ). Fluorescence intensities are given in arbitrary units (excitation max, 390 nm; emission max, 475 nm). The data are corrected for blank.

9,[7] which upon acidification (pH 3.5) was directly converted to the desired 4-phenylspiro[furan-2(3H),1'-phthalan]-3,3'-dione **10** [63% from **8**; mp 154°; uv max (Et_2O) 235 (ϵ 25,900), 276 (3,950), 284 (4,100), and 306 nm (3,800); ir ($CHCl_3$) 1810, 1745, 1722 cm^{-1}; nmr ($CDCl_3$) δ 8.71 (s, OCH=)].

As expected, the spirolactone **10** reacts with primary amines to yield intensely fluorescent substances of the general structure **1**. Most importantly for practical purposes, fluorescence is also produced efficiently in aqueous media at room temperature. Optimal reaction has been found to occur when the solution to be assayed is at pH 8–9 and an excess of the reagent is added in a water-miscible, nonhydroxylic solvent, such as acetone, dioxane, or acetonitrile.

The following experiment illustrates the potential of **10** as a fluorometric peptide reagent. Reaction of equimolar amounts of **10**, pentaglycine, and triethylamine in aqueous acetonitrile afforded the triethylammonium salt of the fluorophor **1** [R = $CH_2(CONHCH_2)_4CO_2H$; 72%; mp 105° dec; uv max (H_2O) 269 (ϵ 15,000), 380 nm (5,450)]. The fluorescence of this compound was measured in aqueous buffer solutions of pH 8 and compared to the fluorescence generated *in situ* by the addition, at room temperature, of the reagent **10** in dioxane (0.5 μmol/ml) to aqueous solutions containing 0.1–2 nmol/ml of pentaglycine. The results, recorded in Figure 1, demonstrate that the fluorogenic reaction of the spirolactone **10** with peptides may proceed to near completion (*ca.* 90%) in aqueous systems.

Efficient fluorogenic reaction has also been observed with a large variety of other aliphatic and aromatic primary amines, including amino acids, catecholamines, sulfonamides, and antibiotics. It is therefore felt that the spirolactone **10** will find many uses as a powerful fluorometric reagent in varied areas of biochemical research.[8]

Acknowledgment. We thank Mrs. Karin Manhart and Dr. V. Toome for fluorescence measurements.

---

[7] Attempts to isolate this intermediate have failed. Its structure is presumed by analogy with the synthesis of **2**.[2]

[8] Reports on specific applications of this reagent are forthcoming (S. Udenfriend, private communication).

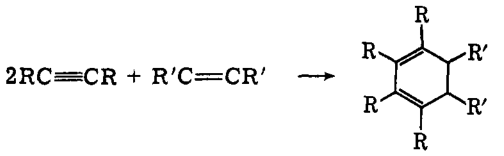
M. Weigele,* S. L. DeBernardo
J. P. Tengi, W. Leimgruber
Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Received April 21, 1972

Catalysis of the Cyclotrimerization of Acetylenes with N-Substituted Maleimides

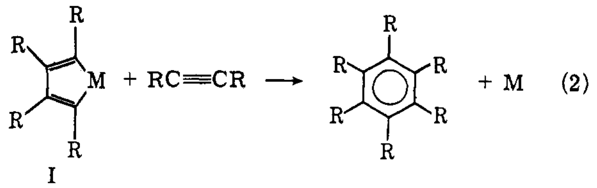
Sir:

The catalysis of the cyclotrimerization of acetylenes by transition metal complexes has been extensively studied but very few examples of the cyclotrimerization of acetylenes with olefins as in eq 1 have been noted.[1]

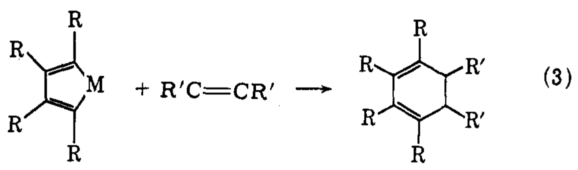


One of the better known examples, the cyclotrimerization of ethyl acrylate catalyzed by $Ni(CO)_2(PPh_3)_2$, appears in fact to proceed *via* a linear intermediate.[2]

This is surprising since among the mechanisms suggested for the catalysis of acetylene cyclotrimerization is one which involves the intermediacy of a metallocyclopentadiene complex I. Complexes such as I have been shown to react with acetylenes to give substituted benzenes as in eq 2.[3,4] In the presence of an olefin bearing electronegative substituents one might hope to intercept I with a Diels–Alder reaction as in eq 3 and thereby catalyze eq 1.



I



Our interest in finding conditions for the catalysis of eq 1 concerns its potential for the synthesis of linear polyphenylenes when a bifunctional acetylene is substituted for the monofunctional acetylene and the resulting polymer is aromatized. A related synthesis of branched polyphenylenes has recently been disclosed based on the cotrimerization of bifunctional and monofunctional acetylenes.[5]

---

[1] C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Logos, London, England, 1967, p 30.

[2] T. L. Cairns, V. A. Engelhardt, H. L. Jackson, G. H. Kalb, and J. C. Sauer, *J. Amer. Chem. Soc.*, **74**, 5636 (1952).

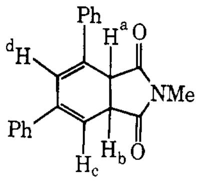
[3] K. Moseley and P. M. Maitlis, *Chem. Commun.*, 1604 (1971).

[4] J. P. Collman, J. W. Kang, W. F. Little, and M. F. Sullivan, *Inorg. Chem.*, **7**, 1298 (1968).

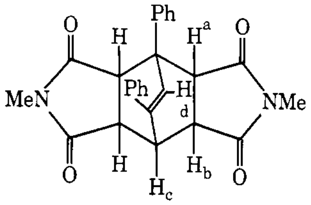
[5] A. J. Chalk and A. R. Gilbert, *J. Polym. Sci., Part A-1*, in press.

At this time we report a new example of eq 1 in which the olefin is an N-substituted maleimide and the acetylene is terminal or conjugated. Interestingly the reaction is catalyzed by $\mathrm{Ni(CO)_2(PPh_3)_2}$ but not $\mathrm{PdCl_2}$. Both these compounds catalyze the cyclotrimerization of acetylenes but probably *via* different mechanisms. While an intermediate such as I is possible in the former case, it is unlikely for $\mathrm{PdCl_2}$.[3]

For the reaction between *N*-methylmaleimide and phenylacetylene the products of the reaction include not only the 2:1 adduct with the cyclohexadiene structure II but also a 1:1 adduct III which is the Diels–Alder product of II with a further mole of maleimide.

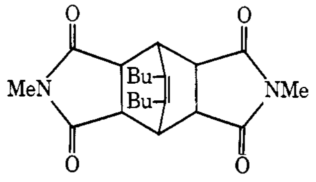


II



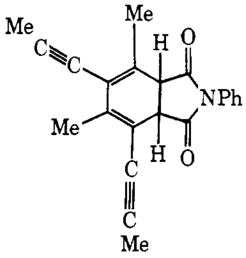
III

For the similar reaction between hexyne-1 and *N*-methylmaleimide a different stereochemistry was evident from the isolation of IV in 32% yield.

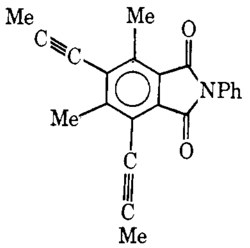


IV

Since $\mathrm{Ni(CO)_2(PPh_3)_2}$ has recently been found to cyclotrimerize conjugated acetylenes,[6] the present reaction was also investigated for this class of acetylenes. Hexa-2,4-diyne and *N*-phenylmaleimide gave 20% V and 8% VI. Thus, the initial diene is apparently too sterically hindered to undergo a Diels–Alder reaction but does aromatize to some extent.



V



VI

It is of interest that Collman, *et al.*, have earlier attempted reactions such as eq 3 and found no reaction between maleic anhydride and an iridium metallocycle [I in which R = COOMe and M = $\mathrm{IrCl(PPh_3)_2}$]. We have attempted the same reaction but substituted *N*-methylmaleimide for maleic anhydride and we were also unable to effect any reaction. It should be noted, however, that the presence of electron-withdrawing substituents on both diene and dienophile makes a Diels–Alder reaction unlikely in this case even if the reaction were to take place completely within the coordination sphere of the metal as seems likely in our catalytic examples.

Satisfactory elemental analyses, molecular weights (mass spectra), infrared spectra, and proton and C-13 nmr spectra were obtained for all the products cited. A typical reaction follows. *N*-Methylmaleimide (1.78 g, 16 mmol) and phenylacetylene (3.28 g, 32 mmol) were refluxed in 20 ml of benzene in the presence of $\mathrm{Ni(CO)_2(PPh_3)_2}$ (0.064 g, 0.1 mmol) for 2.25 hr. On cooling, a white precipitate separated. It was removed by filtration, washed with benzene, and dried *in vacuo* to give 1.7 g (50% yield) of II. It was further purified by recrystallization from dimethyl sulfoxide (mp 349–351°). The filtrate was evaporated down and the resulting solid crystallized from a mixture of toluene and hexane to give 1.1 g (27% yield) of III (mp 150–155°). Their proton nmr spectra were consistent with the structures shown. In particular, the labeled protons in II gave the following δ values in $\mathrm{CDCl_3}$: 4.50 (H_a, unresolved quartet), 4.05 (H_b, q), 5.85 (H_c, q), 6.74 (H_d, q), $J_{ab} = 11.6$, $J_{bc} = 3.8$, $J_{cd} = 1.1$, $J_{ad} =$ 1–2 Hz. The labeled protons in III gave the following δ values in dimethyl sulfoxide: 3.5 (H_a, d), 3.3 (H_b, q), 3.85 (H_c, sext), 6.65 (H_d, d), $J_{ab} = 8$, $J_{bc} = 2.8$, $J_{cd} = 1.7$ Hz. In addition both II and III gave C-13 nmr spectra (natural abundance) with 17 lines each consistent with the postulated structures.

A. J. Chalk
General Electric Research & Development Center
Schenectady, New York 12301

Received May 3, 1972

---

[6] A. J. Chalk, *Tetrahedron Lett.*, 61 (1972).

Divergent Pathways in the Photochemical Reactions of Benzonitrile

Sir:

The photochemical addition of benzonitrile to 2-methyl-2-butene and to ethoxyethylene was reported several years ago to occur at the 1,2 positions of the benzene ring to yield 1-cyanobicyclo[4.2.0]octadienes, to the exclusion of products from reaction at the cyano group.[1] Although aromatic ketones and aldehydes generally undergo photochemical 2 + 2 addition at the carbonyl group to give oxetanes, a process which is especially facile for those carbonyl compounds possessing lowest $n \rightarrow \pi^*$ triplet states,[2] analogous reactions of nitriles have not thus far been documented.[3]

We now report our observations that benzonitrile undergoes photochemical cycloaddition to certain electron-rich olefins at the nitrile function to yield 2-azabutadienes, the products of electrocyclic ring opening of initially formed azetines, and that this process proceeds *via* singlet excited states, in contrast to those additions occurring across the benzene ring,

---

[1] J. G. Atkinson, D. E. Ayer, G. Buchi, and E. W. Robb, *J. Amer. Chem. Soc.*, **85**, 2257 (1963).

[2] (a) D. R. Arnold, *Advan. Photochem.*, **6**, 301 (1968); (b) N. C. Yang and W. Eisenhardt, *J. Amer. Chem. Soc.*, **93**, 1277 (1971).

[3] Photochemical reactions of unsaturated nitriles reported to date have involved transformation only of the hydrocarbon portion of the molecules: 2-cyanobutadiene (a) D. M. Gale, *J. Org. Chem.*, **35**, 970 (1970); acrylonitrile (b) S. Hosaka and S. Wakamatsu, *Tetrahedron Lett.*, 219 (1968); (c) J. A. Barltrop and H. A. J. Carless, *ibid.*, 3901 (1968); fumaronitrile (d) P. DeMayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc.*, 54 (1963); (e) J. A. Barltrop and R. Robson, *Tetrahedron Lett.*, 597 (1963).