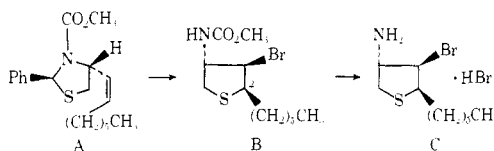


H₂O), in 80% overall yield from **18**. Addition of the two-carbon fragment was achieved by reaction of **20** with sodium diethyl malonate to yield the diester **21**, which was not isolated, but hydrolyzed by barium hydroxide to the corresponding diacid **22**, mp 190° dec. Decarboxylation occurred smoothly in hot water to give *d*-biotin, mp 232–233°, [α]²⁵_D +91.2 (*c* 1.0, 0.1 *N* NaOH), identical in all respects with an authentic sample.

Acknowledgment. We would like to express our gratitude to the staff of the Physical Chemistry Department of Hoffmann-La Roche for their determination of spectral and analytical data.

References and Notes

- (1) A. Lezius, E. Ringelmann, and F. Lynen, *Biochem. Z.* **336**, 510 (1963).
- (2) The absolute configuration of *d*-biotin at C₄ was shown to correlate with L-(+)-cysteine by an X-ray study (J. Trotter and J. A. Hamilton, *Biochemistry*, **5**, 713 (1966)), as well as a chemical correlation of (+)-desthiobiotin with D-glucose (H. Kuzuhara, H. Ohru, and S. Emoto, *Tetrahedron Lett.*, 1185 (1970)).
- (3) S. A. Harris, D. E. Wolf, R. Mazingo, and K. Folkers, *Science*, **97**, 447 (1943); S. A. Harris et al., *J. Am. Chem. Soc.*, **66**, 1756 (1944); S. A. Harris et al., *ibid.*, **67**, 2096 (1945); A. Grussner, J. P. Bourquin, and O. Schnider, *Helv. Chim. Acta*, **28**, 510, 517 (1945); B. R. Baker et al., *J. Org. Chem.*, **12**, 167, 186, 322 (1945); M. W. Goldberg, and L. H. Sternbach, U.S. Patents, 2489232, 2489235, and 2489238 (1949); S. Bory et al., *Tetrahedron Lett.*, 827 (1975).
- (4) All intermediates have the expected spectral properties and analytical data. These details will be reported in the full paper to follow.
- (5) One of the referees suggested that this rearrangement is initiated by attack of bromine at sulfur. This plausible step would then be followed by a trans addition across the olefin functionality leading to the cation 7.
- (6) In a model study, the *cis* olefin A (NMR δ 5.58, 5.64 (m, 2, $J_{\text{cis}} = 6$ Hz)) was brominated under similar conditions to give stereospecifically the *epi* isomer B, in which the alkyl substituent at C₂ is in the undesired β orientation. This was proven by an X-ray structure determination on the derived hydrobromide C.



This result formed the basis for the prediction that the oxidative cyclization on a *trans* olefin would afford an intermediate in which the chain at C₂ would be α as desired.

- (7) We thank Professor D. B. McCormick, Cornell University, for supplying a sample of natural *d*-bisorbiotin. Cf. D. B. McCormick, S. Iwahara, L. D. Wright, and H. C. Li, *J. Biol. Chem.*, **244**, 1393 (1969).
- (8) This alternative route originates from an intermediate in the Sternbach biotin synthesis, U.S. Patent 2489235 (1949). Details will be given in the full paper.

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Nature of the Intermediates Involved in the [2 + 2] Cycloaddition of Tetracyanoethylene and Enol Ethers¹

Sir:

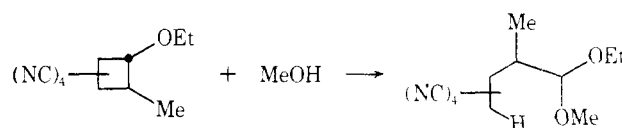
In recent years overwhelming evidence has been published to support the proposition that the cycloaddition of tetracyanoethylene to enol ethers is a stepwise reaction. Thus, it has been found that the reaction is largely but not completely stereospecific in either direction,² that *cis*-*trans* isomerization of the enol ether accompanies the reaction,³ and that an intermediate (with only one bond formed) can be intercepted by means of both alcohols⁴ and 1,4-dipolarophiles.⁵ It is furthermore clear that the intermediate has considerable zwitterionic character: the large negative activation volumes⁶ and entropies,⁷ the large solvent effect on

Table I. Pressure Effect on the Cycloreversion of the TCNE–Ethyl *E*-Propenyl Ether Adduct

<i>p</i> , kbar	10 ⁵ <i>k</i> ₁ , sec ⁻¹	No. of measurements
0.001	6.88	7
0.352	7.86	6
0.559	8.84	6
0.786	10.70	5
1.448	15.22	6
2.068	17.07	6

the reaction rate,⁸ and the effect of substituents in the enol ethers⁹ all suggest this.

There is no known instance of the breakage of a carbon-carbon bond which is promoted by pressure.¹⁰ It has been shown by Neuman¹¹ that the retardation which normally characterizes such reactions can be diminished if a polar component is present in the breaking bond. For this reason it seemed to us that the effect of pressure on the carbon-carbon bond cleavage in the reverse [2 + 2] cycloadditions just mentioned might well be the opposite of what is normally found and—on the assumption that the properties of the transition state foreshadow the incipient product—that the magnitude of the pressure effect would allow us to assess the zwitterionic character of the intermediate. Specifically, we hoped to learn whether the intermediate is truly a zwitterion as has been claimed on the basis of the transition state dipole moment (deduced from the solvent effect on the rate), or whether it is a diradical with dipolar character. If the former description is indeed correct, one may expect an activation volume in these reverse cycloadditions comparable to those observed in solvolysis, i.e., in the range of -20 cm³/mol even in polar solvents;¹² if the latter is a better description, then a much more modest pressure enhancement or even mild retardation may be anticipated. The reaction studied is indicated below; the adduct was prepared as described by McKusick.¹³ Methanol was used as the solvent



at 25°. The reaction was followed by NMR; the disappearance of the methinyl doublet at τ 5.83. The data are recorded in Table I. The activation volume is -16.7 cm³/mol; the precision is estimated to be ± 1.2 cm³/mol. This value may be compared with those obtained in solvolysis reactions in hydroxylic media; we recently noted that S_N1 solvolysis in alcoholic media on the average has an activation volume of -21 ± 2 cm³/mol.¹² Clearly this reaction is comparable in its electrostriction characteristics to limiting S_N1 solvolysis, and the intermediate is as purely zwitterionic as the initial product of solvolysis.

The information gained in this experiment is in good agreement with the solvent effect from which Huisgen and Steiner⁸ deduced a transition state dipole moment of 10–14 D; the calculated value for the intermediate is 17–21 D. Both approaches agree on a charge development of 60–70% in the activated complex.

Acknowledgment. This work is supported by the National Science Foundation. Professors H. Steinberg of the University of Amsterdam and H. Kelm of the University of Frankfurt have kindly informed us of similar studies in progress in their laboratories.

References and Notes

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- (2) (a) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5054 (1973); (b) P. D. Bartlett, *Q. Rev., Chem. Soc.*, **24**, 473 (1970); (c) T. Arimoto and J. Osugi, *Rev. Phys. Chem. Jpn.*, **44**, 25 (1974).
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 (4) R. Huisgen, R. Schug, and G. Steiner, *Angew. Chem., Int. Ed. Engl.*, **13**, 80, 81 (1974).
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 (6) K. F. Fleischmann and H. Kelm, *Tetrahedron Lett.*, 3773 (1973).
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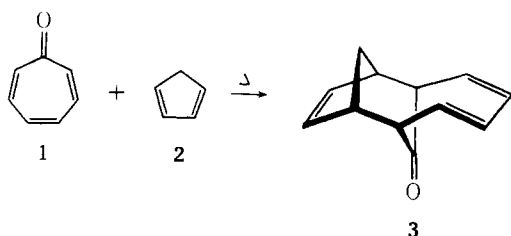
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Effect of Pressure on the [4 + 6] Cycloaddition of Troponone to Cyclopentadiene¹

Sir:

The pressure coefficient of the rate constant has been applied along with several other criteria to establish concertedness as one of the features characteristic of the Diels-Alder reaction.² Thus, it has been found in several laboratories that this reaction in general has a late transition state if the volume is used as a measure of the reaction coordinate; the activation volume is usually comparable to the overall reaction volume (-30 to -40 cm³/mol), implying that both of the newly developing bonds must be nearly formed in the transition state. By contrast, when competition between the Diels-Alder reaction and a [2 + 2] cycloaddition occurs, the result is that the latter reaction is inhibited by the application of high pressure conditions.³ Accordingly, it has a much less negative value of ΔV^\ddagger , and this in turn is interpreted as signifying the formation of only one bond in the transition state. Potentially this technique is one of the most useful methods available for examining concertedness, since no synthesis is involved in its application (as is the case for instance in the stereochemical criterion); however, before this tool can be used on a routine basis it is of course necessary to delineate the possible pitfalls and exceptions to which it may be subject. We recently pointed out, for example, that if the intermediate has zwitterionic rather than diradical character, electrostriction may lower the volume of the transition state in the stepwise reaction to the point that it may compete favorably with a concerted reaction under pressure.⁴ In this communication we present evidence that electrostriction in the *initial state* is likewise a factor that must be kept in mind in the application of high pressure to these problems.

The cycloaddition of troponone (**1**) to cyclopentadiene (**2**) to give **3** is an example of a [4 + 6] cycloaddition.⁵ This type of reaction⁶ has been shown by Houk to be concerted, the arguments resting primarily on the clean stereospecificity



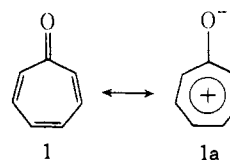
and on the fact that the products at higher temperatures rearrange to isomers expected from the stepwise reactions.⁷ Thus, there is every reason to believe that the activation volume should be large and negative, comparable to that in the Diels-Alder reactions.

We have now measured this term as it applies to the reaction in *p*-dioxane at 60°. Five measurements were made for each rate constant, and this was done at six pressures ranging over 4 kbar; our value obtained at atmospheric pressure agreed exactly with that reported by Tanida.⁸ The result is that ΔV_0^\ddagger equals -7.5 ± 1 cm³/mol; clearly this value differs drastically from that characteristic of the Diels-Alder reaction.

Further investigation by means of a dilatometric experiment then revealed that the overall reaction volume is also exceptionally small: $\Delta V_0 = -4.3 \pm 1$ cm³/mol (also in *p*-dioxane at 60°). The rate constant in this experiment again agreed with that obtained earlier at 1 atm. These data furnish a clear indication that one of the reactants must have an exceptionally low partial volume,⁹ and this was verified by direct measurement. The partial volumes were evaluated¹⁰ by means of pycnometric density determinations at several (five-six) concentrations and subsequent extrapolation to infinite dilution, by means of the expression

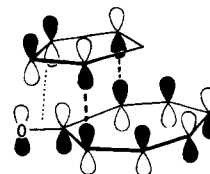
$$\Phi = \frac{M}{d_0} - \frac{1000}{C} \left[\frac{d - d_0}{d_0} \right]$$

The results are that the partial molar volumes of **1**, **2**, and **3** in *p*-dioxane at 60° are 85.6, 97.2, and 177.2 cm³/mol, respectively, with a precision of about 0.5 cm³/mol. On that basis, ΔV_0 equals $177.2 - (97.2 + 85.6) = -5.6$ cm³/mol, in agreement with the dilatometric value. These data clearly show that the partial volume of troponone is responsible for the exceptionally low values of ΔV_0 and ΔV_0^\ddagger ; thus, on the basis of parachor listings¹¹ the molar volume of **1** is predicted to be some 20 cm³/mol larger than that actually found. It is reasonable to attribute this small volume to the polar nature of **1**. There are several other observations testifying to the importance of **1a**; thus, Doering,¹² Dauben,¹³ and



Nozoe¹⁴ have attributed the low value of $\nu_{C=O}$ (1652 cm⁻¹), the high boiling point (105° at 10 Torr), the high dipole moment (4.17 D), the complete miscibility with water, and other anomalous properties of troponone to it.

One notable feature of these results is that the transition state is somewhat smaller than the final state. This has also been observed in those Diels-Alder reactions in which secondary orbital interactions are possible.^{2b} In previous discussions it has been emphasized^{6,7} that the secondary interactions between the diene and triene moieties are repulsive. In the present instance at least, an attractive interaction between the LUMO of the diene and the carbonyl portion of the troponone HOMO is apparently at least partially responsible for the *exo* stereochemistry.



In conclusion, we wish to emphasize that the observation