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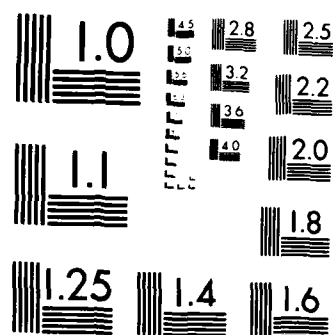
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CHIRAL POLYMERS

Final Report

J. K. Stille

A. I. Meyers

September 1981 - June 1984

U.S. Army Research Office

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Colorado State University

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Chiral vinyl monomers containing the oxazoline units, 2-vinyl-4-methoxy-methyl- and 4-hydroxymethyl-5-phenyloxazoline as well as a chiral oxazoline monomer bearing an acrylate polymerizable group were synthesized. In addition, an acrylamide monomer containing a chiral 1,3-dioxane unit as well as both racemic and (R)- α -methylene- γ -methyl- γ -butyrolactone were synthesized. The vinyloxazoline, 2-vinyl-4-methoxymethyl-5-phenyloxazoline was copolymerized with styrene and divinylbenzene by suspension techniques to give polymer beads ~50 μ in diameter. The oxazoline monomer containing the		

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The styrene-bead copolymers were packed in HPLC columns, but none were especially effective in separating enantiomers in a racemic mixture. The chiral butyrolactone polymer was coated on silica, but this material did not effect resolution of racemic mixtures in an HPLC column.

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INTRODUCTION

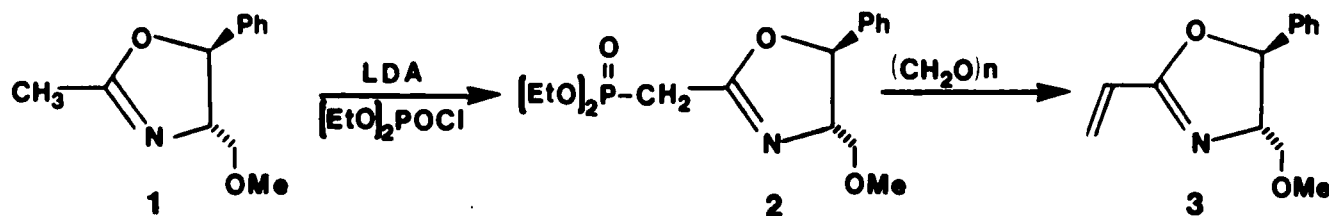
The current trend in synthetic¹ and analytical chemistry toward solid-phase separation and/or syntheses has added new methodology to modern chemical research. Increased efficiency in separations and synthesis are the most important aspects of solid-phase methodology.² The purpose of this research was to prepare chiral polymers by the homo- and copolymerization of chiral monomers. These chiral materials were to be utilized as supports for liquid chromatographic columns in an effort to separate various racemic mixtures, particularly enantiomeric phosphines and other related chiral molecules such as phosphinates.

RESULTS AND DISCUSSION

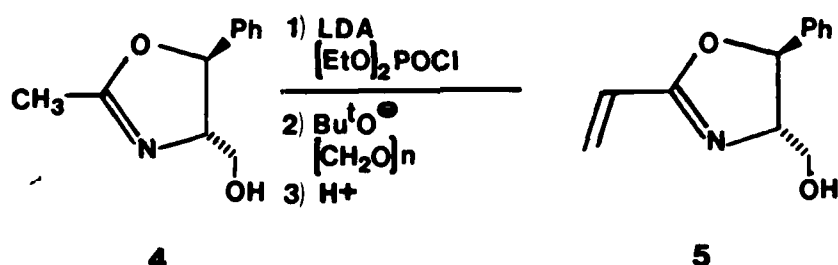
MONOMER SYNTHESIS

Chiral-2-Vinyl Oxazolines.

The successful asymmetric synthesis that had been effected utilizing chiral oxazolines³ prompted the initial efforts to synthesize various chiral 2-vinyl-oxazoline monomers for incorporation into copolymers. The synthesis of a series of 2-alkenyl oxazolines had been worked out,⁴ and this synthetic procedure was improved and scaled up, such that fifty gram batches of 2-vinyloxazoline could be prepared. Conversion of 2-methyloxazoline (1) to the phosphonate (2) on a large scale was accomplished in high yield, and 2-vinyloxazoline was obtained through reaction of the phosphonate with formaldehyde.

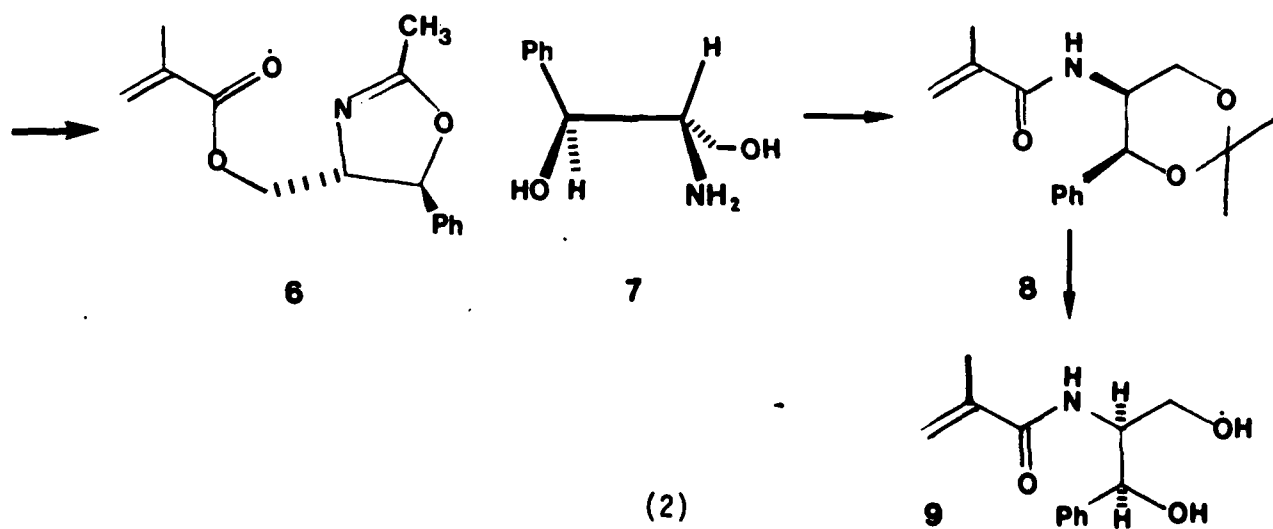


In an effort to obtain a chiral oxazoline-containing monomer that had functionality capable of hydrogen bonding, the vinyloxazoline containing the primary alcohol function (5) was synthesized, by the same procedure, starting with the 4-hydroxymethyl analog (4).



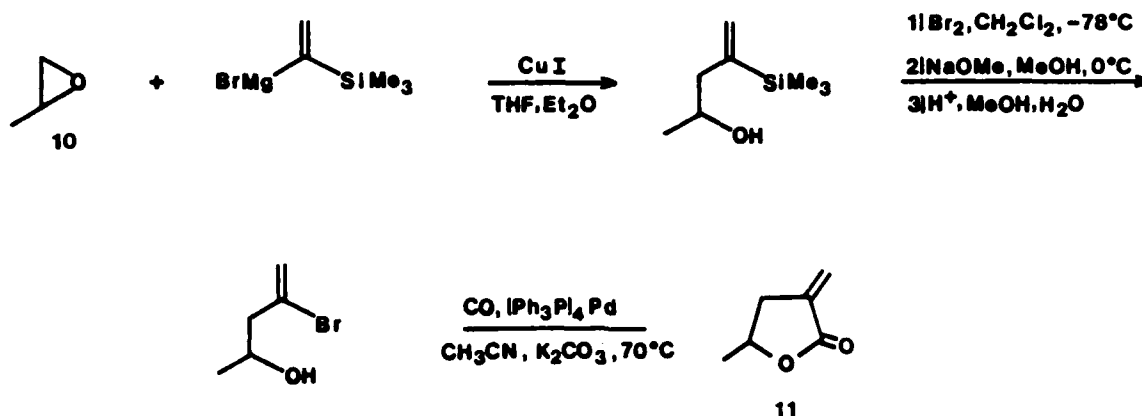
Monomers Containing Chiral Oxazoline or 1,3-Dioxane Groups.

Two other chiral monomers containing polymerizable methacrylate functions were synthesized. The 2-methyl-5-phenyl-4-hydroxymethyl-oxazoline starting material (4) was converted to the methacrylate derivative (6) by reaction with methacryloylchloride. Starting with the commercially available aminodiol (7, used in preparation of oxazolines) the chiral 1,3-dioxane monomer (8) bearing a methacrylamide function was synthesized. Because this monomer could be easily hydrolyzed to 1,3-diol 9, the incorporation of monomer 8 into a copolymer would provide a chiral polymer containing the diol unit via a similar hydrolysis.



α -Methylene- γ -methyl- γ -butyrolactone

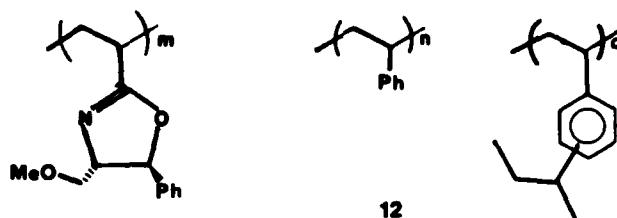
The synthesis of both racemic and chiral α -methylene- γ -methyl- γ -butyrolactone (11) was carried out by a known procedure⁵ starting with either racemic or (R)-propylene oxide (10)⁶. The key step in this synthesis is the palladium catalyzed carbonylation of 4-bromopent-4-en-2-ol. Thus, either racemic or chiral monomer could be obtained pure and in high yield by this procedure.



POLYMER SUPPORTS

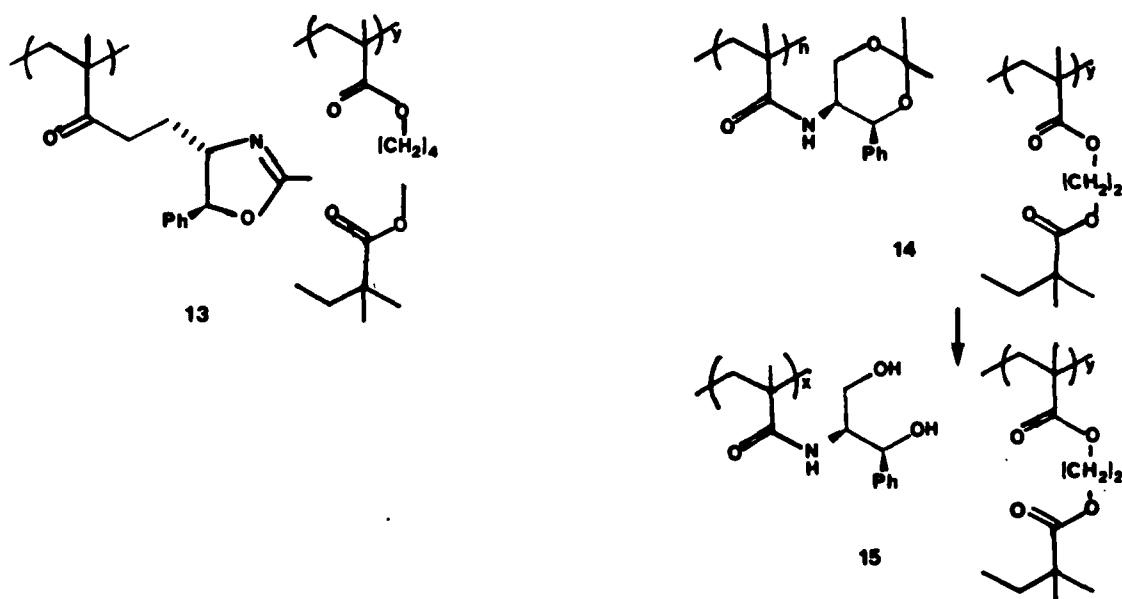
Poly-2-Vinyloxazolines.

Crosslinked random terpolymer beads (12) containing chiral vinyloxazoline 3, styrene and divinylbenzene were prepared by free radical suspension techniques. The size of the beads containing 20 mole percent divinylbenzene could be controlled so that relatively uniform spheres of 20 up to $50\ \mu$ in diameter could be obtained. In samples of these support materials, the incorporation of the vinyloxazoline at 20, 40, and 60 mole percent levels was achieved. Both the elemental analysis and a quantitative determination by ^{13}C nmr, agreed reasonably well for the oxazoline incorporation. Generally the mole ratios of monomers charged were those incorporated into the polymer. Thus, the reactivity ratios of styrene and 2-vinyloxazoline appear to be similar.



Copolymerization of Monomers Containing Chiral Oxazoline or 1,3-Dioxane Units.

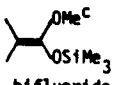
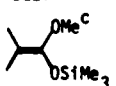
The copolymerization of 6 with 1,4-butanedimethacrylate (cross-linking monomer) in a suspension system followed by size fractionation gave uniform beads of polymer 13, 55 μ in diameter. The hydrolyzed monomer (9) containing two alcohol functions could not be polymerized in a suspension system due to its water solubility. The suspension polymerization of the 1,3-dioxane-bearing acrylamide monomer (8), however, with 1,2-ethanedimethacrylate gave beads of polymer 14, 50-70 μ in diameter. Polymer 14 could be completely hydrolyzed under mild conditions to polymer 15 containing the 1,3-diol functionality.



Poly(α -methylene- γ -methyl- γ -butyrolactone).

The polymerization of both racemic and (R)- α -methylene- γ -methyl- γ -butyrolactone (11) was carried out by radical initiation (benzoyl peroxide) in benzene, by an anionic catalyst (butyllithium) in tetrahydrofuran, or toluene and by group transfer⁷ [1-methoxy-1-trimethylsiloxy-2-methyl-1-propene initiator, tris(dimethylamino)sulfonium bifluoride catalyst in tetrahydrofuran (Table 1)]. Polymerization in bulk with a benzoyl peroxide initiator or by uv irradiation gave a clear hard glass which contained ~20% of unreacted monomer. Higher conversions in bulk generally could not be achieved. The radical and anionic polymerizations in solution proceeded as expected, with no ring opening occurring in the anionic polymerization. Group transfer polymerization of both racemic and optically active monomers took place readily at -78 °C when bifluoride was used as the catalyst, but the tetrabutylammonium flouride catalyst did not provide good conversion at this temperature.

TABLE 1
PROPERTIES OF POLYMER 16

MONOMER	METHOD OF POLYMERIZATION	INITIATOR	POLYMERIZATION CONDITIONS TEMPERATURE/TIME(h)	CONVERSION(%)	$[\eta]_{25}^D$ (solv.)
Racemic 1	radical ^a	BPO ^a	65/2	47	0.49(acetone) 0.84(DMSO)
	anionic ^b	BuLi	-78/2	86	0.26(acetone)
	GTP ^c	 bifluoride	-78/24	70	0.22(acetone)
R-1	radical ^a	BPO ^a	65/2	51	1.06(DMSO)
	anionic ^b	BuLi	-78/2	92	0.58(DMSO)
		BuLi ^d	-78/44	85	0.75(DMSO)
	GTP ^c	 bifluoride	-78/24	78	insol.

^aRadical polymerizations were carried out in benzene with benzoylperoxide as the initiator.
[1] : [BPO] = 300.

^bAnionic polymerizations were carried out in THF; [1]:[BuLi] = 65.

^cGroup transfer polymerizations were carried out with 1 mole % of bifluoride [tris(dimethylamino)sulfonium bifluoride] to initiator [1-methoxy-1-trimethylsiloxy-2-methyl-2-propene].

^dCarried out in toluene.

The racemic poly(α -methylene- γ -methyl- γ -butyrolactones) obtained under different reaction conditions had nearly identical solubility properties, dissolving in such solvents as acetone, acetonitrile, chloroform, dimethylsulfoxide, dimethyl formamide, and propylene carbonate at ambient temperature. Chiral lactone polymerized under radical conditions also was soluble in most of these solvents, with the exception of acetonitrile and chloroform. Polymers obtained from chiral lactone under anionic or GTP showed poor solubility in common organic solvents. The polymers obtained by anionic methods were soluble in dimethyl sulfoxide, dimethyl formamide and propylene carbonate, though only at elevated temperatures. The chiral polymer prepared by group transfer polymerization was the least soluble and would dissolve completely only in hot (230 °C) propylene carbonate. None of these polymers showed any crystallinity by x-ray. Regardless of the method of polymerization and the stereoregularity, the glass transition temperatures of these polymers were all approximately the same, ~215 °C, which was about 20 °C higher than amorphous poly(α -methylene- γ -methyl- γ -butyrolactone). Annealing these polymers above the glass transition temperature failed to develop any crystallinity.

Some information concerning the stereoregularity of these polymers was obtained through the NMR spectra. The most striking feature of both the ^1H and ^{13}C spectra was that the polymer obtained from racemic monomer gave nearly identical spectra, regardless of the method of polymerization. Furthermore, the spectra of the polymers obtained from chiral monomer were nearly identical, regardless of the method of polymerization, but were different from the spectra of the polymers obtained from racemic monomer.

Polymer obtained from racemic monomer showed a poorly resolved overlapping region at $\delta 2.11$ with a detectable upfield shoulder in the 100 MHz ^1H NMR

spectrum at 160 °C in DMSO. Polymer obtained from chiral monomer showed a well resolved doublet at δ 1.87 and δ 2.09 with downfield and upfield shoulders at δ 2.24 and 1.70, respectively. This is in contrast to the ^1H NMR spectra reported for poly(α -methylene- γ -butyrolactone)⁸ in which no resolution was achieved (overlap at δ 2) for the backbone and ring methylene, both of which are adjacent to the quaternary carbon. This lack of resolution in poly(α -methylene- γ -butyrolactone) was attributed in part to coupling from the methylene ($-\text{CH}_2\text{O}-$) adjacent to the ring methylene. In the polymers obtained from chiral monomer, some resolution apparently results from the stereoregular environment and coupling of the ring methylene only to a methine proton.

The proton decoupled ^{13}C spectra of these polymers (50.0288 MHz, 100 °C, DMSO) showed resolved peaks both in the carbonyl region δ 178 and in the quaternary carbon region, δ 45-47. As in the case of poly(α -methylene- γ -butyrolactone), the methylene region was poorly resolved, and was overlapped by DMSO. Unlike poly(α -methylene- γ -butyrolactone), the carbonyl region showed resolved carbonyl at δ 178.74 and 178.67 for polymer prepared from racemic monomer, and 178.67 and 178.87 for polymer obtained from chiral monomer.

Polymers obtained from racemic monomer showed three peaks at δ 45.98, 46.32 and 46.64 for the quaternary carbon (Figure 1). In the spectrum of poly(α -methylene- γ -butyrolactone), peaks at δ 45.15, 45.3 and 45.58 were assigned tentatively to triad sequences, mm, mr and rr, respectively.⁸ This assignment was based on the fact that poly(α -methylene- γ -butyrolactone) obtained by anionic polymerization with phenylmagnesium bromide, which is known to yield highly isotactic poly(methyl methacrylate)⁹ showed a spectrum rich in the upfield peak at δ 45.15, which was assigned to the mm triad. This assignment, rr, mr, mm, in order of increasing field strength, is the opposite of that for

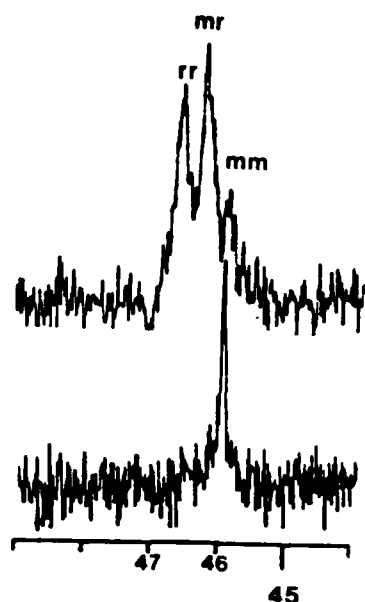


FIGURE 1
 ^{13}C SPECTRA, QUATERNARY CARBON, OF POLYMER FROM
 RACEMIC (TOP) AND CHIRAL (BOTTOM) MONOMERS

the quaternary carbon of poly(methyl methacrylate).¹⁰

If this peak assignment for the triads in poly(α -methylene- γ -butyrolactone) is correct, then the same assignment could be expected for poly(α -methylene- γ -methyl- γ -butyrolactone). Samples obtained from chiral monomer, having a single peak at $\delta 45.95$ in the ^{13}C spectrum suggested that an isotactic polymer (mm triads) was obtained. Polymer from racemic monomer showed a predominance of mr and rr triads at $\delta 46.30$ and 46.58 , respectively, with the peak at $\delta 45.95$ nearly absent. In polymer obtained from racemic monomer, the intensity of these two peaks ($\delta 46.30$ and 46.58) was nearly equal, with that for the mr triad ($\delta 46.30$) being slightly more intense.

The generation of isotactic polymer from chiral lactone, even in radical propagation, indicates that monomer placement is dictated by the chirality of the monomer. When models are examined (Figure 2) the preference for an

isotactic polymer from chiral monomer becomes apparent. Approach of monomer to the growing end of the chain containing either of two conformations for the penultimate unit with respect to the end unit, is shown. In both cases, the least steric approach is that which generates the mm triad. In the case of the polymerization of racemic monomer, addition of monomer of the same chirality as the polymer end generates the m dyad, while addition of monomer of the opposite chirality generates an r dyad, apparently with nearly equal facility from the racemic monomer pool.

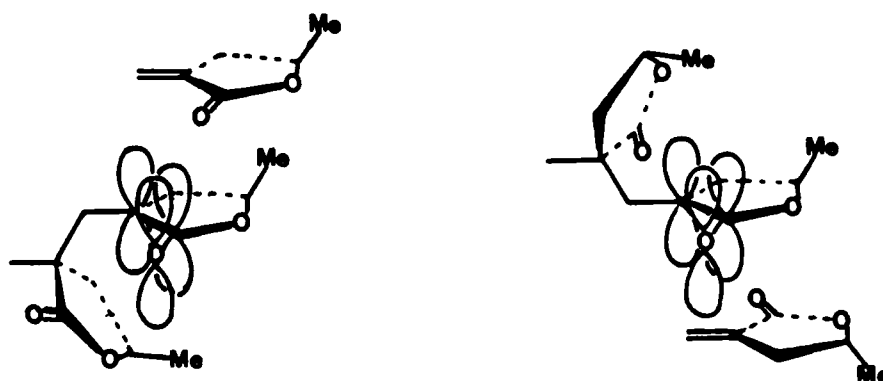


FIGURE 2

APPROACH OF CHIRAL MONOMER TO CHAIN END

HPLC STUDIES

Certain of the polymer beads prepared by suspension polymerization were packed into analytical HPLC columns. Copolymer 12 of poor uniformity (60-120 μ) was packed in a radial compression column, and several racemic alcohols (2-butanol, 2-octanol) were examined with regard to enantiomeric separation. The chiral recognition of the oxazoline was poor, but did show some peak separation.

Analytical columns packed with beads preped from polymers 13-15 did not separate racemic samples of α -phenylethylamine, α -phenylethanol, α -phenylpropanal and α -benzylpropanal.

Silica gel (Perisorb A, 30-40 μ) was coated 0.2 μ thick with chiral poly-(α -methylene- γ -methyl- γ -butyrolactone), using a technique similar to that described¹¹. The material was dry-packed in a 300mm HPLC tube. This polymeric material was considered ideal, since it was not soluble in the common organic solvents used for HPLC resolution, but was soluble only in hot DMSO and hot propylene carbonate.

The resolution of five different racemic compounds with different solvent systems was not achieved.

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J. Suenaga, D.M. Sutherlin and J.K. Stille, Macromolecules, in press.
"Polymerization of Racemic and (R)- -Methylene- -Methyl- - Butyrolactone.

LIST OF SCIENTIFIC PERSONNEL

Co-Principal Investigators: Dr. J. K. Stille
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Dr. Wolfgang Wehnert
Dr. Sheila Woodgate

Graduate Students: Dr. Mike Reuman (PhD, CSU, 1984)
Mr. Dirk Sutherlin
Mr. Manon Talukder
Dr. Steven White (PhD, CSU, 1983)
Mr. Eugene Zimmerman (MS, CSU, 1984)

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