Table III. Entrainment in the Reactions of Sodium Benzenesulfinate with α,*p*-Dinitrocumene[a]

Anion	Entraining anion; mol %[b]	Time, hr	% reaction	R anion;[c] % yield
$^-CH(CO_2C_2H_5)_2$[d]		96	64	$RCH(CO_2C_2H_5)_2$; 57
$C_6H_5SO_2^-$[d]		96	8	$RSO_2C_6H_5$; 8
$C_6H_5SO_2^-$[d]	$^-CH(CO_2C_2H_5)_2$; 5	48	49	$RSO_2C_6H_5$; 48
$^-CH(CO_2C_2H_5)_2$		72	69	$RCH(CO_2C_2H_5)_2$; 65
$C_6H_5SO_2^-$		96	2	$RSO_2C_6H_5$; 1
$C_6H_5SO_2^-$	$^-CH(CO_2C_2H_5)_2$; 5	72	35	$RSO_2C_6H_5$; 35
N_3^-[e]		5	99	RN_3; 95[f]
$C_6H_5SO_2^-$[e]		6	32	$RSO_2C_6H_5$; 29
$C_6H_5SO_2^-$[e]	N_3^-; 5	6	67	$RSO_2C_6H_5$; 60[g]

[a] In the dark in DMSO except as otherwise noted. [b] Relative to $C_6H_5SO_2^-$. [c] R = *p*-nitrocumyl. [d] In HMPA. [e] Exposed to an ordinary fluorescent light. [f] J. W. Manthey, Ph.D. Thesis, Purdue University, 1969. [g] RN_3 also formed; 7% yield.

8% in 96 hr. However, when 5 mol % of the lithium salt of 2-nitropropane is present it goes to completion in 4 hr and gives a 95% yield of *p*-nitrocumyl phenyl sulfone; indeed, even as little as 0.8 mol % of the lithium salt of 2-nitropropane results in a 75% yield of the sulfone after 4 hr (Table I).

Entrainment is not restricted to reactions employing α,*p*-dinitrocumene. Thus, although *p*-nitrocumyl chloride (Ia) and sodium nitrite fail to react after 90 min in the dark, when 5 mol % of the lithium salt of 2-nitropropane is added the reaction goes to completion in 90 min and a 93% yield of α,*p*-dinitrocumene (Ib) is isolated. And while the reaction of *p*-nitrocumyl chloride with quinuclidine[3] is exceedingly slow in the dark (after 36 hr[4] none of the alkylated amine is isolated) with 7 mol % of the lithium salt of 2-nitropropane present a 63% yield of the pure alkylated quinuclidine is obtained after 36 hr. Entrainment is also observed in the reaction of sodium benzenesulfinate with *p*-nitrocumyl chloride (Table II).

While the 2-nitropropane anion is the most effective entraining agent, it is not unique; malonate and azide ions are also able to induce the reactions of other anions (Table III). Nor, as the result with azide ion shows, is entrainment restricted to reactions conducted in the dark.

Entrainment provides powerful support for the radical anion chain mechanism of eq 2–5. The entraining anion initiates chains and the entrained anion carries them along. We have, then, a simple explanation for what would otherwise be an inexplicable phenomenon.

Entrainment is also of interest as regards synthetic organic chemistry for it suggests how the range of these substitution reactions may be extended. Nucleophiles which, on their own, react too slowly to be useful—or which do not react at all—may be caused to react merely by adding a catalytic amount of a reactive nucleophile.

Acknowledgment. This work was generously supported by Eli Lilly and Company, the Hoffmann-La-Roche Foundation, and the Petroleum Research Fund, administered by the American Chemical Society. We also take pleasure in recording our indebtedness to the Crown Zellerbach Corporation and the Dow Chemical Company for gifts of DMSO and HMPA, respectively.

(3) N. Kornblum and F. W. Stuchal, *J. Amer. Chem. Soc.*, **92**, 1804 (1970).

(4) At this time 6% of the theoretical amount of chloride ion has been liberated but it is virtually all due to dehydrohalogenation.

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Synthetic Studies of Amino Acids by the Use of the Copper Complex. I. Syntheses of β-Hydroxy DL-Amino Acids by the Use of the Complex of Copper(II) with the Schiff Base Derived from Glycine and Pyruvic Acid

Sir:

Although the reaction of bis(glycinato)copper(II) (**1**) with aliphatic or aromatic aldehydes under basic conditions, which was first reported by Sato, Okawa, and Akabori,[1] is known to be important for the synthesis of β-hydroxy amino acids,[1-3] the amino acids are produced by the reaction only when the conditions are strongly basic, and hence such conditions are inadequate for the reactions involving aldehydes which easily isomerize or polymerize under basic conditions. The mechanism of this reaction, on the other hand, has generally been assumed to involve the carbanion (**2**) which was produced by the dissociation of the α-hydrogen of **1** attacking the carbonyl group of an aldehyde to give the complex of the resultant amino acid (**3**),[4] as shown in Scheme I. William and Busch[5] clarified by nuclear magnetic resonance study that the proton on the nitrogen atom as well as that on the α carbon of such a complex dissociates even under slightly alkaline conditions. Imado, *et al.*,[6] isolated bis(*N*-ethylidene-DL-threoninato)copper(II) (**4**) and confirmed its structure by X-ray crystal-structure analysis. However, no regard has been paid to the dissociation of the hydrogens

(1) M. Sato, K. Okawa, and S. Akabori, *Bull. Chem. Soc. Jap.*, 30, 937 (1957).

(2) K. Okawa and S. Akabori, British Patent 814063 (1959).

(3) Y. Ikutani, T. Okuda, and S. Akabori, *Bull. Chem. Soc. Jap.*, **33**, 582 (1962).

(4) A. Nakahara, *Yuki Gosei Kagaku Kyokai Shi*, 27, 951 (1969).

(5) D. H. William and D. H. Busch, *J. Amer. Chem. Soc.*, **87**, 4644 (1965).

(6) (a) Y. Sato, T. Takahashi, S. Imado, and N. Sugimoto, *Yakugaku Zasshi*, **81**, 819 (1961); (b) Y. Sato, K. Kodera, S. Imado, and N. Sugimoto, *ibid.*, **81**, 824 (1961); (c) S. Imado, *ibid.*, **81**, 828, 832, 837 (1961).

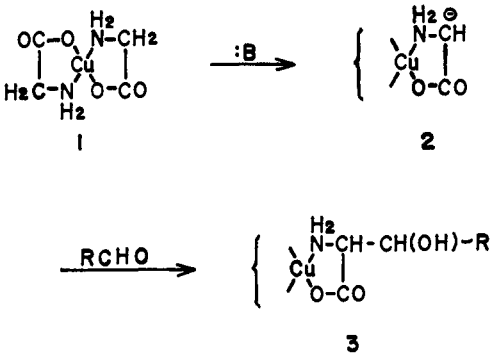
Table I. Reactions of *N*-Pyruvylideneglycinatocopper(II) (**5**) with Some Aldehydes[a]

R (R-CHO)	Molar ratio (R–CHO:**5**)	Solvent system	Temp, °C	Period, hr	β-Hydroxy amino acids— Yield, %	Mp, °C dec
p-NO_2Ph (**6**)	1.0	MeOH-H_2O[b]	25	2	80	181
Ph	3.0	MeOH[c]	30	9	67	194.5[f]
Me (**9**)	1.5	H_2O[d]	30	5	82[e]	
$(Me)_2CH$ (**10**)	3.0	MeOH[c]	30	7	75	226[g]

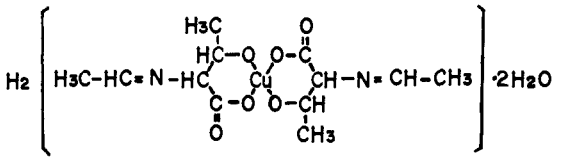
[a] All the reactions were carried out by the use of 10 mmol of **5**. [b] The pH of the reaction mixture was maintained at 9.0 by the dropwise addition of 2 *N* aqueous sodium hydroxide solution. [c] To the methanol (40 ml) solution, 7 ml of 1 *N* methanolic sodium methoxide solution was added. [d] The pH of the reaction mixture was maintained at 9.5 by the dropwise addition of 2 *N* aqueous sodium hydroxide solutions. [e] Determined by amino acid analysis with a Hitachi KLA-3B amino acid analyzer; almost negligible glycine was detected in this case. [f] J. P Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, p 2606. [g] See footnote *f*, p 2589.

on the nitrogen atom in the course of the reaction. It actually seems to be invalid to explain the process of the reaction and the remarkable difference in the reactivity between acetaldehyde[1] and its α-substituted derivatives[3] by the mechanism shown in Scheme I. These results led

Scheme I



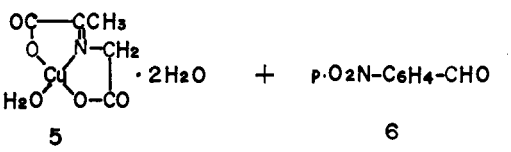
us to one idea that protecting the amino group of **1** with a proper carbonyl compound might have a favorable effect on the reaction.

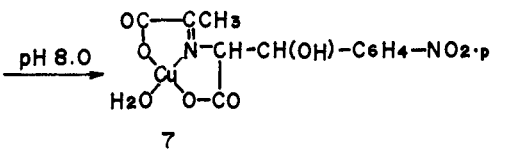


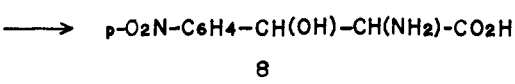
The following advantages are expected. (1) Formation of a copper complex with a Schiff base type chelating ligand may result in enhancing the degree of dissociation of the α hydrogens, thus permitting the reaction to be carried out under more weakly basic conditions. (2) A lower molar ratio of aldehyde to complex may be permitted, compared to the excess of aldehyde (4–10 mol) which has usually been utilized in the reaction with **1**.[1-3] (3) The reaction with labile or stereochemically bulky aldehydes may smoothly proceed even under weakly basic conditions.

On the basis of the above assumptions, the present authors made an attempt at applying the complex (**5**)[7] of copper(II) with the Schiff base derived from glycine and pyruvic acid in place of **1**. In the present communication we wish to report on the reaction of **5** with *p*-nitrobenzaldehyde (**6**), etc., for the syntheses of β-hydroxy amino acids.

(7) A. Nakahara, H. Yamamoto, and H. Matsumoto, *Bull. Chem. Soc. Jap.*, 37, 1137 (1964).







An aqueous methanol ($MeOH:H_2O$ = 2:1, 30 ml) suspension of **5** (2.6 g, 10 mmol) and **6** (1.5 g, 10 mmol) was stirred at room temperature under nitrogen for 2 hr, keeping the pH of the suspension at 9.0 by the addition of 2 *N* aqueous sodium hydroxide solution during the reaction period. After the reaction, the resultant solution was acidified with 3 *N* acetic acid (pH 5.0), and the copper was subsequently removed by treating the solution with hydrogen sulfide gas followed by filtration. The filtrate was treated on a column of Amberlite IR-120B (H form) to adsorb β-(*p*-nitrophenyl)-DL-serine (**8**) and the column was washed with distilled water. **8** was eluted with 0.5 *N* aqueous ammonia, and the effluent was evaporated to a volume of about 5 ml under diminished pressure below 40°, and ethanol (10 ml) was added to the residue to give crystalline **8**, mp 181° dec, in 80% yield. One recrystallization from aqueous methanol gave a pure specimen, mp 182° dec. *Anal.* Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.43; N, 12.39. Found: C, 47.75; H, 4.47; N, 12.30. The specific absorptions of the nitro group are present at 1335 and 1550 cm^{-1}. Glycine and other amino acids could not be detected by thin layer chromatography.

In an attempt to isolate the resultant complex (**7**) by adjusting the pH of the resultant reaction mixture with 2 *N* hydrochloric acid at 3.5, followed by filtration or centrifuging, and by washing with ethanol, pale blue crystals, mp 185° (dec with evolution of gas), were obtained. *Anal.* Calcd for $C_{12}H_{12}N_2O_5Cu$: C, 38.36; H, 3.22; N, 7.45. Found: C, 38.61; H, 3.65; N, 7.33. The specific absorptions of the nitro group are present at 1355 and 1520 cm^{-1}.

Results obtained similarly by the reaction of **5** with benzaldehyde, acetaldehyde (**9**), and isobutylaldehyde (**10**) are summarized in Table I along with the reaction

conditions applied. As seen from the table, **9** and **10**, which are susceptible to self-condensation under basic conditions, gave DL-threonine and β-hydroxy DL-leucine in good yield, even under these mild reaction conditions.

Detailed investigations of this reaction and those with complexes composed of other metal species and the application of these complexes to the synthesis of polyhydroxy amino acids and related compounds are now in progress in our laboratory.

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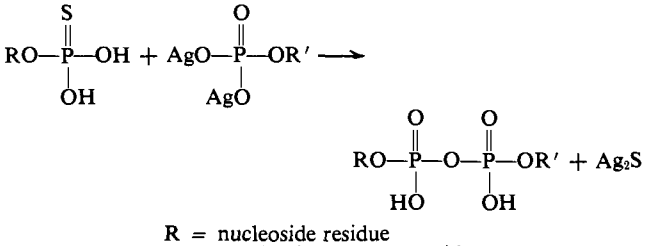
Synthesis of Nucleotide Coenzymes *via* Nucleoside 5′-Phosphorothioate Intermediates

Sir:

Unsymmetrical diesters of pyrophosphoric acid, to which class the nucleotide coenzymes belong, have been synthesized *via* nucleoside phosphoromorpholidates,[1] phosphoroimidazolidates,[2] phosphorochloridates,[3] diphenylphosphoric anhydrides,[4] and *S*-ethyl phosphorothioates.[5] We now wish to report a synthesis of nucleotide coenzymes *via* nucleoside 5′-phosphorothioate intermediates as shown in the following equation.



R = nucleoside residue
R′ = nucleoside or sugar residue

When 1 equiv of the bis[tri-*n*-butyl]ammonium salt of 2′,3′-*O*-dibenzoyluridine 5′-phosphorothioate[6] was treated with 1.2 equiv of the disilver salt of α-D-glucose 1-phosphate in dry pyridine at room temperature for 5 hr, uridine diphosphoglucose (UDPG) [$\lambda_{max}^{H_2O}$ 262 mμ (ε 10,000)] was isolated in 70% yield as the dilithium salt after removal of protecting group.

According to this method, uridine diphosphogalactose (UDPGal) [$\lambda_{max}^{H_2O}$ 262mμ (ε 10,000)], flavin adenine dinucleotide (FAD) [$\lambda_{max}^{H_2O}$ 264, 375, 450 mμ; $\lambda_{260}/\lambda_{375} = 4.00$; $\lambda_{375}/\lambda_{450} = 0.95$; $\lambda_{260}/\lambda_{450} = 3.80$], P^1-*p*-nitrophenyl P^2-uridine 5′-pyrophosphate [$\lambda_{max}^{H_2O}$ 267 mμ (ε 14,000)], P^1-*p*-nitrophenyl P^2-adenosine 5′-pyrophosphate [$\lambda_{max}^{H_2O}$ 262 mμ (ε 18,400)], and P^1-*n*-butyl P^2-adenosine 5′-pyrophosphate [$\lambda_{max}^{H_2O}$ 260 mμ (ε 15,400)] were obtained in 63, 51, 86, 54, and 61% yields, respectively. The structures were confirmed by paper electrophoresis, paper chromatograms, and ultraviolet spectra, and by detection of the corresponding nucleotides on hydrolysis.

It is noted that this method has three advantageous points, namely: (1) no symmetrical diester of pyrophosphoric acid was detected when only 1.2 equiv of disilver salt of nucleotide was treated with 1 equiv of nucleoside 5′-phosphorothioate; (2) satisfactory yields of nucleotide coenzymes and their analogs are maintained even when the relatively insoluble disilver salts of nucleotides, such as flavin mononucleotide (FMN), are empolyed; (3) these coenzymes and their analogs can be prepared on a relatively large scale by conventional organic techniques.

A complete report of these results will be published later.

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MINDO/2 Study of the Cope Rearrangement

Sir:

As Doering and Roth[1] first pointed out, the Cope rearrangement of biallyl (I) can take place by either of two geometrically distinct reaction paths, the corresponding transition states II and III being analogous to the chair and boat forms of cyclohexane. The reaction is of considerable topical interest since, whereas both processes are "allowed" in terms of arguments based on the conservation of orbital symmetry,[2,3] that proceeding *via* II should be favored in terms of the treatment of electrocyclic reactions based on aromaticity of the transition state,[5] for the interaction between the AO's of the "para" carbon atoms, a and b, in III is predicted to be antibonding. The course of the reaction indicates[1] that the transition state does indeed have the "chair" geometry II.

Recent work[6] in these laboratories has led to the

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(6) (a) F. Eckstein, *ibid.*, **88**, 4292 (1966). (b) Uridine 5′-phosphorothioate was first prepared by Eckstein[6a] by way of thiophosphorylation using triimidazolyl-1-phosphine sulfide. In this experiment, the nucleoside 5′-phosphorothioates were conveniently prepared in high yields (73–89%) from nucleosides and thiophosphoryl chloride by modification of Murray's method.[7]
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(3) In a recent review,[4] Woodward and Hoffmann tried to account for the differences in energy between II and III in terms of orbital correlations during hypothetical dimerizations of two allyl radicals. This rather forced explanation is open to several obvious criticisms; in any case, it is clear that no simple interpretation is possible in terms of orbital correlations during the rearrangement of I.
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(5) M. J. S. Dewar, *Tetrahedron, Suppl.*, **8** (1), 75 (1966); article in "Aromaticity," Special Publication No. 21, The Chemical Society, London, 1967, p 177; "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 335.
(6) (a) M. J. S. Dewar and E. Haselbach, *J. Amer. Chem. Soc.*, **92**, 590 (1970); (b) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **92**, 3854 (1970); (c) M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **91**, 7521 (1969).