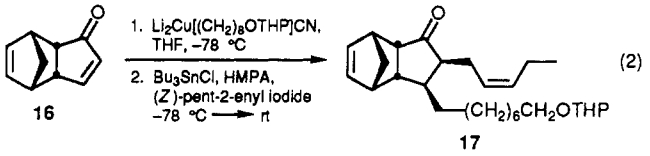
ponent coupling process[9] to assemble intermediate 17 (cf. eq 2) followed by cleavage (PPTS,[10] MeOH, 50 °C, 2 h)



(2)

of the THP ether and oxidation (Jones reagent, acetone, 0 °C, 35 min) of the resultant primary hydroxyl afforded norbornene 18, $[\alpha]^{25}_D$ +71.2° (c 10.0, $CHCl_3$), in ca. 40% overall yield. Treatment of a 0.03 M solution of 18 in 1,2-dichloroethane with 2.5 equiv of ethylaluminum dichloride and 5.0 equiv of fumaronitrile at ambient temperature for 2 h gives rise (60%) to (+)-12-oxophytodienoic acid (3), $[\alpha]^{25}_D$ +104.0° (c 9.5, $CHCl_3$), whose distinctive ^1H NMR spectrum was identical with a ^1H NMR spectrum of the natural product kindly provided by Professor Harris.[4,11] Indeed, upon brief contact with acid 12-oxoPDA underwent equilibration at C(13) with formation of 19, which is spectroscopically (^1H NMR) and chromatographically (TLC) quite different from natural 12-oxoPDA.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant from the National Institute of General Medical Sciences (GM 33605). We thank Professor Thomas Harris for the ^1H NMR spectrum of 12-oxoPDA and Professor Alan Marchand for a generous sample of norbornene derivative ii.

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Discrimination between Amino Acid Amide Conformers by Imprinted Polymers

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Summary: By a molecular imprinting technique based on noncovalent interactions polymers were obtained which selectively discriminate between amino acid amides, different only in a single methyl group, as well as between their enantiomers. The selective recognition is ascribed to a difference in conformation between the print molecules, resulting in recognition sites of different shapes. The sites are able to recognize the amide conformation of the original print molecule.

Sir: The technique of molecular imprinting allows the preparation of polymers containing "tailor-made" recognition sites.[1-11] During the last years we have developed an imprinting technique based on noncovalent interactions.[4-7] Its key steps, outlined in Scheme I, are: (I) mixing of a print molecule (template), an L-amino acid derivative, and methacrylic acid (MAA) in solution, (II) copolymerization of the formed assemblies with a crosslinking monomer (EDMA), (III) removal of the print molecule by simple extraction, and (IV) chromatographic evaluation of the polymer recognition sites by comparing their ability to separate the enantiomers of the substrate and of substrate analogues.

The binding selectivity of imprinted polymers was shown to be influenced by the number of potential interaction sites,[5,6] by their intramolecular distance,[8,9] as well as by the shape[5,10,11] of the print molecule. An important question is to what extent the shape of the print molecule contributes to the polymer selectivity.

This paper reports on the molecular recognition properties of polymers prepared using as print molecules either L-phenylalanine anilide (L-PheNHPh) or L-phenylalanine-*N*-methylanilide (L-PheNMePh), two molecules that should have different amide conformations. To our knowledge this is the first example of imprinted polymers where the recognition properties depend on the confor-

Scheme I

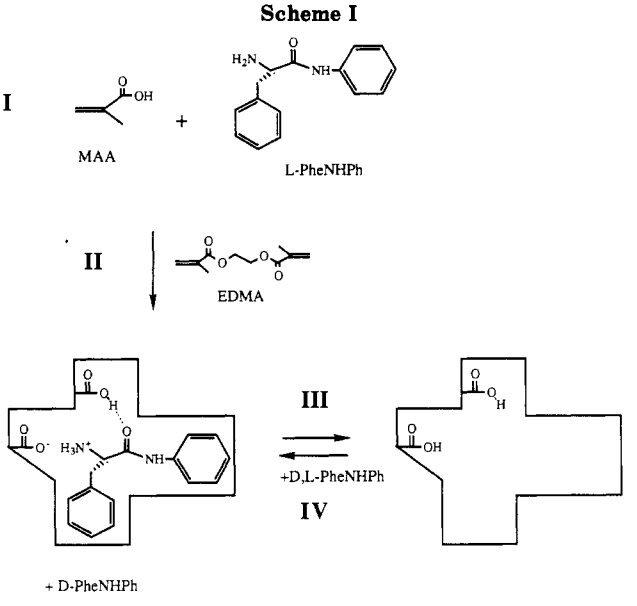

Table I. Chromatographic Data[a] for Polymers Imprinted with either L-PheNHPh or L-PheNMePh[12]

	substrate					
	D- or L-PheNHPh			D- or L-PheNMePh		
polymer	k'_D	k'_L	α ($=k'_L/k'_D$)	k'_D	k'_L	α ($=k'_L/k'_D$)
L-PheNHPh	1.57	6.57	4.18	0.98	1.05	1.07
L-PheNMePh	1.24	1.68	1.36	1.05	2.13	2.03

[a] Eluent: 10% (v/v) acetic acid in acetonitrile. Temperature: 23 °C. Flow rate: 0.4 mL/min. Amount applied: 0.2 μmol/g of polymer. k'_D = capacity factor of the D-form. α = separation factor.

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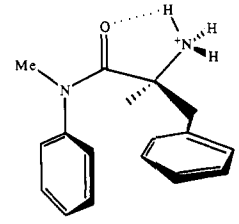
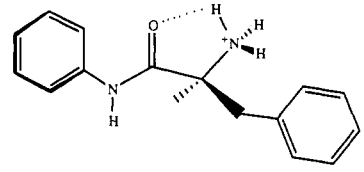
Scheme II

L-PheNMePh:



L-PheNHPh:



mation of the print molecule.

The polymers were evaluated in chromatography regarding their ability to separate the enantiomers of the print molecules (Table I).[12] This is reflected in the separation factor α defined as the ratio of the capacity factor (retention) of the L-form to that of the D-form ($\alpha = k'_L/k'_D$).

Polymers prepared using L-PheNHPh as print molecule show as expected[5] a high selectivity for the original print molecule. *Interestingly when applying on the same polymer* D- *and* L-*PheNMePh, which contain just an additional amide methyl group, almost no separation was observed. The reversed situation was observed for the polymer imprinted with* L-*PheNMePh although the difference in the separation factors was here somewhat smaller, showing that this polymer to some extent also recognized* L-*PheNHPh.*

The recognition was earlier suggested to involve electrostatic and hydrogen-bonding interactions between amino and amide groups of the substrate and carboxyl groups of the sites.[5] Comparing L-PheNHPh and L-PheNMePh, the latter lacks the hydrogen-bond donor NH of the amide group. If the recognition would be controlled exclusively by the difference in hydrogen-bonding properties, it is reasonable to assume that the sites created using L-PheNMePh as print molecule would be able to accommodate L-PheNHPh as well as L-PheNMePh. The results in Table I show however that this polymer is clearly more selective for L-PheNMePh than for L-PheNHPh. Apparently the polymer recognition sites possess a defined shape complementary to the conformation of the print molecule.

The low-energy conformations of L-Phe-NHPh and L-PheNMePh,[13] in the presence of MAA, are proposed in Scheme II. The anilide ring plane is forced out of the amide plane mainly due to steric factors. In acetanilide[14] and in our MMP85 energy-minimized conformation of L-PheNHPh[13] this angle is 18° and 26°, respectively, whereas in *N*-methylacetanilide[15] and in the MMP85 calculation on L-PheNMePh[13] the ring is orthogonal to the amide plane. This was supported by a difference in their ^{1}H NMR shifts of the anilide ortho protons[17] and by a comparison of the UV absorption spectra of the compounds, where an absorption maximum at 240 nm was observed for PheNHPh (ϵ_{240} = 9.2 mM^{-1}) but not for PheNMePh (ϵ_{240} = 2.3 mM^{-1}).

Acetanilide and the minimum energy conformer of L-PheNHPh have the anilide ring cis to the carbonyl oxygen, the *Z* conformer, whereas in *N*-methylacetanilide and in the proposed structure of L-PheNMePh, a trans or *E* conformer dominates (see Scheme II). Experimental evidence for the *E*–*Z* preference in L-PheNHPh and in L-PheNMePh were found. The shifts at lower frequencies of the α and β protons of L-PheNMePh (δ_α = 3.40 ppm, δ_β = 2.87 ppm, $\delta_{\beta'}$ = 2.53 ppm) compared to those of L-PheNHPh (δ_α = 3.67 ppm, δ_β = 3.21 ppm, $\delta_{\beta'}$ and 2.85 ppm) can be explained by the anisotropic shielding in L-PheNMePh of the α- and β-protons by the anilide ring (see Scheme II).[16]

^{1}H–^{1}H nuclear Overhauser enhancement (NOE) experiments were performed in order to compare intramolecular H–H distances.[18] In L-PheNHPh, no NOE was observed at the α-proton upon saturation of the anilide ortho protons. In this case only weak effects where seen at the anilide meta and para protons. On the other hand in L-PheNMePh a positive NOE was observed at the anilide ortho protons (+8%) upon saturation of the α-proton, indicating that the anilide ring now is closer to the α-proton. Saturation of the *N*-methyl protons resulted in positive NOE's at the anilide ortho protons only.

The difference in the amide conformation between the print molecules in this study is obviously large enough for specific sites of a defined shape to be created in the imprinting process. It should be noted that conformers of higher energy can be stabilized if the binding energy is sufficiently high. It is possible that this causes the weak recognition of L-PheNHPh by the L-PheNMePh-imprinted polymer. Although it is difficult to assess the binding energy accurately, a low estimate is provided in the difference in binding energy between the D and the L forms,

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(12) D- and L-PheNHPh and D- and L-PheNMePh were synthesized following standard procedures as described in the supplementary material. The chromatographic evaluation followed procedures earlier described.[5,7]
(13) L-PheNHPh and L-PheNMePh were minimized by MMP85 calculations using an additional parameter set for anilides. This set was modified to fit the crystal- and solution-structural data for acetanilide[14] and *N*-methylacetanilide.[15] Rigid rotations were performed around the CO–C_α and C_α–C_β bonds. The difference in energy between the *E* and *Z* forms of all local minimum energy conformers of L-PheNHPh and L-PheNMePh where larger than 2.2 and 2.7 kcal/mol, respectively. This results in a distribution for L-PheNHPh and L-PheNMePh of at least 98% in favor of the *Z* form and 99% in favor of the *E* form respectively.
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(17) The assignments of the aromatic protons were based on a previous ^{1}H NMR study on acetanilide and *N*-methylacetanilide[16] and on intramolecular NOE's.[18]
(18) The NOE experiments were performed, in the presence of 2 equiv of MAA, on a Varian XL-300 FT NMR 300-MHz spectrometer. The decoupler was turned on for 15 s prior to acquisition. A 60° pulse was applied, and the FID was acquired with the decoupler off. Reference spectra were obtained with a decoupler offset of >500 Hz and the NOE's calculated by the differential spectrum technique.

which had a maximum of 0.8 kcal/mol (α = 4.18 in Table I). A comparison of this figure with the *E-Z* energy difference of 2–3 kcal/mol (obtained from the MM calculations)[13] indicate that the stabilization of high-energy conformations may be significant.

The results here reported should be of use in the design of synthetic polymers possessing antibody- or enzyme-like properties.

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Supplementary Material Available: The experimental procedure for the synthesis of PheNHPh and PheNMePh and the full characterization of these compounds are available (3 pages). Ordering information is given on any current masthead page.

The Chemistry of Vicinal Tricarbonyls. Preparation and Reactions of Acetylenic Tricarbonyls

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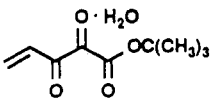
Received October 3, 1989

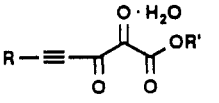
Summary: The acetylenic tricarbonyl **2** serves as a polyelectrophile in addition reactions of primary amines substituted with nucleophilic groups.

Sir: We have previously reported studies on the use of vicinal tricarbonyl derivatives as potent electrophiles. When substituted on β-lactam rings, they have served as acceptor centers for the construction of the fused 4,5-bicyclic systems of carbapenams and penems.[1] In combination with neighboring ester or vinyl groups, they have taken part in cyclization reactions leading to vincamine,[2] erythrina,[3] and phthalideisoquinoline alkaloids.[4] Other applications have been reported in the synthesis of hydroxypyrroles[5] including the bacterial pigment, prodigiosin.[6]

A particularly useful intermediate prepared in this series of investigations has been the vinyl tricarbonyl ester **1**, which has served as a versatile dielectrophile for the tandem addition of primary amines to the α,β-unsaturated ketone as well as to the central carbonyl group.[7] We now report that the related acetylenic derivatives **2a–e** may be used to extend this methodology, providing new polyelectrophiles of unusual potential in organic synthesis.



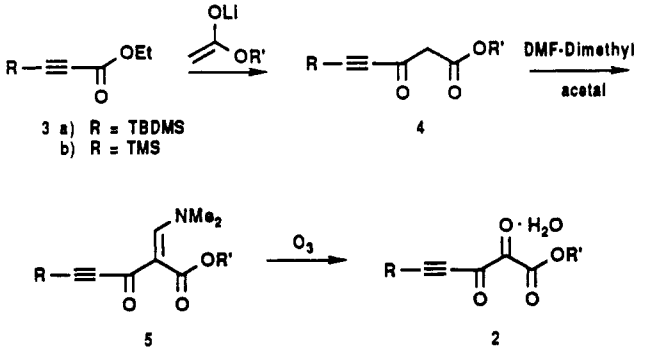
1



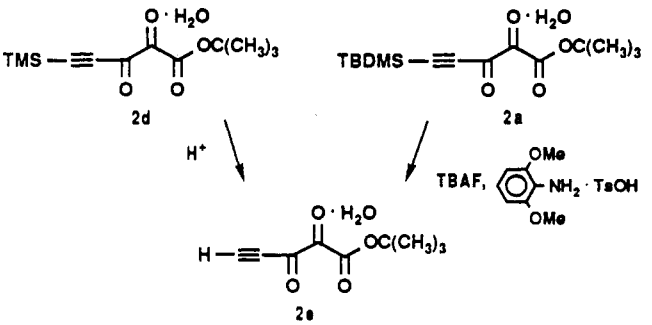
2 a) R = TBDMS, R' = *t*-Bu
b) R = TBDMS, R' = Et
c) R = TBDMS, R' = Me
d) R = TMS, R' = *t*-Bu
e) R = H, R' = *t*-Bu

The acetylenic tricarbonyl compounds **2a–c** were prepared most efficiently by using the procedure shown in Scheme I. Thus, in forming **2a**, Claisen condensation of lithio-*tert*-butyl acetate with ethyl (*tert*-butyldimethylsilyl)propiolate (**3a**)[8] gave the β-keto ester **4** (R = TBDMS, R' = *tert*-butyl), which was then allowed to react with *N,N*-dimethylformamide dimethyl acetal to give the enamine **5** (R = TBDMS, R' = *tert*-butyl). Selective ozonolysis of this product using the indicator dye Sudan III[9]

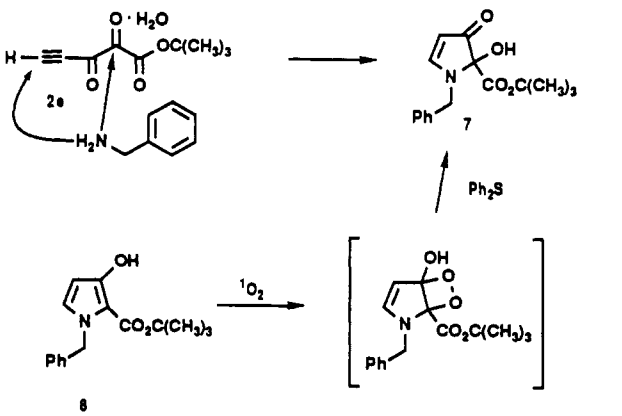
Scheme I



Scheme II



Scheme III



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(8) Compound **3a** was prepared by the reaction of ethyl propiolate with *tert*-butyldimethylsilyl chloride in the presence of sodium hydride.

0022-3263/89/1954-6012$01.50/0