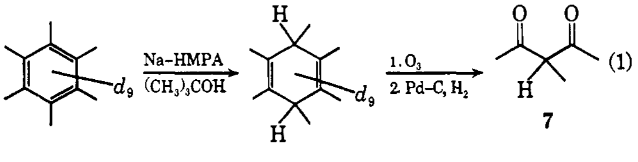
hexamethylbenzenes in having three *adjacent* labeled methyl groups. Degradation of a mixture of **4**, **5**, and **6** to corresponding isotopically substituted 3-methyl-2,4-pentanediones (**7**) by reduction with sodium in hexamethylphosphoramide–*t*-butyl alcohol, followed by ozonolysis, isolates sets of three adjacent methyl groups in separate molecules (eq 1). This degradation does not scramble or exchange methyl groups; hence, mass spectral determination of the proportion of **7** having three labeled methyl groups, followed by appropriate statistical corrections to account for the distribution of labeled methyl groups expected on reduction of each of the hexamethylbenzenes, provides a method of determining the relative yield of **4**.



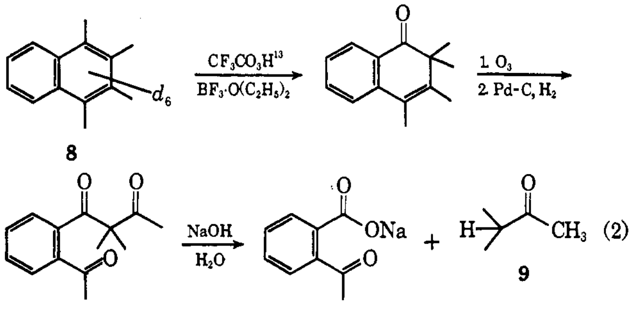
The observed isotopic composition of **7** obtained by degradation of the hexamethylbenzenes from cyclization of **1** with triphenyltris(tetrahydrofuran)chromium(III)[3] is given in Table I, together with the isotopic distribution calculated assuming that the reaction proceeds through a tetramethylcyclobutadiene intermediate and that calculated assuming a concerted cyclotrimerization (or some geometrically equivalent path).[10] Experimental results obtained by a parallel degradation of the hexamethylbenzene from cyclotrimerization of **1** using aluminum chloride in benzene are also included in this table.[11] Comparison of the observed and calculated values shows that no **7**, $(CD_3)_3$ was formed in the chromium-catalyzed reaction beyond that attributable to the isotopic composition of the starting 2-butyne and consequently indicates that within our experimental error no **4** was formed in this cyclization. The close agreement between the isotopic composition observed for the aluminum chloride catalyzed reaction and that calculated on the basis of a cyclobutadiene intermediate provides assurance that the degradation yields reliable results.[12] Taken together, these results exclude a cyclobutadiene intermediate in the cyclotrimerization of 2-butyne over triphenylchromium(III).

Table I. Calculated and Observed Isotopic Compositions (%)[a]

	7, $(CH_3)_3$	**7**, $(CH_3)_2$-(CD_3)	**7**, (CH_3)-$(CD_3)_2$	**7**, $(CD_3)_3$
Calcd: concerted	0.0	48.9	50.5	0.5
Calcd: cyclobutadiene	4.0	44.9	46.4	4.6
Obsd:[b] $(C_6H_5)_3Cr(III)\cdot$3THF	0.0	47.4	52.0	0.6
Obsd:[b] $AlCl_3$	3.7	43.7	48.1	4.5

[a] The starting 2-butyne had isotopic composition corresponding to 98.9% CD_3CH_3 and 1.1% $(CD_3)_2$. The experimental compositions include contributions to the spectra from the approximately 1.1% isotopic impurity (CHD_2) in the CD_3 groups. [b] Experimental error in these values is estimated to be ±0.2%.

We have used a similar approach to demonstrate that a tetramethylcyclobutadiene–chromium complex is not an intermediate in the production of 1,2,3,4-tetramethylnaphthalene (**8**) in the chromium-catalyzed cyclization of 2-butyne. In particular, isolation of sets of *two* adjacent methyl groups from **8**, using the degradation outlined in eq 2, and mass spectral determination of the isotopic composition of **9** have established that no 1,2-dimethyl-3,4-di(methyl-d_3)naphthalene (**10**) is formed in the reaction of triphenyltris(tetrahydrofuran)chromium(III) with **1**.[13,14]



Acknowledgment. We wish to express our thanks to H. L. Mitchell and E. R. Stedronsky for their assistance in obtaining the mass spectral data.

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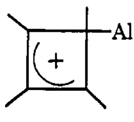
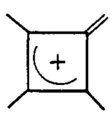
(10) Mass spectra were obtained using a nominal ionizing voltage of 8.3 eV: K. Biemann, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill Book Co. Inc., New York, N. Y., 1962, p 223 ff.

(11) W. Schäfer and H. Hellmann, *Angew. Chem. Intern. Ed. Engl.*, 6, 518 (1967).

(12) The aluminum chloride catalyzed cyclizations were carried out at 100°. Since hexamethyl(Dewar benzene) can be isolated from this reaction under milder conditions, this result is expected. Whether tetramethylcyclobutadiene is actually an intermediate in this reaction is presently a moot question since, *e.g.*, a cyclobutenyl cation of type i offers an equally satisfactory rationalization of our labeling results. However, the mass spectral data do indicate that no appreciable scrambling of deuterium between labeled and unlabeled methyl groups takes place during this cyclization. Hence cation ii is *not* an intermediate.



i



ii

(13) H. Hart and R. K. Murray, *J. Org. Chem.*, **32**, 2448 (1967).

(14) This degradation was checked using an authentic sample of **10**.

(15) National Science Foundation Trainee, 1965–1966; National Institutes of Health Predoctoral Fellow, 1966–1968.

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Received November 14, 1967

The Detection of Apical Interaction in Copper(II) Complexes of Potential Tridentate α-Amino Acids by Optical Rotatory Dispersion[1]

Sir:

Except for a number of studies involving histidine, evidence for apical coordination in copper(II) complexes by potential tridentate ligands is lacking. This communication presents optical rotatory dispersion (ORD) evidence demonstrating that tridentate coordination involving the apical position of copper does occur in a

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(1) (a) Structure and Optical Activity in Metal Complexes. IV. Part III: K. M. Wellman, S. Bogdansky, W. Mungall, and T. G. Mecca, *Tetrahedron Letters*, in press. (b) Reported in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract O-37.

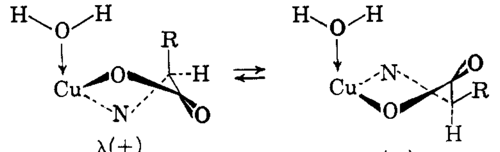
Table I. d–d Cotton Effect Amplitudes ($([\phi]_{1:\mathrm{Gly}:1})$[a]) for Some Mixed 1:Gly:1 Copper(II) Complexes

Compd	Acid	$[\phi]_{1:\mathrm{Gly}:1} \times 10^2$ pH 8[b]	$[\phi]_{1:\mathrm{Gly}:1} \times 10^2$ pH as indicated
1a	L-2-Aminobutanoic	−3.60	−3.60 (10.1)
1b	L 2-Aminopentanoic	−3.83	−3.8 (10.1)
2a	L-2,4-Diaminobutanoic	+28.2 (8.6)	+29.2 (10.1)
2b	N^4-Benzoyl-L-2,4-diaminobutanoic	Negative (7)[c]	
3	4-Amide of L-2-aminobutanedioic	−2.1	+10.8 (11.2)
4	L-2,5-Diaminopentanoic	−1.85 (7.3)	+12.5 (10.1)
5	N^5-Benzoyl-2,5-diaminopentanoic	−3.96	−3.92 (10.2)
6	L-2,6-Diaminohexanoic	−3.20	−3.20 (10)
7	N^6-Benzoyl-L-2,6-diaminohexanoic	−3.92	−3.92 (10.2)
8	L-2-Aminobutanedioic	−1.72	−1.72 (11.2)
9	L-2-Aminopentanedioic	−3.00	−2.92 (11.1)
10	L-2-Amino-4-hydroxybutanoic	−3.65	
11	L-2-Amino-5-guanidopentanoic	−3.16	−2.24 (10.5)

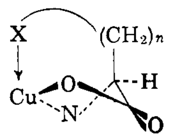
[a] Expressed in molecular rotation units according to the relation $[\phi] = [\alpha] \times$ molecular weight/100; see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 9. All amino acids used in this work were obtained from Sigma Chemical Co. The benzoylated compounds were prepared according to A. C. Kurtz, *J. Biol. Chem.*, **180**, 1253 (1949). [b] Unless otherwise indicated. [c] Precipitation, even at 10^{-5} *M*, precluded a quantitative determination.

number of multidentate amino acids. Furthermore, such behavior is found to be a sensitive function of ring size, pH, and the heteroatom, X (defined below).

An important consequence of the ring-conformation hypothesis[2] is that an α-amino acid substituted with a heteroatom X (*e.g.*, $HOOCCHNH_2(CH_2)_nX$), capable of coordinating with the apical position, may disturb the conformational equilibrium (λ ⇄ δ) in favor of an increased λ population (see I) with a concomitant shift in the observed Cotton effect amplitude toward more positive values. Simple amino acids such as **1a** and **1b** in Table I exhibit negative Cotton effects[3] for their mixed 1:Gly:1 complexes.[4] In contrast, L-2,4-diaminobutanoic acid (**2a**, Table I) and L-histidine[2] give positive Cotton effects over the pH range 4–11. In these latter two cases, apical coordination *via* the ω-amino group apparently dominates the ORD spectrum even at low pH.[5] On the other hand, certain potential tridentate complexes (see **5**, **7**, and **10** in the table) exhibit a negative Cotton effect at pH 8 similar in magnitude to that observed for the model compounds **1a,b** while several of the amino acids, notably **3**, **4**, **6**, **8**, **9**, and **11**, exhibit negative but significantly weaker Cotton effects than those of **1a,b** (column 3 of Table I). The diminished amplitudes imply that appreciably larger amounts of the positively rotating conformer are present compared with the model compounds. The shift toward more positive Cotton effect amplitudes can reasonably be attributed to apical coordination *via* the ω heteroatom. This conclusion draws support from the fact that two of these compounds (**3** and **4**) show a striking Cotton effect inversion to positive values at high pH (compare columns 3 and 4 in Table I). The difference between consistently negative [(**1b**)(Gly)Cu^{II}], consistently positive [(**2a**)(Gly)Cu^{II}], and pH-dependent, inversional behavior [(**3**)(Gly)Cu^{II} and (**4**)(Gly)Cu^{II}] is shown in Figure 1. Judging from the pH required for inversion, the coordinating ω group is the free amino group in **4** and the CONH⁻ in **3**.



λ(+) δ(−)



I(λ, +)

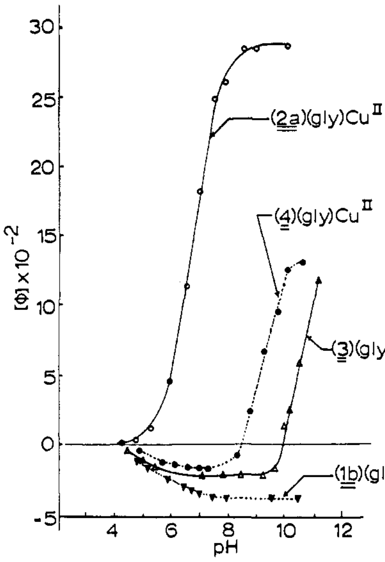


Figure 1. The d–d Cotton effect amplitude, [φ], as a function of pH for several mixed 1:Gly:1 complexes: (L-2,4-diaminobutanato)-(glycinato)copper(II) ≡ (**2a**)(Gly)Cu^{II}; (L-2,5-diaminopentanato)-(glycinato)copper(II) ≡ **4**(Gly)Cu^{II}; (L-asparaginato)(glycinato)-copper(II) ≡ (**3**)(Gly)Cu^{II}; and (L-2-aminopentanato)(glycinato)-copper(II) ≡ (**1b**)(Gly)Cu^{II}.

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(2) K. M. Wellman, W. Mungall, T. G. Mecca, and C. R. Hare, *J. Am. Chem. Soc.*, **89**, 3647 (1967).

(3) For other examples of normal behavior see K. M. Wellman, T. G. Mecca, W. Mungall, and C. R. Hare, *ibid.*, **89**, 3646 (1967).

(4) The mixed complexes used in the present work are the (α-substituted glycinato)(glycinato)copper(II) complexes, hereafter referred to as 1:Gly:1 complexes. The method of preparation and spectral measurements are reported in ref 2.

(5) Work in these laboratories and elsewhere[6] has clearly established that the ω-substituted α-amino acids used in this work coordinate *via* the α-amino acid grouping in the square-planar positions of copper(II).

(6) (a) G. R. Brubaker and D. H. Busch, *Inorg. Chem.*, **5**, 2110 (1966); (b) J. H. Ritsma, G. A. Wiegers, and F. Jellinek, *Rec. Trav. Chim.*, **84**, 1577 (1965), and references therein.

From the foregoing observations several important conclusions can be drawn. First, copper(II) does promote tridentate behavior in some multidentate amino acids. Second, apical coordination is sufficiently important that it occurs to an appreciable extent even when seven- and eight-membered chelate rings result (see compounds **4**, **6**, and **11**). Finally, ORD spectroscopy is a particularly sensitive tool for detecting apical coordination in these complexes.

Acknowledgment. We wish to thank the U. S. Public Health Service (1 RO1 GM 13,692-01) and the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

[7] National Science Foundation Undergraduate Research Participant.

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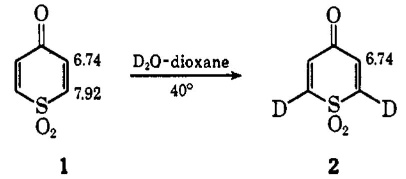
Received August 9, 1967

Deuterium Substitution in the 4H-Thiopyran-4-one 1,1-Dioxide System[1]

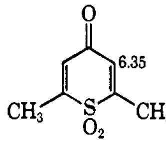
Sir:

The capability of 4-pyrones and 4-pyridones to undergo deuterium exchange under selected conditions has been recently recognized.[2,3] Interestingly, whereas exposure of 4-pyrone to deuterium oxide at 98° for 26 hr results in exchange exclusively at the 3,5 (α-carbonyl) positions,[2] treatment of N-methyl-4-pyridone with 0.5 *N* sodium deuterioxide at 100° for 12 hr produces exchange only at the 2,6 positions.[3] The origin of the contrary course of these deuterations has been attributed to the intervention of different mechanisms. Thus, the formation of ring-opened intermediates has been implicated in the pyrone example and reactive ylides produced by vinyl proton abstraction have been proposed for the pyridone series. In this communication we wish to present evidence concerning specific deuterium exchange in 4H-thiopyran-4-one 1,1-dioxides. This system has been studied in an effort to evaluate the effects imparted to such six-membered heterocycles by two powerful, but opposed, electron-withdrawing groups.



1 **2**

When a solution of **1**[4] in neutral dioxane–deuterium oxide (3:1) was maintained at 40° for 16 days,[5] there could be recovered in 60% yield a highly crystalline yellow solid which was shown by spectroscopic criteria and deuterium analysis (falling drop method[6]) to be the 2,6-d_2 counterpart of **1** (**2**). The rather low recovery reflects difficulties encountered in isolation and purification of this substance,[5] since subsequent kinetic runs (see below) indicated only minimal decomposition of **1** under these conditions. The positions of the deuterium atoms in **2** were suggested by comparison of the chemical shifts (δ units, $CDCl_3$) of the protons in **1** and **2** with those observed for **3**,[7] **4**,[8] and **5**.[9] Whereas the nmr spectrum of **1** consists of two doublets (J = 12.0 Hz) of equal area at 7.92 and 6.74 ppm, that of **2** consists of a broadened singlet at 6.74 ppm and only minor absorption in the 7.92-ppm region.



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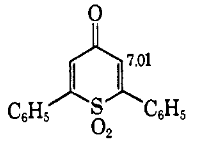

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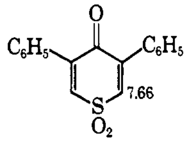

5

The rate of deuteration of **1** in dioxane–D_2O (3:1) at 40° could be conveniently measured by nmr spectroscopy. The pseudo-first-order rate constant was found to be $(4.06 \pm 0.37) \times 10^{-7}$ sec^{-1} on the basis of four runs, each involving at least eleven points.[12] For the purpose of calibration 1,1,4,4-tetramethylcyclobutanedione was employed as an internal standard.[13]

In subsequent experiments, it was established that **3** and **4** do not undergo isotopic exchange in this medium, even after being heated for 2 weeks at 80°. Although **3** and **4** are considerably more heat stable than **1**, they likewise react immediately with base to give tars. The 3,5-diphenyl isomer **5** was also little affected by these conditions; exposure of **5** to this deuterated medium for 2 weeks at 60° resulted in less than 5% deuterium incorporation.

However, addition of 30% aqueous sodium hydroxide to solutions of **5** in acetone or tetrahydrofuran at 30° gave rise instantaneously to deep red solutions which proved to be stable for considerable time. Acidification of these solutions led to the almost quantitative recovery of the keto sulfone. When the same reaction was performed with 30% NaOD–D_2O in acetone-d_6 and the colored solution examined shortly thereafter by nmr, it was seen that the α-sulfonyl protons formerly present in the 7.65-ppm region of the neutral solution were totally absent in the basic medium; rather, the spectrum displayed only the ten-proton phenyl absorption at 7.35 ppm. Acidification of such a solution in

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[1] Unsaturated Heterocyclic Systems. XXXV. For the previous paper in this series, see L. A. Paquette and L. D. Wise, *J. Am. Chem. Soc.*, **89**, 6659 (1967).

[2] (a) P. Beak and G. A. Carls, *J. Org. Chem.*, **29**, 2678 (1964); (b) D. W. Mayo, P. J. Sapienza, R. C. Lord, and W. D. Phillips, *ibid.*, **29**, 2682 (1964).

[3] P. Beak and J. Bonham, *Tetrahedron Letters*, 3083 (1964); *J. Am. Chem. Soc.*, **87**, 3365 (1965).

[4] E. A. Fehnel and M. Carmack, *ibid.*, **70**, 1813 (1948).

[5] It must be pointed out that **1** is extremely unstable to base and to most acids; red-brown or black tars invariably result. Furthermore, when solutions of **1** in a variety of solvents (including dioxane–D_2O) are maintained at elevated temperatures (50–100°) for short periods of time, extensive decomposition is also encountered. The keto sulfone **1** is most conveniently purified by sublimation at 120° (0.1 mm), although some loss in weight due to a residue is inevitably encountered.

[6] This analysis demonstrated that 41% of the available protons (*i.e.*, 82% of the 2,6-hydrogens) had been exchanged. The determination was performed by Josef Nemeth, Urbana, Ill.

[7] F. Arndt, R. Schwarz, C. Martins, and E. Arvon, *Rev. Faculti Sci. Univ. Istanbul*, **A13**, 57 (1948); *Chem. Abstr.*, **42**, 4178 (1948).

[8] R. Arndt, P. Nachwey, and J. Pusch, *Chem. Ber.*, **58**, 1633 (1925).

[9] Compound **5** represents the first 3,5-disubstituted 4H-thiapyran-4-one 1,1-dioxide to be reported to date; its synthesis was achieved by the sequence 2,6-dimercapto-3,5-diphenyl-4H-thiopyran-4-one[10] → 3,5-diphenyl-4H-thiopyran-4-one[11] → **5**.

[10] H. Apitzsch, *Chem. Ber.*, **37**, 1599 (1904); **38**, 2888 (1905).

[11] A. Schönberg and R. von Ardenne, *ibid.*, **99**, 3316 (1966).

[12] The limited stability of **1** and **2** in this solvent system at higher temperatures precluded the measurement of activation parameters.

[13] The slight decrease in the relative intensity of the signal at 6.74 (H-3 and H-5) observed at the end of the reaction period was attributed to a small amount of decomposition of **1** and/or **2**.