Polymerization by Oxidative Coupling. V. Catalytic Specificity in the Copper–Amine-catalyzed Oxidation of 2,6-Dimethylphenol[1a]

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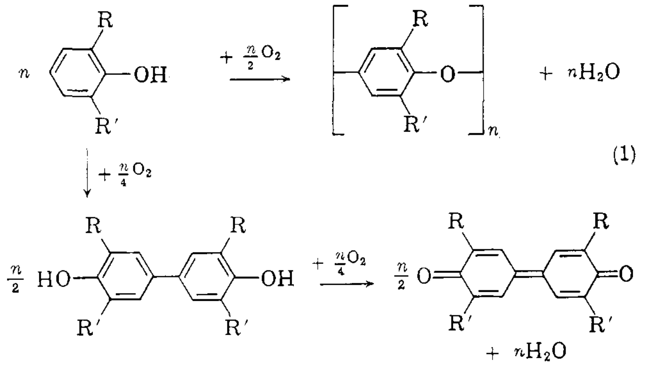
A study was made of the influence of certain reaction variables on the relative rates of carbon–oxygen and carbon–carbon coupling in the oxidation of 2,6-dimethylphenol in the presence of homogeneous catalysts derived from copper(I) chloride and pyridine, in solution under oxygen (one atmosphere). With all other conditions held constant, the relative coupling rates are little affected by variation of the 2,6-dimethylphenol or copper(I) chloride concentrations. However, C–O coupling is markedly favored relative to C–C coupling by an increase of the ligand ratio [molar ratio of pyridine to copper(I) chloride] at constant copper(I) chloride concentration, or an increase of the catalyst concentration at constant ligand ratio. Increasing temperature or use of the sterically hindered ligands quinoline or 2,6-lutidine favors C–C coupling, but there is little effect of solvent dielectric constant in the range 2.3–7.5. An explanation of catalytic specificity in this system is advanced, which involves catalytic activity by two copper–amine complexes, differing in coördination number with respect to the ligand. It is proposed that the complex with the lower coördination number catalyzes predominantly C–C coupling, while that with the higher coördination number is specific for C–O coupling.

Previous papers in this series have been concerned with the scope of the oxidative coupling of 2,6-disubstituted phenols in the presence of copper–amine catalysts,[2,3] and with the problem of over-all mechanistic type in the polymerization *via* carbon–oxygen coupling.[4] It was demonstrated[3] that in a series of 2,6-dialkyl substituted phenols, two different types of product tend to form, depending on the bulk of the substituents R and R′ (equation 1).



(1)

With larger groups, such as *t*-butyl, carbon–carbon coupling predominates and tetrasubstituted diphenoquinones are produced *via* intermediate dihydroxydiphenyl derivatives. On the other hand, with smaller substituents, such as methyl, a facile carbon–oxygen coupling can occur, resulting in poly(2,6-dialkyl-1,4-phenylene ethers) of high molecular weight. It will be shown in the present paper that C–O and C–C coupling can be competitive reactions even in the oxidation of 2,6-dimethylphenol, and that their relative rates are very sensitive to certain reaction conditions. It is believed that an examination of the dependence of the relative coupling rates on the conditions is desirable, not only from the point of view of synthetic utility, but also because this system is a novel example of transition metal coördination catalysis in homogeneous solution.[5] Further, as a phenol oxidation with a catalytic system involving a copper–nitrogen coordinate linkage, a study of this system might help to clarify the mechanism of the action of certain important enzymes of the oxidase type.[6,7] Indeed, it recently has been reported[8] that an enzyme of this type converts 2,6-dimethylphenol into 3,5,3′,5′-tetramethyldiphenoquinone in 30% yield. The oxidation of phenol itself in methanol solution using a morpholine–copper(II) acetate catalyst has already been very well studied.[9] We believe that the study of 2,6-dimethylphenol in the present system can shed considerable further light on the subject, owing to the relative simplicity of the reaction sequence and products, and the high degree of specificity that can be achieved.

Experimental

Copper(I) chloride, pyridine, and 2,6-dimethylphenol were purified as described previously.[4] Quinoline (Eastman Synthetic), 2,6-lutidine, chlorobenzene, and *o*-dichlorobenzene (all Matheson Coleman and Bell) were fractionally redistilled, retaining constant-boiling middle fractions. Gas chromatographic analysis of the *o*-dichlorobenzene indicated that a considerable amount of the *meta* isomer was still present after such treatment. Benzene (Mallinckrodt AR) was used without further purification.

All oxidation experiments reported here were carried out in closed systems in stirred constant-temperature water baths, permitting quantitative measurement of the rate and extent of oxygen absorption. The reaction vessel was constructed from a 60/50 standard taper ground glass joint. The female half was rounded into a vessel of 40–80-ml. liquid capacity, and fitted with a 10/30 female joint at the side to receive a small self-contained dropping funnel. The male half was fashioned into a vessel head, with two 10/30 female joints to receive gas inlet or exit tubes and a port at the center to accommodate the shaft of a Vibro-Mixer stirrer. The latter was connected to the port with short overlapping sleeves of vinyl tubing, making a gas-tight but flexible seal. Volume changes in the system were measured and atmospheric pressure maintained with a 100-ml. capacity gas

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[1] (a) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961; (b) Chemistry Department, Cornell University; (c) Capacitor Department, General Electric Company, Hudson Falls, N. Y.

[2] A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Am. Chem. Soc.*, **81**, 6335 (1959).

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[5] Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, Division of Inorganic Chemistry, Symposium on Homogeneous Catalysis and the Reactions of Coördinated Ligands.

[6] W. D. McElroy and B. Glass, ed., "Copper Metabolism," Johns Hopkins Press, Baltimore, Md., 1950.

[7] C. R. Dawson and W. B. Tarpley, in "The Enzymes," Vol. II, Academic Press, New York, N. Y., 1951, Chap. 57.

[8] S. M. Bocks, B. R. Brown, and A. H. Todd, *Proc. Chem. Soc.*, 117 (1962).

[9] W. Brackman and E. Havinga, *Rec. trav. chim.*, **74**, 937, 1021, 1070, 1100, 1107 (1955).

buret and reservoir filled with dibutyl phthalate, and a U-tube manometer open at one end to the atmosphere.

The usual procedure was to add the copper(I) chloride, pyridine (as a solution aliquot if the quantity was too small for accurate pipette measurement), and anhydrous magnesium sulfate to the solvent in the vessel (30-ml. solution volume), with the 2,6-dimethylphenol in 10 ml. of solvent in the funnel. After flushing the system with oxygen, the catalyst solution was "preoxidized" by agitation under oxygen for 20–45 min. (longer times are required at the lower ligand ratios). At zero time the monomer solution was run in quickly, with continued vigorous agitation, and the monomer solution was run in quickly, with continued vigorous agitation, and the absorption of oxygen at atmospheric pressure was recorded as a function of time. Reaction was continued in each case until absorption of oxygen had ceased or become very slow.

The products were worked up as follows. Under conditions where no tetramethyldiphenoquinone was detectable, the reaction mixture was poured into four volumes of methanol containing an excess of concentrated hydrochloric acid relative to the copper salt, a procedure which deactivates the catalyst. The precipitated polymer was filtered off, washed with methanol, and resuspended in 5% (vol.) concentrated hydrochloric acid in methanol. After refiltration and rewashing, the polymer was dried superficially under vacuum, redissolved in chloroform, and reprecipitated in 1% (vol.) concentrated hydrochloric acid in methanol. The work-up was completed with a final filtration on a tared sintered glass funnel, washing and drying under vacuum at 65°. Where tetramethyldiphenoquinone was detected, the reaction mixture was chilled and filtered directly. The vessel and residue were washed with a little chloroform, and the residue was air-dried and resuspended in dilute aqueous hydrochloric acid (to dissolve magnesium sulfate and any residual copper salts). The finely crystalline red product was filtered onto a tared funnel, washed with distilled water, and dried under vacuum at room temperature. The first filtrate was added to four volumes of 1% lithium chloride in methanol, and the precipitated polymer filtered onto a tared funnel, washed with methanol, and dried under vacuum at room temperature. Hydrochloric acid was not normally used in the work-up of such polymers since it sometimes led to a darkening of the color of the suspension, and the reprecipitation was omitted in order to minimize solubility losses of these low polymers. It was found that the infrared spectra of polymers worked up in this way were not significantly changed after reprecipitation in methanol containing hydrochloric acid.

Intrinsic viscosities were measured in Ubbelohde dilution viscometers in chloroform solution at 25°, using the customary extrapolation of several values of the reduced viscosity to zero concentration.

Infrared spectra were recorded with a Beckman IR-7 grating instrument, as differential spectra of 1.5% solutions (wt./vol.) in carbon disulfide in 0.5-mm cells, or as potassium bromide disks.

Results and Discussion

The particular system chosen for study was the oxidation of 2,6-dimethylphenol in solution under oxygen gas at atmospheric pressure, using as catalysts complexes derived from copper(I) chloride and pyridine or certain derivatives. Data concerning the effects on the relative rates of carbon–oxygen and carbon–carbon coupling were obtained for the following variables: (1) concentrations of phenol, copper salt and amine ligand, (2) temperature, (3) dielectric constant of the medium, and (4) steric hindrance in the ligand. Although pyridine can be used as both ligand and solvent for the reaction, it was necessary in the examination of these variables to introduce another solvent. In most of this work *o*-dichlorobenzene was used, since it is inert as far as coördination with copper ions is concerned, and a reasonably good solvent for both the catalytic complexes and the C–O coupled polymeric products. It was soon found that one of the most critical and interesting variables is the ligand ratio, or stoichiometric molar ratio of amine ligand to copper salt. When attempts were made to extend the study into the region of low ligand ratios, where the concentration of amine is relatively low, difficulties were encountered with auto-retardation effects, and frequently complete reaction could not be observed in a reasonable period of time. An example of this is shown in Fig. 1, for an oxidation of 2,6-dimethylphenol at ligand ratio 2.0. It was also frequently observed that separation of another liquid phase or a solid copper salt accompanies autoretardation, suggesting that the effect is due to interference with catalysis by the water formed as reaction product (equation 1). This is confirmed by the fact that the effect can be eliminated by suspending anhydrous magnesium sulfate or other inert drying agent in the reaction mixture (Fig. 1), and this procedure was followed in all experiments at low ratios reported here. At relatively high ligand ratios autoretardation effects have not been observed and a drying agent is unnecessary.

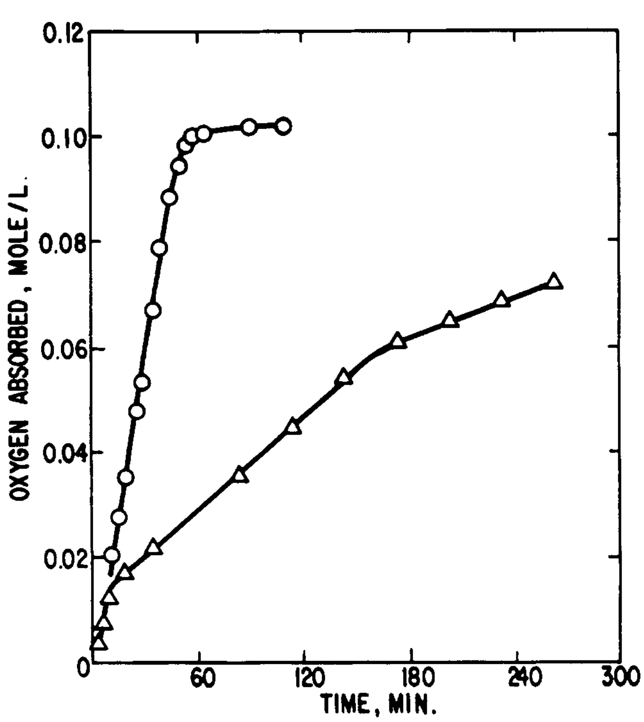

Fig. 1.—Oxidation of 2,6-dimethylphenol (0.2 M) in the presence of 0.01 M copper chloride and 0.02 M pyridine, in *o*-dichlorobenzene at 30°: ○, magnesium sulfate, 0.2 mole/l.; △, without magnesium sulfate.

The effects of ligand ratio (or varying pyridine concentration at fixed copper salt concentration) are summarized in Table I, for values ranging from 0.67 to 2,420. The lower limit represents the minimum ligand ratio required for complete oxidation of copper(I) chloride in inert solvent (to be described in a following publication), while the upper corresponds to pyridine at 0.005 M copper salt. Plots of oxygen absorption *vs.* time for the experiments of Table I are of varying form, and the reaction kinetics are quite complex. Accordingly, the maximum slope of the plot in each case, given as $R_{\max}$ in the tables, is used as a measure of overall reaction rate. The data for per cent oxygen absorption in the tables are calculated on the basis of the stoichiometry of equation 1, and represent reaction times at which absorption has either ceased or become relatively very slow. Over a wide range of ligand ratios the final oxygen absorptions are close to the ideal 100%, but at both low and high ratios an excess is observed which is greater than the experimental uncertainty. The fractional yields of C–O and C–C coupled products (methanol-insoluble polymer and tetramethyldiphenoquinone, respectively) are based on the dry weights of the isolated products, and the weight of 2,6-dimethylphenol originally present. The total yields are seen to be less than quantitative, and this is believed to be due primarily to loss of methanol-soluble low polymer fractions in the workup, and the mechanical losses involved in isolating a few hundred milligrams of material in pure condition. The fractional yield of C–C coupled product is the most reliable measure of relative coupling rates, since the poorly soluble tetramethyldiphenoquinone is filtered directly from the reaction mixture, and losses should be relatively constant. The data are believed to be sufficiently accurate to serve as qualitative measures of the relative coupling rates.[10]

TABLE I

EFFECTS OF VARYING PYRIDINE CONCENTRATION[a]

Pyridine M	Ligand ratio, N/Cu	R_{max} × 10^3, mole $l.^{-1}$ $min.^{-1}$	Oxygen absorbed, %	Fractional yields		Intrinsic viscosity decil. $g.^{-1}$
				f_{C-O}	f_{C-C}	
0.0033	0.67	0.091	107	0.072	0.56	c
.0050	1.0	.206	105	.16	.49	c
.0100	2.0	.662	96.5	.40	.34	0.086
.0150	3.0	1.26	100	.51	.26	.097
.050	10	5.20	99	.75	.10	.17
.50	100	11.4	98.5	.86	0	.49
2.79	558	7.70	99	.82	0	.725
9.00	1800	1.30	108	.785	0	.71
9.00	1800	1.33	111	.79	0	.76
12.1[b]	2420	0.666	109	.80	0	.94

[a] Conditions: 2,6-Dimethylphenol 0.2 M; copper(I) chloride 0.005 M; *o*-dichlorobenzene solvent; 30°. At ligand ratios 0.2 to 100, anhydrous magnesium sulfate was also present at 0.2 mole/l. [b] Pyridine solvent. [c] Insufficient sample for determination.

From the fractional yield data of Table I, and their graphical representation in part in Fig. 2, it is evident that the relative rates of C–O and C–C coupling are profoundly affected by the ligand ratio. Also affected are the maximum rate of oxygen absorption and the intrinsic viscosity of the C–O coupled polymer, as shown in Fig. 3 and 4. (The latter figures are plotted on a semilog scale for the sake of clarity.) At the lowest ligand ratio (0.67) a rather slow reaction leads predominantly to C–C coupling. Increasing the ligand ratio favors C–O coupling at the expense of C–C, so that C–O coupling is dominant at ligand ratio 10 and C–C coupled products are no longer isolated at ligand ratio 100. The over-all rate rises to a maximum in the region of ligand ratio 100, falling off as pyridine becomes the major part of the reaction mixture.[11] The intrinsic viscosity data indicate that the polymers formed along with the C–C coupled product at low ligand ratio are of low degree of polymerization. Increasing ligand ratio causes a rise which levels off at about ratio 500, with a further increase when pyridine is the solvent.[12]

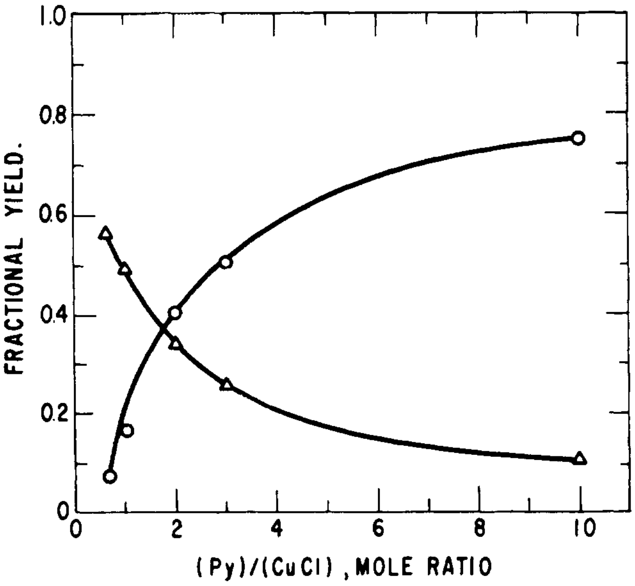

Fig. 2.—Dependence of fraction yields on the ligand ratio (Table I). ○, f,   ; △, f_{C-C}.

Unlike the low polymers formed in the intermediate stages of oxidation of 2,6-dimethylphenol at high ligand ratio,[4] those formed on complete oxidation at low ligand ratio exhibit no absorption in the hydroxyl region of the infrared spectrum. Evidently a molecular termination reaction has occurred in the latter cases. Since C–C coupling takes place simultaneously under these conditions, the possibility emerges that the tetramethyldiphenoquinone or the intermediate dihydroxydiphenyl (equation 1) is functioning as a molecular terminating agent in the C–O coupling polymerization. To test this possibility, 2,6-dimethylphenol was oxidized under conditions favorable for high polymerization, with the dihydroxydiphenyl derivative present as an additive from the start. The experiment of Table I at ligand ratio 558 was repeated with 0.05 M 3,5,3′,5′-tetramethyl-4,4′-dihydroxydiphenyl added with the 2,6-dimethylphenol. The final oxygen absorption was 98% (based on phenol plus diol) with R_{max} = 8.44 × 10^{-3} mole $l.^{-1}$ $min.^{-1}$. An 81% yield of polymer (based on 2,6-dimethylphenol) of intrinsic viscosity 0.86 and an 85% yield of tetramethyldiphenoquinone (based on diol) were recovered. Thus, the oxidations of 2,6-dimethylphenol and its dihydroxydiphenyl derivative appear to have occurred independently, and there is no decrease of the intrinsic viscosity of the polymeric product.

A further important effect on the relative coupling rates is evident in Table II and Fig. 5, where the catalyst concentration is varied at a constant ligand ratio of 1.0 or 2.0. Higher concentrations result in increased over-all rates and favor C–O coupling, with a changeover from mainly C–C to mainly C–O coupling observed in a tenfold variation at ligand ratio 1.0. On the other

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[10] In principle, the fractional yields can be combined with the over-all rate data in the calculation of the "partial rates" of the competing processes, and this was done in a preliminary communication.[1] However, such partial rates can be compared meaningfully under varying conditions only if that step in the reaction sequence which determines the relative coupling rates is also the rate determining step in oxygen absorption. Since this has not been demonstrated, partial rates are not employed in the present paper.

[11] This is probably not a gross medium effect, since the dielectric constants of pyridine and *o*-dichlorobenzene are similar. It is noteworthy that the slow reaction in pyridine is accompanied by a small amount of C–C coupling. The tetramethyldiphenolquinone is not formed in sufficient quantity to separate from the reaction mixture, but it can be observed as a hydrophobic red precipitate if the solution is diluted with water.

[12] This latter effect may be related to the fact that in pyridine solvent a precipitate of polymer and some catalyst separates from the reaction mixture toward the end of the reaction.

hand, variation of the copper(I) chloride concentration at a constant pyridine concentration (0.05 *M*) causes the over-all rate to pass through a maximum, but has little effect on the relative coupling rates, except where the concentration of the copper salt approaches that of the ligand (Table III and Fig. 6). These results can be accounted for as a near balance between two opposing effects, *i.e.*, increasing catalyst concentration and decreasing ligand ratio. The data of Table IV and Fig. 7 show little dependence of the relative coupling rates on the initial concentration of 2,6-dimethylphenol over a sixfold range, at a constant catalyst ligand ratio (3.0).

Table II

Effects of Varying Catalyst Concentration at Constant Ligand Ratios[a]

CuCl *M*	Ligand ratio, N/Cu	$R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}	Intrinsic viscosity decil. g.$^{-1}$
0.005	1.0	0.206	105	0.16	0.49	[b]
.010	1.0	.535	102	.305	.40	0.096
.050	1.0	3.27	101	.465	.18	.16
.005	2.0	0.662	96.5	.40	.34	.086
.010	2.0	2.1	102	.54	.23	.16

[a] Conditions: 2,6-Dimethylphenol 0.2 *M*; anhydrous magnesium sulfate, 0.2 mole/l.; *o*-dichlorobenzene solvent; 30°. [b] Insufficient sample for determination.

Table III

Effects of Varying Copper(I) Chloride Concentration[a]

CuCl, *M*	$R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}	Intrinsic viscosity decil. g.$^{-1}$
0.005	5.20	99	0.75	0.10	0.17
.010	7.35	99	.75	.12	.21
.020	8.25	100	.73	.15	.20
.040	5.71	100	.66	.19	.15
.050	3.27	101	.465	.18	.16

[a] Conditions: 2,6-Dimethylphenol 0.2 *M*; pyridine 0.05 *M*; anhydrous magnesium sulfate, 0.2 mole/l.; *o*-dichlorobenzene solvent; 30°.

Table IV

Effects of Varying Initial 2,6-Dimethylphenol Concentration[a]

2,6-Dimethyl phenol, *M*	$R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}	Intrinsic viscosity, decil. g.$^{-1}$
0.10	0.99	102	0.47	0.18	0.092
.20	1.26	100	.51	.26	.097
.40	2.21	103.5	.565	.27	.098
.60	3.05	108	.58	.29	.12

[a] Conditions: Copper(I) chloride 0.005 *M*; pyridine 0.015 *M*; fanhydrous magnesium sulfate; *o*-dichlorobenzene solvent; 30°.

Table V summarizes data for an increase of temperature from 30° to 60°, with ligand ratio 1.0 at two catalyst concentrations. The higher temperature is seen to favor C–C coupling at the expense of C–O, leading to a change-over from C–O to C–C domination at 0.05 *M* catalyst. However, in the absence of knowledge of the temperature dependence of oxygen solubility in *o*-dichlorobenzene and the effect of oxygen concentration on the relative coupling rates, it is not certain that this observation is purely a temperature effect.

The solvent could conceivably affect the structure of the catalyst or the active complex in the present system in at least two ways: (1) the more active solvents could function as ligands and coördinate with copper ions in the inner sphere, or (2) solvents of relatively weak

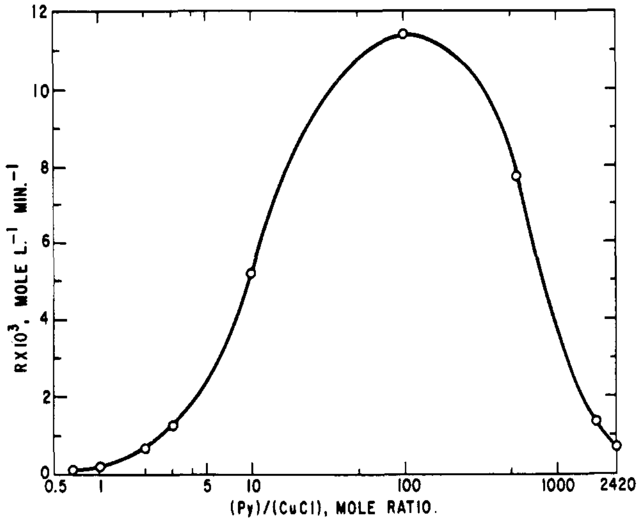

Fig. 3.—Dependence of maximum rate of oxygen absorption on the ligand ratio (Table I).

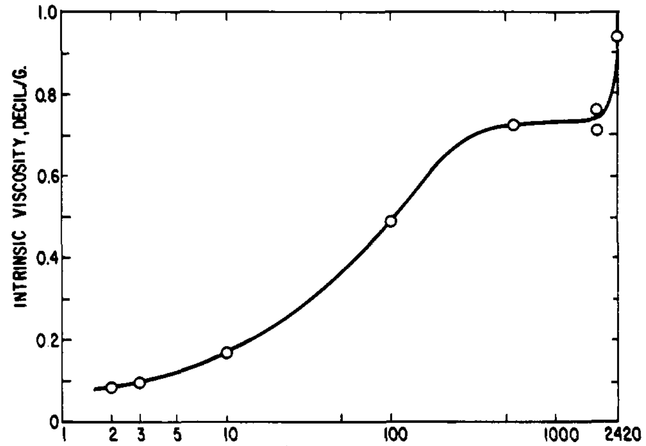

Fig. 4.—Dependence of intrinsic viscosity of C–O coupled polymeric products on the ligand ratio (Table I).

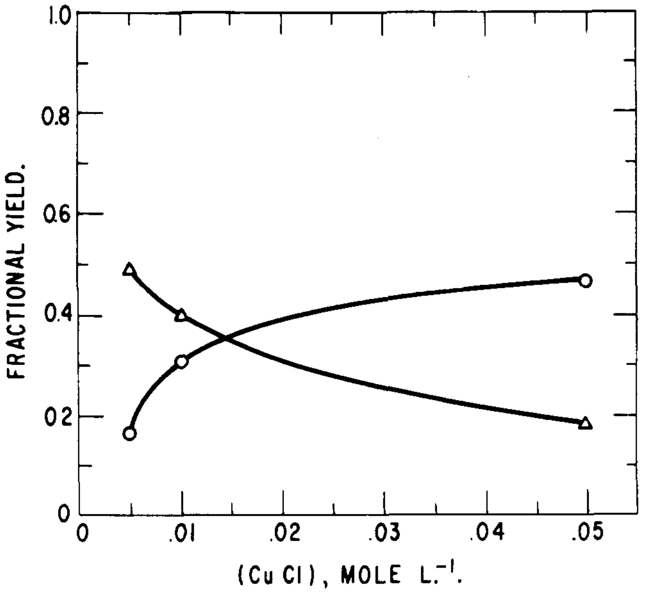

Fig. 5.—Fractional yields as functions of copper chloride concentration, at constant ligand ratio (1.0) (Table II): ○, f_{C-O}; △, f_{C-C}.

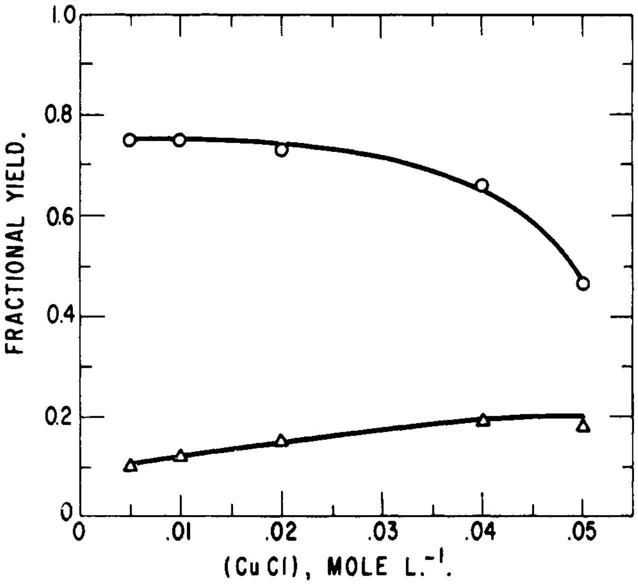

Fig. 6.—Fractional yields as functions of copper chloride concentration, at constant pyridine concentration (0.05 *M*) (Table III): O, f_{C-O}; △, f_{C-C}.

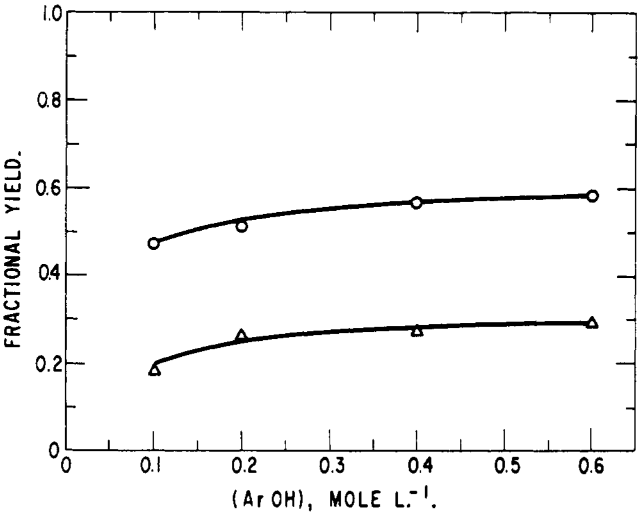

Fig. 7.—Fractional yields as functions of initial 2,6-dimethylphenol concentration, at constant ligand ratio (3.0) (Table IV): O, f_{C-O}; △, f_{C-C}.

Table V

Effects of Varying Temperature[a]

CuCl, *M*	Temp., °C.	$R_{max} \times 10^3$, mole l.⁻¹ min.⁻¹	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}
0.005	30	0.206	105	0.16	0.49
.005	60	.870	102	.01	.75
.05	30	3.27	101	.465	.18
.05	60	7.20	86	.11	.63

[a] Conditions: 2,6-Dimethylphenol 0.2 *M*; ligand ratio 1.0; anhydrous magnesium sulfate, 0.2 mole/l.; *o*-dichlorobenzene solvent.

coördinating power could still play an important role through solvation of the complexes as a whole, the solvents of higher dielectric constant promoting ionic dissociation or ion-pair formation. The first effect seemed too broad in scope for the present investigation, but an attempt was made to assess the importance of the second. The series of solvents benzene, chlorobenzene, *o*-dichlorobenzene offers a moderate range of dielectric constant (2.3–7.5) without strong coördinating ability, and oxidations were carried out in these solvents at ligand ratio 3.0. The results (Table VI) indicate little effect on the relative coupling rates under these conditions.

Table VI

Effects of Varying Solvent Dielectric Constant[a]

Solvent	Dielectric constant	$R_{max} \times 10^3$, mole l.⁻¹ min.⁻¹	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}	Intrinsic viscosity decil. g.⁻¹
Benzene	2.3	0.56	99	0.60	0.35	0.17
Chlorobenzene	5.9	.97	103	.56	.29	.135
o-Dichlorobenzene	7.5	1.26	100	.51	.26	.097

[a] Conditions: 2,6-Dimethylphenol 0.2 *M*; copper(I) chloride 0.005 *M*; pyridine 0.015 *M*; anhydrous magnesium sulfate, 0.2 mole/l.; 30°.

In order to assess the effects of steric hindrance in the ligand, oxidations of 2,6-dimethylphenol were carried out with quinoline or 2,6-lutidine in place of pyridine, with the results summarized in Table VII. Owing to the relatively low reaction rates observed with these ligands compared to pyridine, it was necessary in these experiments to increase the copper(I) chloride concentration to 0.05 *M*. Insufficient data were obtained to determine the precise form of the dependence of the fractional yields on ligand ratio, but comparison data are available at both low and high ratios (1.0 and 55.8). Using the fractional yield of C–C coupled product as the most reliable measure of relative coupling rates, it is seen that at the low ligand ratio both quinoline and 2,6-lutidine favor C–C coupling appreciably in comparison to pyridine. Increasing the ligand ratio favors C–O coupling and results in polymers of higher intrinsic viscosity in each case, although the over-all rate is not enhanced in the hindered examples.

Table VII

Oxidation of 2,6-Dimethylphenol with Pyridine and Derivatives[a]

Ligand	Ligand ratio, N/Cu	$R_{max} \times 10^3$, mole l.⁻¹ min.⁻¹	Oxygen absorbed, %	Fractional yields f_{C-O}	f_{C-C}	Intrinsic viscosity, decil. g.⁻¹
Pyridine	1.0	3.27	101	0.465	0.18	0.16
	55.8	21.3	100	.85	0	1.35
Quinoline	1.0	0.935	105	.48	0.30	.13
	55.8	.53	104	.82	0	1.15
2,6-Lutidine	1.0	1.80	118	.29	0.375	0.08
	10.0	1.54	107.5	.73	0	.205
	55.8	1.98	103	.93	0	.55

[a] Conditions: 2,6-Dimethylphenol, 0.2 *M*; copper(I) chloride 0.05 *M*; anhydrous magnesium sulfate, 0.2 mole/l.; *o*-dichlorobenzene solvent; 30°.

The effects of the variables examined on the relative coupling rates can be summarized as follows. Carbon–carbon coupling is favored by increasing temperature or steric hindrance in the ligand, while carbon–oxygen coupling is favored by increasing ligand ratio or catalyst concentration at constant ligand ratio. The concentration of 2,6-dimethylphenol and the dielectric constant of the solvent have relatively little effect, at least over the ranges examined. Thus, the most critical variables are those which would be expected to affect the structure of the catalytic complex.

It will be shown in a following publication that both C–O and C–C coupling in the present system are brought about by oxidized forms of the copper–amine catalytic system. It is well established that in a solution of a copper salt and a coördinating ligand, various complexes are capable of existence in equilibrium. These will differ in the number of ligand molecules coördinated with the metallic ion, and their relative concentrations will be governed by the stoichiometric concentrations of ligand and metal, and by the various associative equilibrium constants.[13] The results of the present investigation strongly indicate that such equilibria are important here, and constitute the key to catalytic specificity. It is proposed that two copper–amine complexes are catalytically active, differing in coördination number with respect to the amine ligand, and that the complex with the lower coördination number leads predominantly to C–C coupling, and the complex with the higher coördination number leads to C–O coupling. This situation can be represented schematically as in equation 2 where L represents the amine ligand, with these qualifications: the two complexes may actually differ in nuclearity, and the difference in coördination number is not necessarily unity.

$$\begin{tikzcd}
\mathrm{Cu^{II}L}_n + \mathrm{L} \arrow[r, shift left] \arrow[d, "+\ \mathrm{ArOH}"] & \mathrm{Cu^{II}L}_{n+1} \arrow[l, shift left] \arrow[d, "+\ \mathrm{ArOH}"] \\
\mathrm{C{-}C} & \mathrm{C{-}O}
\end{tikzcd} \qquad (2)$$

The other ligands involved in the complexes (chloride, oxide, or hydroxide ions) are omitted for the sake of clarity. Indeed, since both reactions are believed to involve intermediate complexes in which the anion derived from 2,6-dimethylphenol is coördinated with copper, this anion could be shown as a ligand on both sides of equation 2. In any event, this scheme accounts qualitatively for the observed effects of ligand ratio, catalyst concentration and steric hindrance in the ligand.[14] It is believed reasonable to expect that the predominant structures present in oxidized solutions of copper(I) chloride and amines in a noncoördinating solvent should change drastically as the stoichiometric ligand ratio is increased from a low value like 0.67 or 1.0. Succeeding papers will present evidence concerning the structure and role of the catalytic complexes, and the nature of the bond-forming processes in carbon–oxygen and carbon–carbon coupling.

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(13) For the formation constants of pyridine–copper ion complexes in aqueous media, see (a) J. Bjerrum, *et al.*, "Stability Constants of Metal–Ion Complexes," Part I, "Organic Ligands," The Chemical Society, London, 1957, p. 28; (b) B. R. James and R. J. P. Williams, *J. Chem. Soc.*, 2007 (1961).

(14) The decrease in oxidation rate observed with pyridine at high ligand ratio may be due to formation of catalytically inactive complexes of higher coördination number. Both valence states of the copper ion can achieve four-coördination with pyridine (ref. 13.)

The Synthesis of 2-Purin-6-ylaminoethanethiol and Some Related Compounds[1]

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Syntheses of 2-purin-6-ylaminoethanethiol (II), 2-purin-8-ylaminoethanethiol (VI), and 2-(2-pyrimidinylamino)ethanethiol (VII) were achieved by the surprisingly facile catalytic hydrogenolysis of the corresponding disulfides in basic media. An N → S migration of the purin-6-yl group under acidic conditions and a novel formation of 7,8-dihydrothiazolo[2,3-*i*]purine (V) were encountered during development of the hydrogenolysis procedure for II. Compound II was also prepared from purine-6(1*H*)-thione in low yield *via* a rearrangement of the intermediate 6-(2-aminoethylthio)purine (I) under basic conditions.

As an extension of the previously reported series of *S*-substituted derivatives of purine-6-thiol,[2] the preparation of 6-(2-aminoethylthio)purine (I) was attempted by the reaction of purine-6(1*H*)-thione and 2-bromoethylamine hydrobromide in *N*,*N*-dimethylformamide containing potassium carbonate. This effort led to the isolation of pure 2-purin-6-ylaminoethanethiol (II) in low yield (5%), an equal yield of the impure disulfide III, unchanged purine-6(1*H*)-thione, but none of the intended product I. The thiol II reacted positively in the sodium nitroprusside test and showed ultraviolet absorption compatible with that of N^6-alkyladenines[3] and incompatible with that of 6-(alkylthio)purines[2]; it obviously resulted from an intramolecular rearrangement of I. The limited preparative value of this procedure prompted an investigation of other synthetic routes to II and related *N*-(heteroaromatic-substituted) aminoethanethiols.

II. R = H
IV. R = $CH_2C_6H_5$

N^6-[2-(Benzylthio)ethyl]adenine (IV), prepared from 6-chloropurine and 2-(benzylthio)ethylamine, was debenzylated with sodium in liquid ammonia, but the product isolated was apparently a mixture of the desired thiol II and the disulfide III; a pure monohydrate of III was obtained in low yield by dilution of a 2-methoxyethanol solution of the crude product with an equal volume of water. Chu and Mautner[4] performed a

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(2) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).

(3) For example, *cf.* the spectra of N^6-methyladenine [S. F. Mason, *J. Chem. Soc.*, 2071 (1954)].