but the *exo/endo* ratio is still only about 30. This low ratio stands in striking contrast to the one observed for solvolyses,[8] which is $\sim 10^5$ at 25°, and it is concluded *that neighboring group assistance is energetically less favored in the gas phase than in solution.* Two reasons probably do account for this: firstly, neighboring group migration is usually associated with some loss of rotational entropy for the reactant on ring closure to the transition state.[9] This entropy loss, which impedes reactivity, will inevitably be more pronounced in the gas phase than in solution. Secondly, since neighboring group assistance depends, among other factors, critically upon the charge development at the migrating center, the driving force for migration in the gas phase is reduced.

For the solvolysis of the 2-norbornyl chlorides, the *exo/endo* ratio is about 10^2–10^3,[8a,10] *i.e.*, smaller than for I and II, and it is therefore not surprising that *exo*-norbornyl chloride eliminates at a rate even closer to *sec*-butyl chloride in the gas phase.

Finally, it should be noted that the small *exo/endo* ratios of these norbornyl derivatives in the gas phase and the high ratios in solution provide more evidence for a "nonclassical" transition state in the solvolysis of the *exo* isomers, as has been suggested some time ago,[8b-d,11] and, in the light of some recent doubts, reaffirmed.[8a,10]

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The Synthesis of D-Oxytocin, the Enantiomer of the Posterior Pituitary Hormone, Oxytocin[1]

Sir:

The synthesis of the optical antipode of the posterior pituitary hormone oxytocin (Figure 1) has now been completed as part of a general study of the relationship of the stereochemistry of the hormone to its biological activity.

The desired protected nonapeptide amide, N-carbobenzoxy-S-benzyl-D-cysteinyl-D-tyrosyl-D-isoleucyl-D-glutaminyl-D-asparaginyl-S-benzyl-D-cysteinyl-D-prolyl-D-leucylglycinamide, was prepared by the stepwise nitrophenyl ester method,[2] as employed for the synthesis of oxytocin,[3] starting from the protected tripeptide amide, N-carbobenzoxy-D-prolyl-D-leucylglycinamide. Preparation of the latter compound was accomplished

(1) This work was supported in part by Grant HE-01675 from the National Heart Institute, U. S. Public Health Service.

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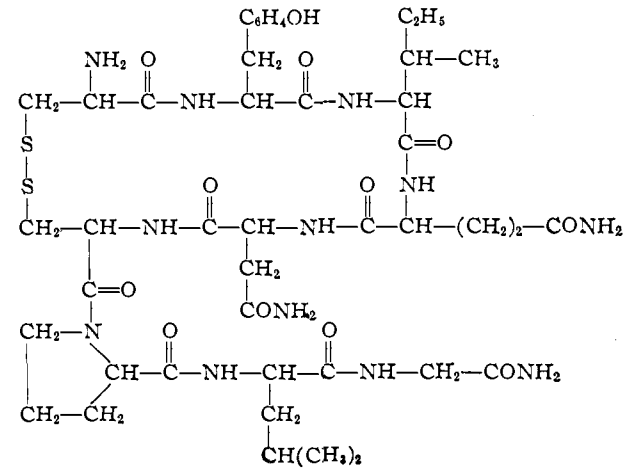

Figure 1. Structure of oxytocin.

by ammonolysis of ethyl N-carbobenzoxy-D-prolyl-D-leucylglycinate, made by the method used by Cash[4] for the synthesis of the L- isomer.[5]

The protected nonapeptide amide possessed m.p. 250–252° and $[\alpha]^{19}D$ +51.2° (*c* 1, dimethylformamide) (*Anal.* Calcd. for $C_{65}H_{86}N_{12}O_{14}S_2$: C, 59.0; H, 6.55; N, 12.7. Found: C, 59.0; H, 6.61; N, 12.6); lit.[3] (L- isomer) m.p. 245–248°, $[\alpha]^{20}D$ −50.5° (*c* 1, dimethylformamide).

The protected nonapeptide amide was treated with sodium in liquid ammonia, as employed in the original synthesis of oxytocin,[6] and the resulting disulfhydryl compound was oxidized in dilute aqueous solution with potassium ferricyanide.[7] After removal of ferrocyanide and ferricyanide ions with the ion-exchange resin AG3X4, in the chloride form, the solution gave a negative reaction to nitroprusside and to Ellman's reagent.[8] This solution of the crude material, on bioassay, did not appear to possess any avian-vasodepressor[9] or oxytocic[10] activity. The solution was concentrated to a small volume and subjected to countercurrent distribution in the system 1-butanol–1-propanol–0.5% aqueous acetic acid containing 0.1% pyridine (6:1:8).[11] The distribution pattern, as detected by determination of the Folin–Lowry color values,[12] was identical with that obtained for oxytocin in the same system. The material obtained from the main peak (K = 0.48) by lyophilization was a white fluffy powder, $[\alpha]^{20}D$ +22.2° (*c* 0.5, 1 *N* acetic acid) *Anal.* Calcd. for $C_{43}H_{66}N_{12}O_{12}S_2 \cdot C_2H_4O_2$: C, 50.6; H, 6.61; N, 15.8. Found: C, 50.2; H, 6.52; N,

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16.1. Oxytocin possesses $[\alpha]^{22.5}D$ −23.1° (*c* 0.51, 1 *N* acetic acid).[13]

A sample was hydrolyzed with 6 *N* HCl at 120° for 20 hr. and analyzed with a Beckman-Spinco amino acid analyzer according to the procedure of Spackman, Stein, and Moore.[14] The following molar ratios were obtained, glycine being taken as 1.0: aspartic acid 1.0, glutamic acid 1.0, proline 1.1, glycine 1.0, leucine 1.0, tyrosine 0.9, cystine 1.0, isoleucine 0.95, alloisoleucine 0.05, ammonia 3.0.

Paper electrophoresis, with pyridine acetate buffer pH 5.6 for 20 hr., showed D-oxytocin to have a mobility identical with that of oxytocin and to travel as a single spot. A similar finding was made when the compound was subjected to paper chromatography in two different solvent systems, 1-butanol–acetic acid–water (4:1:5) and pyridine–acetic acid–water (10:7:3).

No avian-vasodepressor[9] or oxytocic activity[10] was detected upon bioassay of D-oxytocin, whereas oxytocin possesses approximately 500 units/mg. of each of these activities. No indication of an inhibitory effect of D-oxytocin on these activities of oxytocin could be detected.

Recently Yajima and Kubo[15] synthesized D-histidyl-D-phenylalanyl-D-arginyl-D-tryptophylglycine, the enantiomer of which corresponds to positions 6 to 10 of α-melanocyte-stimulating hormone. The L-pentapeptide was found to possess a slight degree of melanocyte-stimulating activity, whereas the D-pentapeptide was found to antagonize the action of its enantiomer as well as that of α-MSH.[15,16] Schröder, *et al.*,[17] have synthesized the D-heptapeptide, glycyl-D-alanyl-D-phenylalanyl-D-valyl-glycyl-D-leucyl-D-methioninamide, the enantiomer of which corresponds to an analog of the heptapeptide sequence of positions 5 to 11 of eledoisin with glycine in place of aspartic acid and valine in place of isoleucine. The D-heptapeptide was reported to have $^1/_{2500}$ of the activity of the L- isomer in lowering the blood pressure of the rabbit. More recently, Stewart and Woolley[18] have synthesized D-bradykinin and found that amounts of this D-nonapeptide up to 50,000 times the standard challenge of bradykinin showed neither any inhibition of the response to bradykinin nor any bradykinin-like effects on the isolated rat uterus, duodenum, and stomach.

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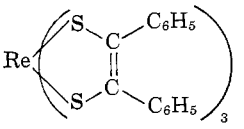
Trigonal Prismatic Coordination. The Molecular Structure of Tris(*cis*-1,2-diphenylethene-1,2-dithiolato)rhenium[1]

Sir:

Since their initial preparation,[2-4] tris complexes of bidentate sulfur ligands have been under intensive study.[4-7] As with the square-planar bis compounds, these systems appear to undergo electron-transfer reactions during which the coordination remains unchanged. In interpretations of the physical properties of these systems, the complexes were assumed to have D_3 symmetry with a distorted octahedral coordination about the central metal.[3,6,8] Because of the activity in this field and the need for a structure determination on which to base the interpretations of other physical measurements, we undertook the structure determination of what is probably a representative example of these compounds, the neutral complex tris(*cis*-1,2-diphenylethene-1,2-dithiolato)rhenium.[9] This communication reports the results of that investigation.



I

Green crystals of I, kindly supplied by G. N. Schrauzer, were examined by precession techniques and found to be triclinic. A Delaunay reduction failed to suggest a higher crystal system. The compound crystallizes in a cell with dimensions $a = 19.73 \pm 0.04$, $b = 11.94 \pm 0.03$, $c = 9.87 \pm 0.03$ Å., $\alpha = 120.1 \pm 0.1$, $\beta = 73.6 \pm 0.1$, $\gamma = 102.5 \pm 0.1$°. The assumption of a center of symmetry (space group $P\bar{1}$) appears justified by the satisfactory agreement ultimately obtained between observed and calculated structure factors. An experimental density of 1.53 ± 0.05 g./cm.^{3}, determined by flotation in zinc chloride solutions, agrees well with a calculated value of 1.572 g./cm.^{3} for two molecules in the unit cell. Thus, all atoms are in general positions and no crystallographic symmetry conditions need be imposed on the molecule.

Intensity data were collected at room temperature from a single crystal with the G.E. XRD-5 goniostat.

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(8) However, Langford, *et al.*,[5] speculated that an "interesting possibility" for the structure might be a "trigonal prismatic, or at least a strongly trigonally distorted, six-coordinate structure."
(9) Previous names for these compounds have included[4] tris(dithiobenzil)metal(0) and tris(*cis*-1,2-stilbenedithiolato)metal(VI). We suggest the present name because it is more descriptive of the ligand; we do not wish to imply that we know the formal charge on the metal atom.