

Table I. Line Positions for the ^{13}C Nmr Spectrum of **1** (ppm from TMS)

Solvent	Temp., °C		CCH ₂	NCH ₃	NCH ₂
(CD ₃) ₂ CO	Ambient		23.4	40.9	54.1
(CD ₃) ₂ CO	-87	Set A	25.5	44.7	58.3
		Set B	20.0	35.4	48.0
1:1 (CD ₃) ₂ CO-CF ₂ Cl ₂	-88	Set A	25.6	44.8	58.5
		Set B	20.4	35.8	48.4
1:1 (CD ₃) ₂ CO-CF ₂ Cl ₂	-121	Set A	25.4	44.7	58.2
		Set C	15.6, 25.4 ^a	26.5, 43.5 ^b	43.0, ^b 54.2

^a This line was not observed, and presumably is obscured by the "set A" line at this position. ^b The assignments of these two lines may be inverted.

unobserved sixth line must then fall under a **1ee** line and remain unobserved), the averages being 20.5, 35.0, and 48.6 (at -121°), and set B coming at 20.4, 35.8, and 48.4 (at -88°). We observed no lines attributable to **1aa**, and, since substantial upfield shifts would be sure to result from the presence of two axial N-methyl groups, we doubt that a substantial amount of this conformation can be present at low temperature. Although line shape analysis remains to be carried out, ΔG^\ddagger will probably not turn out to be far from the 7–7.5 kcal/mol estimated from the temperature of maximum broadening.

It is interesting to compare the observed shifts for **1ea** with those expected for the effect of having an axial methyl group replace an equatorial one (Table II).

Table II. Comparison of Chemical Shifts for **1ee** and **1ea** at -121.3° (ppm from TMS)

Position	1ee	1ea	Shift difference	Predicted ^a
Me-1	44.7	43.5 ^b	-1.2	0
Me-2	44.7	26.5	-18.2	-8.5
C-3	58.2	54.2	-4.0	-2.6
C-4	25.4	15.6	-9.7	-5.5
C-5	25.4	Unobsd	~0	0
C-6	58.2	43.0 ^b	-15.2	-5.5

^a Using Grant's parameters derived for cyclohexane rings.

^b These assignments are rather arbitrary and might well be reversed.

We used the parameters derived by Grant's group for methyl substituents on cyclohexane rings.⁴ It may be seen that Grant's $\gamma_{2\text{HH}}$ and γ_{HH} parameters are too small for the hexahydropyridazine ring, and furthermore, that a higher γ_{HH} parameter would be necessary for C₄ than for C₆. Both of these effects are expected because of the shorter C–N and N–N bond lengths present in **1**, compared to the uniform C–C bond lengths in the cyclohexanes studied by Grant.

Another point of interest is the ratio of **1ee**:**1ae**:**1aa**. As stated before, no evidence for the presence of **1aa** is in hand. By comparing the peak positions for the three-line spectrum at -15° with those of set A and set B, and attempting to correct for the temperature dependence of the peak positions, a crude estimate of 56% **1ee** at -15° was obtained. By comparison of areas of the set A and set B peaks in the -53 to -68° region, estimates between 60 and 70% **1ee** were obtained, with an apparent increase as the temperature was lowered. From vapor phase photoelectron spectroscopy work, the ratio of **1ee**:other conformations ap-

(4) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **96**, 1874 (1974), and references therein.

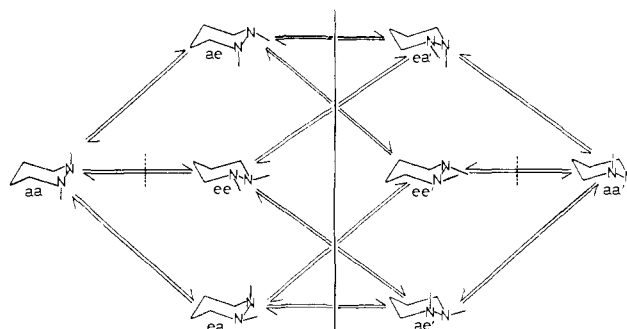


Figure 1. A diagram showing the possible interconversions between the isomers possible for **1**, assuming double nitrogen inversions and nitrogen inversions simultaneous with ring flips will be too slow to need consideration.

peared to be significantly higher, approximately 3:1.⁵ Although we consider it reasonable that the lowest dipole moment **1ee** conformation would be relatively more favored in the vapor phase than in solution, this conclusion must remain tentative until more extensive work is done.

Variable temperature ^{13}C nmr has been shown to be an extremely useful technique for conformational studies of cyclic hydrazines, which are being actively pursued in this laboratory.⁶

(5) (a) S. F. Nelsen, J. M. Buschek, and P. J. Hintz, *J. Amer. Chem. Soc.*, **95**, 2013 (1973); (b) S. F. Nelsen and J. M. Buschek, *ibid.*, **96**, 2392 (1974).

(6) We thank the National Science Foundation for support of this work, including the Major Instrument program for funds used in purchasing the spectrometer employed.

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The Three-Phase Test for Reactive Intermediates. Cyclobutadiene

Sir:

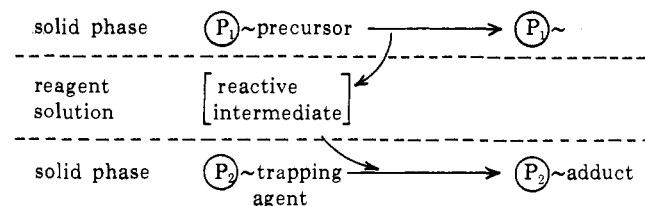
Previous applications of reactions on polymeric supports have emphasized either the ease of phase separations (ion exchange, affinity chromatography, peptide synthesis) or the benefits of matrix isolation (monofunctionalization,¹ Dieckmann cyclization²) available for reagents bound to insoluble supports. We now report the use of solid phase chemistry as a mechanistic probe for the detection of reactive intermediates.

(1) J. Y. Wong and C. C. Leznoff, *Can. J. Chem.*, **51**, 2452 (1973).

(2) J. I. Crowley and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 6363 (1970).

Our method is reminiscent of the Paneth³ test for organic free radicals in which reactive intermediates are generated in one phase, carried through a flow system, and detected on another phase. In the three-phase test, a precursor for a suspected intermediate is attached to one solid phase and liberated by solution of an appropriate reagent in the presence of a second solid phase bearing a trapping agent (Scheme I). The detection

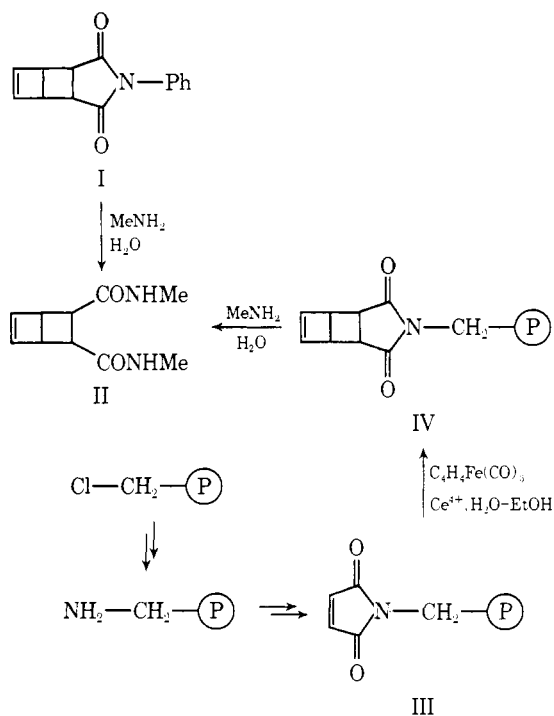
Scheme I



of an adduct gives positive evidence for a free intermediate.

The viability of the method was demonstrated for cyclobutadiene through the experiments outlined below. The reference compound II (Scheme II) was

Scheme II



prepared from the known⁴ cyclobutadiene-maleanil adduct by methaminolysis.⁵ The polymeric trapping agent was prepared from the chloromethylated Merrifield resin by conversion to the amine⁶ (Gabriel synthesis) then to the maleimide III by successive treatment

(3) F. Paneth and W. Hofeditz, *Chem. Ber.*, **62**, 1335 (1920). A three-phase experiment using adsorbents was first described by H. Kautsky and H. de Bruijn, *Naturwissenschaften*, **19**, 1043 (1931). We thank Professor C. S. Foote for bringing this to our attention.

(4) E. K. G. Schmidt, L. Brener, and R. Pettit, *J. Amer. Chem. Soc.*, **92**, 3240 (1970). The reference compound II, mp 195 (dec), was characterized by elemental analysis and ir, nmr, and mass spectra.

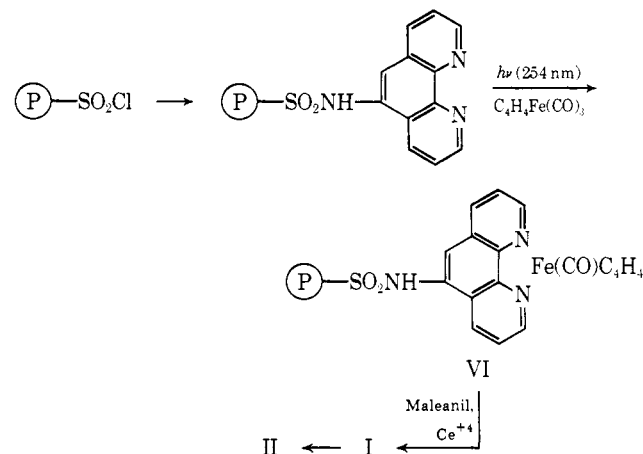
(5) S. Wolfe and S. Hasan, *Can. J. Chem.*, **48**, 3572 (1970).

(6) M. Weinschenker and C. Shen, *Tetrahedron Lett.*, 3281 (1972).

with maleic anhydride and hot NaOAc-Ac₂O.⁷ A suspension of III (ir 1790, 1705 cm⁻¹) in 95% ethanol containing excess cyclobutadiene iron tricarbonyl was treated with aqueous ceric ammonium nitrate to give the polymeric adduct IV (ir 1710 cm⁻¹) from which II was obtained by methaminolysis.

In a complementary series of experiments, chloro-sulfonated macroreticular resin⁸ was converted to the ligand V (Scheme III) with 5-amino-*o*-phenanthroline

Scheme III



then to the cyclobutadiene precursor VI (ir 2050, 1005, 910 cm⁻¹)⁹ by irradiation of an ethanolic solution of C₄H₄Fe(CO)₃ in which V was suspended. Oxidation of VI suspended in an ethanolic solution of maleanil gave the adduct I from which II was again obtained.

For the three-phase test, a suspension of the precursor polymer VI and the trapping polymer III (in excess) was oxidized with either ceric ion¹⁰ or pyridine *N*-oxide.¹¹ The resins were separated (flotation or screening) and the adduct resin was treated with methylamine to give a mixture of *N,N'*-dimethylmaleamide and II, from which II could be isolated by fractional crystallization or preparative tlc (Scheme IV).

The isolation of the adduct in the three-phase experiment provides additional evidence that cyclobutadiene is free of iron when generated by this method and agrees with the evidence obtained by Grubbs¹² and Schmidt.¹³ Further, ceric ion is not required as a carrier, as organic oxidants also liberate cyclobutadiene from its iron carbonyl precursors. The new method has been used to demonstrate the existence of other reactive inter-

(7) J. V. Dichard, R. A. Bate, and R. A. Keller, *Separ. Sci.*, **2**, 357 (1967). All reactions on the solid phase were monitored by ir (KBr pellets), changes in polymer weight and, where appropriate, titrations and combustion analysis.

(8) W. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, 1391 (1974).

(9) That the resin VI contained other iron species was evidenced by a second carbonyl ir absorption at 1960 cm⁻¹. This carbonyl remained after exhaustive washing of the resin (wash solutions were monitored by atomic adsorption).

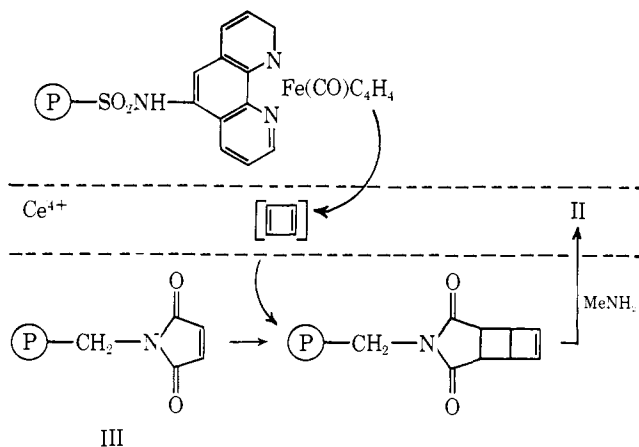
(10) Atomic absorption analysis of the solution after oxidation revealed only those traces of iron present in the ceric ammonium nitrate reagent; combustion analysis indicated that the iron remained on the resin after oxidation.

(11) Y. Shvo and E. Hazum, *J. Chem. Soc., Chem. Commun.*, 336 (1974).

(12) R. H. Grubbs and R. A. Grey, *J. Amer. Chem. Soc.*, **95**, 5765 (1973).

(13) E. K. G. Schmidt, *Angew. Chem.*, **85**, 820 (1973).

Scheme IV



mediates, and measurements of lifetimes through separation of the resins to increasing distances are underway.

Acknowledgments. We are pleased to acknowledge encouragement and advice from Professors H. D. Kaesz and J. I. Zink and F. A. L. Anet. Financial support was provided through the Fulbright Commission's Program of Cultural Cooperation between the U. S. A. and Spain, the Eli Lilly Co., and the Research Corporation.

(14) Visiting Fulbright Scholar on leave from the University of Valencia, Spain.

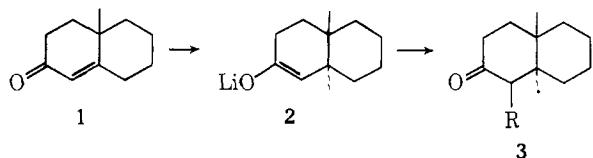
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Condensation of Formaldehyde with Regiospecifically Generated Anions

Sir:

Sophisticated synthesis design has been greatly helped by the demonstration¹ that enolate ions can be regiospecifically generated, *e.g.*, from enones, and that if these enolates are *lithium* enolates they can, in many cases, be alkylated without loss of structural integrity (*cf.* **1** → **2** → **3**).^{1,2}



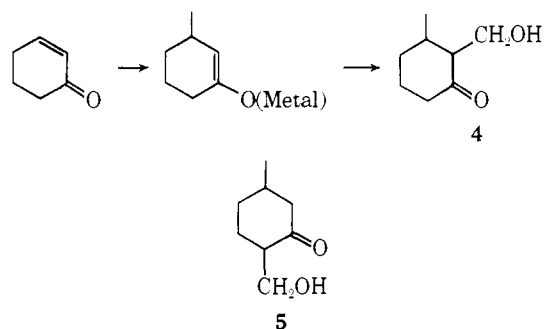
These important methods for regiospecific formation of carbon-carbon bonds have been extended recently to the Michael condensation with α -silyl vinyl ketones (and

(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83**, 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).

(2) For other methods of kinetic generation of enolates *cf.* (a) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (b) D. Caine, *J. Org. Chem.*, **29**, 1868 (1964); (c) G. Stork and P. F. Hudrlík, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); (d) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); (e) R. M. Coates and L. Ofenshain Sandefur, *ibid.*, **39**, 275 (1974), and references therein cited.

esters)³ and to directed aldol condensations between methyl ketones and aldehydes.⁴ We report here on the successful trapping of regiospecifically generated enolate ions from cyclic ketones with formaldehyde,⁵ a method which promises to be of considerable importance because the derived hydroxymethyl ketones are well-known intermediates in a number of useful constructions. They, for instance, are precursors of α -methylene ketones which can be used, *inter alia*, for Michael additions, *e.g.*, annelation with β -ketoesters (*vide infra*), for chain extension *via* addition alkyl cuprates or dialkylaluminum acetylenes,⁶ and for Diels-Alder additions.⁷ In spite of their potential importance, α -hydroxymethyl ketones of predictable structures have remained difficultly accessible. The base-catalyzed condensation of formaldehyde with ketones is usually unsatisfactory,⁸ and introduction of a hydroxymethyl group has previously been accomplished by a variety of multistep processes.⁹

Our initial experiments were conducted with the enolates resulting from 1,4-addition of organometallic reagents to enones. Addition of methylmagnesium bromide, catalyzed with 1% $\text{CuI} \cdot \text{Bu}_3\text{P}$, to cyclohexenone in ether in the usual manner, was followed by passage at -10° of anhydrous gaseous formaldehyde¹⁰ in a stream of nitrogen (8.8 g of formaldehyde absorbed, starting with 0.3 mol of cyclohexenone), and by acidification (ammonium chloride at 0°). Distillation gave, in $\sim 70\%$ yield, 2-hydroxymethyl-3-methylcyclohexanone which was obtained as a mixture of stereoisomers, bp $73-76^\circ$ (0.5 mm), R_f (major) 0.55, (minor) 0.40 (60:40 benzene:ethyl acetate on silica); ratio of methyl doublets at δ (CCl_4) 0.83 and 1.13 is $\sim 1:5$. The carbinols **4** formed *via* trapping were different (tlc) from



the single regioisomer **5** formed in 20% yield by base-catalyzed condensation of 3-methylcyclohexanone with formaldehyde.¹¹ The identity of **4** was established by

(3) (a) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, **95**, 6152 (1973); (b) G. Stork and J. Singh, *ibid.*, **96**, 6181 (1974); (c) R. K. Boeckman, Jr., *ibid.*, **95**, 6867 (1973); (d) R. K. Boeckman, Jr., *ibid.*, **96**, 6179 (1974).

(4) G. Stork, G. Kraus and G. Garcia, in press.

(5) A recent interesting example of reaction of an enolate with formaldehyde in aprotic media has been described by P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972). In that case, however, the problem of regiospecific control does not arise.

(6) J. Hooz and R. B. Layton, *J. Amer. Chem. Soc.*, **93**, 7320 (1971).

(7) Cf. A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 188 (1967).

(8) Cf. E. J. Corey and D. E. Cane, *J. Org. Chem.*, **36**, 3070 (1971).

(9) Cf. D. Stauffacher and H. Schinz, *Helv. Chim. Acta*, **37**, 1227 (1954).

(10) The formaldehyde was generated by the thermal depolymerization of paraformaldehyde (dried over phosphorus pentoxide, under vacuum) at 150° . Higher temperatures must be avoided because small amounts of protic impurities (methanol?) can then be carried into the reaction mixture. See also footnote 16.

(11) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).