

the interaction favors the five-coordinate, HS form. The TNB signal is broadened and shifted upfield considerably,¹² confirming a specific interaction with at least one of the porphyrin species. In a solution containing only the LS form, the diamagnetic TNB signal is unaffected, as is the rate of ligand exchange⁹ in reaction 1. In the presence of only the HS form, the TNB peak is again broadened past detection by paramagnetic relaxation¹³ and shifted upfield by the porphyrin ring current; the shifts and line width of TPPFeCl are unaffected. This clearly demonstrates that TNB interacts only with, and stabilizes, TPPFeCl.

The kinetics of chloride exchange¹⁰ in eq 2 were monitored by the collapse of the α -CH₂ doublet of OEPFeCl upon addition of excess Cl⁻ in the form of Bu₄N⁺Cl⁻. The second-order exchange rate ([OEPFeCl] = 0.04 M, [Bu₄NCl] = 0.65 M) was 600 sec⁻¹ for the HS complex at 76°, decreasing to 400 sec⁻¹ in the presence of an equimolar amount of TNB. Since chloride exchange has been demonstrated¹⁰ to proceed *via* a six-coordinated intermediate, the results again indicate that formation of the molecular complex stabilizes the five-coordinate, HS species. The effect of TNB on the thermodynamics of eq 1 and the kinetics of eq 2 must reflect a specific interaction with the HS form and not just a solvent effect, since numerous other, similar molecules failed to produce detectable changes at comparable concentrations.¹⁴

Preliminary analysis suggests that the reduced affinity for axial ligands originates in an electronic effect due to porphyrin-TNB interaction which is transmitted to the metal, rather than from a steric blocking of the axial site by TNB. Hence the TPPFeCl-TNB interaction is envisaged to occur at the periphery of the porphyrin involving a single pyrrole. The basis of this conclusion is that molecular models¹⁵ indicate that, due to the perpendicular phenyl rings, planar π complexes can occur either directly over the metal, or at the periphery with a single pyrrole at a time. The former configuration is considered unlikely since the TPPFeCl line widths are unaffected by TNB interaction. Previous work had shown¹⁶ that the line width is a very sensitive indicator of the axial field strength, such that a TNB over the metal should lead to a significant increase in line width.¹⁷ Similar peripheral interactions have been characterized for LS biscyano hemins.¹⁸

Previous analyses of iron-porphyrin π bonding have

(12) At the ratio [TNB]/[TPPFeCl] \sim 8, the TNB shift is 2.6 ppm upfield from its diamagnetic position, and the line width is \sim 80 Hz. At lower ratios the line width is so great that the TNB peak cannot be resolved under the TPP phenyl resonances.

(13) T. J. Swift in "NMR of Paramagnetic Molecules: Principles and Application," G. N. La Mar, W. D. Horrocks, Jr., and R. H. Holm, Ed., Academic Press, New York, N. Y., 1973, Chapter 2.

(14) The organic molecules hexamethylbenzene, phenanthrene, phenazine, perylene, acridine, and dimethylaniline produced little changes even at concentrations much greater than for TNB. Furthermore, TNB unlike the other ligands above, causes changes in the optical spectrum of TPPFeCl. The changes in K_{eq} due to TNB are larger than predicted by any 1:1 interaction of TNB with *N*-methylimidazole.

(15) The models used are "CPK Atomic Models," The Ealing Corporation, Cambridge, Mass.

(16) G. N. La Mar and F. A. Walker, *J. Amer. Chem. Soc.*, **95**, 6950 (1973).

(17) The lack of changes in the TPPFeCl line widths upon addition of TNB argues strongly against direct coordination of TNB. ¹³C T₁ measurements on TNB in the presence of TPPFeCl reveal that the two carbons have very similar relaxation times, which is also inconsistent with direct coordination of the TNB *via* the NO₂ group.

(18) G. N. La Mar and D. B. Viscio, *J. Amer. Chem. Soc.*, in press.

indicated^{19,20} the dominance of Fe \rightarrow P π^* and P \rightarrow Fe π charge transfer in the HS and LS forms, respectively. Hence the preferred interaction of TNB is consistent with the larger ligand charge density in the HS form. The reduced affinity for additional axial ligand in the HS form is suggested to be the result of the stabilization of the Fe-P bond as a result of interaction with TNB.

The demonstrated reduced affinity for a sixth ligand due to the molecular interaction with an acceptor may be relevant to the action of oxygen binding hemoproteins. In such proteins, the aromatic amino acid residues are generally donors, which would be expected to increase the affinity for the axial ligand over that of the free porphyrin. We have failed to observe effects with a strong donor, probably due to unfavorable free energy considerations.²¹ In the protein, however, such interactions could occur due to steric constraints imposed by the folding of the polypeptide backbone.

Current work is aimed at a more detailed description of the molecular interaction with iron as well as other metalloproteins with respect to changes in the axial ligation and redox properties of the metal ion.

Acknowledgments. This research was supported in part by the National Institutes of Health, Grant No. HL-16087.

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(20) G. N. La Mar, G. R. Eaton, R. H. Holm, and F. A. Walker, *J. Amer. Chem. Soc.*, **95**, 63 (1973); F. A. Walker and G. N. La Mar, *Ann. N. Y. Acad. Sci.*, **206**, 328 (1973).

(21) An effect on the equilibrium in eq 1 due to the presence of a donor (*o*-phenanthroline) has been detected (E. H. Abbott, private communication) by monitoring the optical absorption bands of the HS and LS species. The presence of the donor has the effect of increasing the apparent K_{eq} , suggesting that the six-coordinate, LS form is stabilized.

(22) Fellow of the Alfred P. Sloan Foundation.

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Generation and Reactivity of α -Carbethoxyvinylcuprate

Sir:

While the search for new syntheses of prostaglandins has generated considerable interest and development in the area of terminal vinyl cuprate reagents,¹ the applications of functionalized nonterminal vinyl copper reagents are few indeed.² α -Carbalkoxy- and α -carboxyvinyl cuprates have been generated *in situ* from conjugate addition of organocopper reagents to acetylenic esters and acids.³⁻⁵ Whereas oxidation, protonation, and iodination of these intermediates have

(1) (a) F. S. Alvarez, D. Wren, and A. Prince, *J. Amer. Chem. Soc.*, **94**, 7823 (1972); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827, 9256 (1972); (c) C. J. Sih, R. G. Salomon, P. Price, G. Peruzzoti, and R. Sood, *J. Chem. Soc., Chem. Commun.*, 240 (1972); (d) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzoti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972); (e) K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972); (f) E. J. Corey and T. Ravindranathan, *J. Amer. Chem. Soc.*, **94**, 4013 (1972).

(2) G. H. Posner, *Org. React.*, **19**, 1 (1972).

(3) E. J. Corey and J. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969).

(4) J. Klein and R. Levene, *J. Chem. Soc., Perkin Trans. 2*, 1971 (1973).

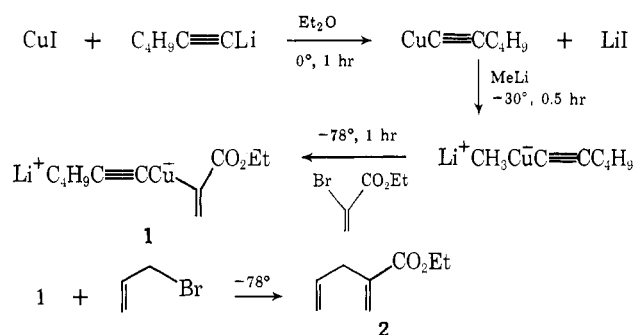
(5) J. B. Siddall, M. Biskup, and J. H. Fried, *J. Amer. Chem. Soc.*, **91**, 1853 (1969).

met with success^{3,5} alkylations with external alkyl halides have not been reported except for methyl iodide.⁵ Klein and Levene⁶ have recently generated α -carbalkoxycuprates from α -bromo α,β -unsaturated esters and lithium dimethylcuprate. These authors demonstrated that nucleophilic displacement of the vinylic bromide with the alkyl cuprate occurs with retention of configuration. Once again, no alkylations or chemistry besides protonation and iodination was described for these α -carbalkoxyvinylcuprates.

We have been interested in developing nonterminal and functionalized vinyl copper reagents, which would allow the formation of a carbon-vinyl bond and introduce a three-carbon synthetic unit. In this communication we wish to report on the generation of a novel organocuprate reagent **1** derived from ethyl α -bromoacrylate, its reactivity toward alkylation, and its application to the synthesis of α -methylenebutyrolactones. Our results indicate that our mixed organocuprate **1** is a highly specific reagent whose nucleophilicity differs significantly from divinyl cuprate² and other terminal vinyl-copper reagents.

In order to maximize the synthetic efficiency and selective transfer of the ethyl acrylate synthon, we have designed our reagent with an unreactive acetylenic ligand.⁷ Thus, reaction of lithium hexynylmethylcuprate, generated *in situ* from the copper acetylide and methyl lithium, with the α -bromoacrylate in ether produced the mixed vinyl acetylene cuprate **1**.⁸ When the cuprate **1** was treated with allyl bromide at -78° , a good yield of the 1,4-diene product **2** was obtained.⁹ The overall sequence and reaction conditions are summarized in Scheme I.

Scheme I



A survey of the chemical reactivity of the mixed vinyl cuprate with various organohalides revealed that the reagent is very specific for allyl and propargyl halides. With crotylbromide and 3,3-dimethylallyl bromide, transfer of the ethyl acrylate moiety occurred

(6) (a) J. Klein and R. Levene, *J. Amer. Chem. Soc.*, **94**, 2520 (1972); (b) ref 4.

(7) H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973), and references therein.

(8) The reaction of lithium dimethylcuprate with α -bromoacrylate usually yields, after acid quench, 15–20% of ethyl butyrate. Similar side reactions are not observed with the mixed cuprate **1**. In contrast to Klein's work (see ref 6) we have found that 5–10 equiv of lithium dimethylcuprate is unnecessary in the reaction with methyl α -bromocrotonate. In fact, the reaction is complete in less than 30 min using only 2 equiv of the cuprate. We have found that preformed hexynyl copper did not give reproducible results while the *in situ* generation of hexynyl copper did.

(9) All new compounds gave satisfactory nmr, ir, and mass spectral data as well as acceptable elemental analyses (within 0.3%).

only at the carbon bearing the halogen, while the reaction of propargyl bromide gave the expected acetylenic acrylate. Alkyl iodides such as *n*-heptyl iodide as well as iodobenzene and 2-bromopropene were completely unaffected by the reaction conditions. Even the highly reactive benzyl bromide did not alkylate the α -carbomethoxyvinylcuprate, in direct contrast to lithium divinylcuprate and alkylcuprates. A summary of the yields of these alkylations is given in Table I.

Table I

RX	Product	% yield ^a
		70 ^b
		70
		55
		65
		50
HC≡CCH ₂ Br	HC≡CCH ₂ C(=CH ₂)CO ₂ Et	70
PhCH ₂ Br	No reaction ^c	0
<i>n</i> -C ₇ H ₁₅ I	No reaction	0
PhI	No reaction	0
	No reaction	0

^a All yields are based on halide. In general, 1.5 equiv of **1** was used. Except where noted all yields were calculated by nmr using an internal standard. ^b Yields were determined by vpc with a calibrated internal standard. ^c Except for 2-bromopropene, all unreactive halides were recovered in near quantitative yield, even after 20 hr at room temperature. The reaction of **1** with benzyl bromide has been repeated four times.

The above results suggest that the reduced nucleophilicity of our α -carbomethoxyvinyl cuprate **1** is possibly due to the inductive effects of the ester moiety and the acetylenic ligand. Furthermore, the specificity of the reagent for allyl halides could possibly be a consequence of the copper atom of **1** seeking additional electron donation.¹⁰

A typical experimental procedure follows.¹¹ To a slurry of CuI (4 mmol) in 20 ml of ether at 0°C was added a cold solution of 1-hexynyl lithium (4 mmol) in 20 ml of ether. After the resulting canary yellow mixture was stirred for 1 hr, the temperature was lowered to -30° and 4 mmol of methyl lithium¹² was added to produce a turbid yellow solution. After 30 min,

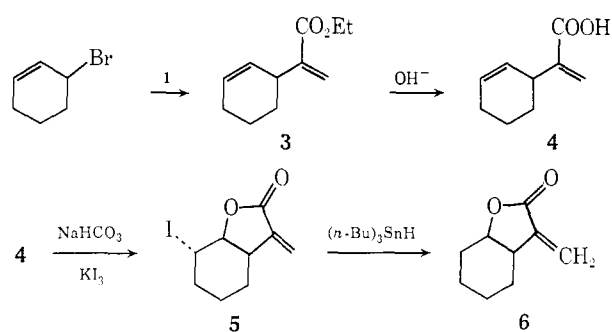
(10) Normant has observed significant olefin complexation with several mixed cuprate species. See J. F. Normant and M. Bougain, *Tetrahedron Lett.*, 2659 (1970); M. Bourgauss, J. Villieras, and J. F. Normant, *C. R. Acad. Sci., Ser. C*, **276**, 1477 (1973).

(11) All experiments were carried out under a nitrogen atmosphere with rigorously dry apparatus. The cuprous iodide (Alfa, ultrapure) was extracted with refluxing tetrahydrofuran before use.

(12) Problems of nonreproducibility initially encountered were traced to variations in the concentration of methyl lithium at various temperatures below 0°C. Consistent results were obtained by storing methyl lithium at room temperature and titrating just prior to use with 1,10-phenanthroline.

an ether solution of freshly distilled ethyl α -bromoacrylate (2 mmol) was added at -78° ; this caused an immediate precipitation of a yellow solid. After 1 hr at -78° , the allylic bromide (1.33 mmol) was added, and the reaction mixture turned red-orange in color. The reaction mixture was stirred overnight at -78° , quenched with a 10% ammonium chloride solution, and then allowed to come to room temperature, at which time a standard extraction work-up was employed.

To illustrate one of the unique synthetic applications of this novel reagent, we have developed a new route to α -methylene lactones from allyl halides. The product **3** from 3-bromocyclohexene possesses all the necessary functionality for α -methylenebutyrolactones. Thus, **3** was cleanly converted to the acrylic acid derivative **4** upon base hydrolysis (10% sodium hydroxide at 70° overnight). The unsaturated acid **4** was cyclized to the crystalline iodolactone **5** (mp 78.5 – 80°)¹³ in high yield; subsequent reduction of the iodine yielded pure *cis*- α -methylenebutyrolactone (**6**).¹⁴ Further devel-



opments in α -methylenebutyrolactone synthesis utilizing our copper reagent **1** will be published shortly.

In summarizing the synthetic features of this new α -carbomethoxyvinyl cuprate **1**, we wish to point out: (a) the completely selective transfer of only the vinyl moiety to introduce a three carbon unit, (b) the near ideal 1:1 stoichiometry of the cuprate **1** to allyl halide, (c) the high degree of specificity for only allyl halides,¹⁵ and (d) the convenience of a one-flask sequence to form a new carbon-carbon bond at an sp^2 center under extremely mild conditions. Further work is in progress to explore the full range of reactivity of this useful, nonterminal vinyl cuprate with other electrophiles and to gain some insight into the mechanistic details of the above coupling reactions.

(13) To our knowledge, this is the first instance of direct iodolactonization of an acrylic acid derivative such as **4**. For an example of a cyclohexene acetic acid, see H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

(14) The overall yield of α -methylene lactone **6** from compound **3** is high and does not necessitate purification of any intermediates. Final confirmation of structure **6** was made by spectral comparison with an authentic sample kindly provided by Professor R. G. Lawton.

(15) Less pronounced selectivity has been noted in a few "stabilized" organocuprate(I) systems: (a) E. J. Corey and M. Jautelet, *Tetrahedron Lett.*, 5187 (1968); (b) I. Kuwajima and Y. Doi, *ibid.*, 1163 (1972); (c) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 7926 (1973).

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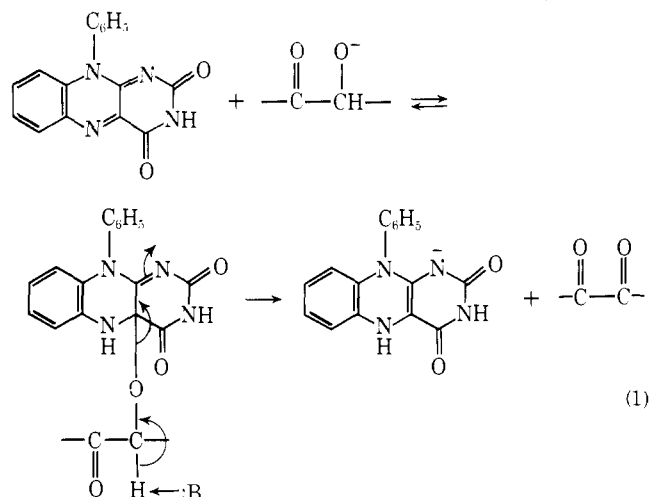
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The Importance of 1,2-Enediols in the Reduction of Lumiflavin by α -Ketols

Sir:

We consider herein the mechanism of α -ketol oxidation by oxidized flavin. Brown and Hamilton¹ examined (as a representative α -ketol) the oxidation of methyl mandelate by 10-phenylisoalloxazine. Though no intermediate species could be detected, they suggested 4a addition of the alkoxide species of the substrate followed by base-catalyzed elimination of ketoester (eq 1). An electron transfer from the base generated



1,2-enediolate has been suggested as a preferred alternative to the mechanism of eq 1.^{2,3} A 1,2-enediolate ion would have much appeal as an intermediate since it would serve as a π -donor toward oxidized flavin forming a charge transfer complex⁴ in a preequilibrium step to electron transfer. The intermediacy of an enediol intermediate would also be consistent with the observation that chloride ion is eliminated competitively, by α -proton ionization, in the enzymatic oxidations of β -chloro- α -amino acids.⁵

α -Ketols are oxidized to the corresponding diketones by molecular oxygen.⁶ The rates of this reaction and of the oxidation of α -ketols by Fehling solution are proportional to $[\text{HO}^-]$ and are identical at identical pH. These results imply rate determining enolization of ketol to the 1,2-enediolate ion followed by rapid oxidation of the latter so that the observed rate constants are independent of the nature of the oxidizing agent. In this study the rates of oxidation of furin and benzoin by lumiflavin (LF), 2,6-dichlorophenolindophenol (DCI) (anerobic, dark), and O_2 are compared. DCI, known as Tillman's reagent, quickly traps enediols and is frequently employed for their quantitative determination.⁷ Reactions were followed at λ_{max} 443

(1) L. E. Brown and G. A. Hamilton, *J. Amer. Chem. Soc.*, **92**, 7225 (1970).

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(4) M. A. Slifkin, "Charge Transfer Interactions of Biomolecules," Academic Press, New York, N. Y., 1971.

(5) C. T. Walsh, A. Schronbrunn, and R. H. Abeles, *J. Biol. Chem.*, **246**, 6855 (1971); C. T. Walsh, A. Schronbrunn, O. Lockbridge, V. Massey, and R. H. Abeles, *ibid.*, **247**, 6004 (1972); C. T. Walsh, E. Krodol, V. Massey, and R. H. Abeles, *J. Biol. Chem.*, **248**, 1946 (1973).

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(7) B. Eistert, "Methodien. der Organischen Chemie," Vol. II, 4th ed, George Thieme Verlag, Stuttgart, 1952, p 395.