of an adduct mixture which contained 86% of **6** (mp 114–115°, ABCD spectrum for ring protons) and 14% of **4** + **5**. Dehydrogenation of this adduct mixture by chloranil to tetramethyl 1-(*p*-methoxyphenyl)-pyrrole-2,3,4,5-tetracarboxylate and the independent synthesis of this pyrrole have been described earlier.[6]

(6) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966).

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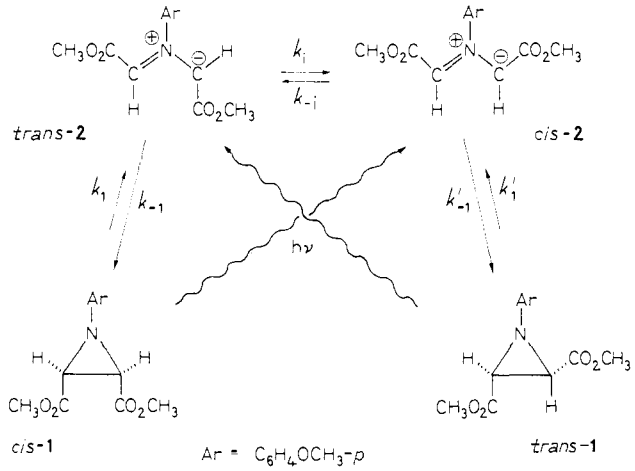
Azomethine Ylides by Photolysis of Isomeric Dimethyl 1-(*p*-Methoxyphenyl)aziridine-2,3-dicarboxylates. Elaboration of the Total Energy Profile

Sir:

The title compounds *cis*-**1** and *trans*-**1** maintain thermal equilibria with small concentrations of the isomeric azomethine ylides, *trans*-**2** and cis-**2**. The rate of cycloaddition to very active dipolarophiles is only determined by the first-order electrocyclic ring scission *cis*-**1** → *trans*-**2** and *trans*-**1** → *cis*-**2**.[1,2] The Eyring parameters of the ring-opening reactions have been evaluated. Kinetic measurements of the net isomerization rate *cis*-**1** ⇌ *trans*-**1** in the absence of dipolarophiles provided additional information; two out of three molecules of *cis*-**1** which overcome the ring-opening barrier at 120° and arrive in the energy trough of *trans*-**2** will roll back to *cis*-**1**, while the third makes the next pass which leads to *cis*-**2**. The corresponding *cis*-**2** is partitioned in the ratio 9:2 between *conrotatory* ring closure to *trans*-**1** and geometrical isomerization to *trans*-**2**.[3]

Scheme I



Only the depths of the energy troughs which belong to the open-chain intermediates **2** are still missing. We earlier[4] established that uv light induces *disrotatory* ring opening of **1**. If one succeeded in generating a high population of the azomethine ylides **2** by flash photolysis, then it would be possible to measure the rate of thermal cyclization **2** → **1**.

Dilute dioxane solutions of *cis*- and *trans*-**1** (10^{-4} *M*, 5 cm quartz cell) were exposed to a 25-J flash generated with an argon-filled quartz tube, whereby a species with λ_{max} 420 mμ was formed; *cis*-**1** absorbs at 286 mμ, *trans*-**1** at 288 mμ. Photometry (halogen lamp, 377.5-mμ interference filter to prevent noticeable photochemical conversion by the monitoring light) allowed one to measure the first-order kinetics of thermal disappearance of the intermediates to which we ascribe structures *trans*-**2** and *cis*-**2**. The half-lives of *trans*-**2** → *cis*-**1** and of *cis*-**2** → *trans*-**1** at 25° were found to be 5.4 and 7.8 sec, respectively. The corresponding $\Delta G^{\pm}$ values were 18.7 and 18.9 kcal mol^{-1}. Measurements at different temperatures enabled activation enthalpies and entropies to be calculated (Table I).

Table I. Kinetics of Thermal Reversion of the Cis–Trans Isomeric Azomethine Ylides **2** to the Aziridines **1** after Flash Photolysis in Dioxane

trans-**2** → *cis*-**1**		*cis*-**2** → *trans*-**1**	
Temp, °C	k_{-1}, sec^{-1}	Temp, °C	k_{-1}', sec^{-1}
24.6	0.136	27.1	0.106
26.1	0.143	36.4	0.183
41.8	0.291	44.1	0.400
42.4	0.291	51.4	0.517
51.4	0.465	67.4	1.45
67.7	1.12		
$\Delta H^{\pm}$ = 9.1 ± 0.7[a]		12.7 ± 0.8 kcal mol^{-1}	
$\Delta S^{\pm}$ = −32 ± 2[a]		−21 ± 2 eu	

[a] Eyring parameters were computed with the program ARRHEY assuming a ±10% range of error for the rate constants and ±0.5° for temperature. So far we have no explanation for the high negative entropies of activation and a systematic error cannot be excluded.

After the flash photolysis of **1**, a second-order reaction in the millisecond range was observed besides the slow first-order reaction which we dealt with above. How can one be sure that the rate data of Table I refer to the electrocyclic ring closure, **2** → **1**? The previously mentioned absorption maximum of 420 mμ made it possible for the first time *to see the colored intermediate.* On irradiating rather concentrated solutions of *cis*-**1** and *trans*-**1** in dioxane (0.07–0.2 *M*) with a medium-pressure mercury arc for 5 sec at room temperature, a yellow color appeared which faded within *ca.* 20 sec. Extinction measurements at 380 and 420 mμ led to rate constants which roughly corresponded to the ones of Table I. On addition of a drop of diethyl fumarate, an active dipolarophile,[2] the yellow color of the solution disappeared suddenly. The result was especially striking with the deep-yellow solution which we obtained by irradiating **1** in acetone at −30°. *Thus, the yellow intermediate must be the 1,3 dipole, the azomethine ylide* **2**.

Combination of all the rate data and their extrapolation to 120° permits the construction of the free-energy profile of the four-component system (Figure 1).[5] The troughs of the azomethine ylides **2** are of re-

(1) R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, **8**, 602 (1969).
(2) R. Huisgen and H. Mäder, *J. Amer. Chem. Soc.*, **93**, 1777 (1971), preceding communication.
(3) The somewhat different ratios given elsewhere[1] are based on the simplified assumption of an undisturbed ring-opening equilibrium. The correct treatment requires a rather cumbersome rate equation.
(4) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).
(5) The rate data for ring opening and geometrical isomerization refer to measurements in ethyl acetate solutions while k_{-1}' and k_{-1} were measured in dioxane.

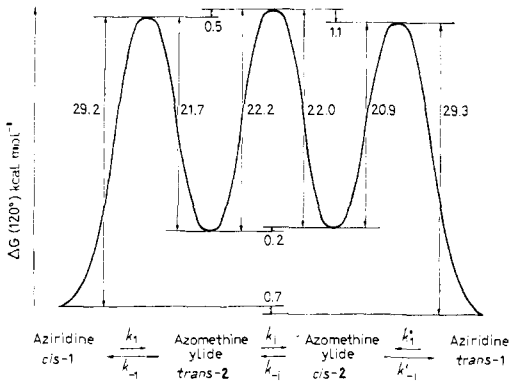


Figure 1. Energy profile for the thermal equilibration of the cis–trans isomeric dimethyl 1-(*p*-methoxyphenyl)aziridine-2,3-dicarboxylates (**1**) *via* the azomethine ylides **2** at 120°.

markable depth. The height of the barrier for the cyclization of **2** → **1** discloses a deep-seated change of the bond system. The geometrical isomerization *trans*-**2** ⇌ *cis*-**2** demands $\Delta G^{\ddagger}(120°)$ = 22.2 or 22.0 kcal mol^{-1}, respectively. If *trans*-**2** ⇌ *cis*-**2** takes place by rotation around a NC bond, the energy barrier gives a rough measure of the resonance energy of the heteroallyl anion system found in **2**. The *cis*- and *trans*-azomethine ylides **2** virtually do not differ in their energy levels; hence, there must be other reasons for the differing 1,3-dipolar activities of the ylides.[6]

Nevertheless, the net gain of converting a π into a σ bond in the change of **2** → **1** is exothermic by 8 kcal mol^{-1}. That explains the failure of spectroscopic means to detect the azomethine ylide **2** in thermal equilibrium with **1**. For each molecule of the 1,3-dipole **2** there are 30,000 aziridine molecules at 120°, while the ratio at 25° amounts to even 1:50 million.

The nitrones, considered as azomethine oxides, are structural relatives of azomethine ylides. Cis–trans isomerization of *C*-cyano-*C*,*N*-diphenylnitrone shows $\Delta G^{\ddagger}(120°)$ = 27.5 kcal mol^{-1}.[7] In contrast to the azomethine ylides, the azomethine oxides are thermodynamically favored as against the cyclic oxaziridines. The ring scission of 2-*tert*-butyl-3-phenyloxaziridine to form the nitrone occurs with $\Delta G^{\ddagger}(120°)$ = 29.2 kcal mol^{-1}.[8]

(6) R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *Angew. Chem., Int. Ed. Engl.*, **8**, 604 (1969).
(7) Calculated from the data given by K. Koyano and I. Tanaka, *J. Phys. Chem.*, **69**, 2545 (1965).
(8) Calculated from the data given by M. F. Hawthorne and R. D. Strahm, *J. Org. Chem.*, **22**, 1263 (1957).

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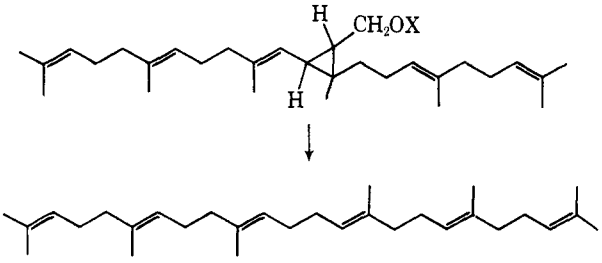
Mechanism of Presqualene Pyrophosphate–Squalene Biosynthesis

Sir:

None of the numerous, diverse speculations concerning the mechanism of squalene biogenesis published during the 1960's[1] anticipated the role of "presqualene pyrophosphate," a natural product shown by Rilling to be an intermediate in the biosynthesis of squalene from farnesyl pyrophosphate[2] and assigned structure **1** by Rilling and Epstein.[3] In view of the recently accomplished unequivocal synthesis by Altman of cyclopropylcarbinol possessing structure **2** and the demonstration that the synthetic material was well incorporated into squalene,[4] detailed consideration of



1, X = POP
2, X = H

the bioorganic chemistry of squalene synthesis seems desirable at this time.

In order to rationalize the formation of presqualene, the following individual steps are proposed. Initially, a new σ bond is formed through interaction of the allylic pyrophosphate units present in two farnesyl pyrophosphate molecules, specifically involving SN2 displacement by the π bond in one center, of the pyrophosphate anion in the second (**3**). In this process, attack of external or internal pyrophosphate would be expected to occur in such a way as to maintain the stereochemical relationship of the substituents on the original olefinic center. Once formed, the new pyrophosphate **4** is subjected to the action of an isomerase which produces the disubstituted olefin **5**. Such a process, although thermodynamically unfavorable, is precedented by the observed biological interconversion of isopentenyl pyrophosphate and dimethylallyl pyrophosphate.[5] The resulting homoallylic system is subject to chemically well-precedented cyclopropane ring closure, which in this case is accompanied by proton elimination to establish a trans-trisubstituted olefinic bond at the original site, prior to isomerase action. It should be emphasized at this point that in the entire mechanistic sequence, only *one* of the four original C-1 hydrogens present in the two starting farnesyl pyrophosphates will have been lost, in conformance with the biochemical findings.[1a,b] The established stereochemistry,[4] de-

(1) (a) G. Popják, DeW. S. Goodman, J. W. Cornforth, R. H. Cornforth, and R. Ryhage, *J. Biol. Chem.*, **236**, 1934 (1961); (b) J. W. Cornforth, R. H. Cornforth, C. Donninger, and G. Popják, *Proc. Roy. Soc., Ser. B*, **163**, 492 (1966); (c) G. Krishna, H. W. Whitlock, Jr., D. H. Feldbruegge, and J. W. Porter, *Arch. Biochem. Biophys.*, **114**, 200 (1966); (d) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (e) G. E. Risinger and H. D. Durst, *Tetrahedron Lett.*, 3133 (1968); (f) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).
(2) H. C. Rilling, *J. Biol. Chem.*, **241**, 3233 (1966).
(3) (a) H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, **91**, 1041 (1969); (b) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **18**, 4597 (1970). The mechanistic considerations described by these authors differ in several important respects from those presented in this contribution.
(4) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971).
(5) B. W. Agranoff, H. Eggerer, U. Henning, and F. Lynen, *ibid.*, **81**, 1254 (1959); *J. Biol. Chem.*, **235**, 326 (1960). The isomerization reaction could well proceed by a thiol addition–elimination sequence. In that case, the observed inhibition of squalene biosynthesis by thiols[1c] would find an explanation.