with a standard inversion-recovery pulse sequence; T_1's for H5 (8.13 ppm), H13 (8.07 ppm), and H21 (8.20 ppm) were 5.05, 5.19, and 5.08 s, respectively, while T_1's for the α-protons H1, H7, and H15 (5.46, 5.38, and 5.28 ppm) were 1.97, 1.66, and 1.65 s, respectively.

Stereochemical Analaysis. A 0.5-mg portion of 1 and 2 (9.9×10^{-4} and 9.4×10^{-4} mmol) was ozonized in CH_2Cl_2 for 5 min. Solvent was removed, and the residue was dissolved in 6 N HCl and placed in a sealed bomb at 104 °C for 21 h. After removal of HCl by repeated evaporation in vacuo, the hydrolysate was resuspended in 300 μL of water, 200 μL of which was then derivatized with (1-fluoro-2,4-dinitrophenyl)-5-L-alanineamide (FDAA).[20] HPLC analysis [Waters NOVAPAK C_{18}; 4.6 × 100-mm column; linear gradient elution, triethylammonium phosphate (50 mM, pH 3.0)/MeCN, 90:10 ramped to 60:40 in 45 min; 1.5 mL/min; UV detection at λ 340 nm] of the FDAA-derivatized ozonized hydrolizates versus similarly derivatized amino acid standards established L-Val and L-Ala for 1 and L-Val and L-Thr (from L-mOzn) for 2.

Molecular Modeling. Modeling studies were carried out using Quanta/CHARMm 3.2.3 (Molecular Simulations, Inc.) on a Silicon Graphics Iris 4D/25 workstation. A CHARMm patch file containing descriptions of the cyclically modified residues was required to incorporate energy terms for these residues. Minimization and dynamics protocols approached those recently described.[3c] The first 10-ps simulation was conducted at 3000 K to probe conformational space and arrive at a population of stable structures. A second 10-ps simulation was conducted at 300 K to assess the average structure of the peptide at room temperature for evaluation of NMR data.

Acknowledgment. We thank Dr. Elliot Rachlin for mass spectral data and Dr. Louis Barrows and Mr. Kim Jamison for cytotoxicity testing. This work was supported by NIH grants CA 36622, CA 01179, and CA 50750 (CMI). Partial funding for the Varian Unity 500 NMR spectrometer was provided by NIH grant S10 RR06262 (CMI). The Finnigan MAT 95 mass spectrometer was provided via NSF grant CHE-9002690 and the University of Utah Funds Committee. Work in the U.P. M.S.I. was supported by the International Foundation for Science, Sweden, and the National Research Council of the Philippines.

Supplementary Material Available: 1D ^1H and selected traces from HMBC of 1 and 1D ^1H spectrum of 2 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) Marfey, P. *Carlsberg Res. Commun.* 1984, *49*, 591.

Kinetics and Thermodynamics of Cis–Trans Isomerization of Captopril and Related Compounds

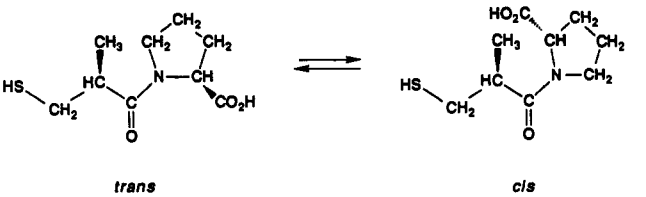
S. V. Santhana Mariappan and Dallas L. Rabenstein*

Department of Chemistry, University of California, Riverside, California 92521

Received June 25, 1992

Introduction

Captopril (I), 1-[(2*S*)-3-mercapto-2-methyl-1-oxopropyl]-L-proline, is an orally active angiotensin converting enzyme (ACE, EC 3.1.15.1) inhibitor used in the treatment of hypertension and congestive heart failure.[1,2] As shown below, captopril can exist in two conformations across the proline amide bond:



The trans conformation is the more populated. However the distribution between the cis and trans conformations is highly dependent on the protonation states of the carboxylic acid and thiol groups. The equilibrium constant for cis ⇌ trans isomerization, $K_{t/c}$ = [trans]/[cis], is 5.9, 1.45, and 3.3 for the (CO_2H, SH), (CO_2^-, SH), and (CO_2^-, S^-) forms, respectively, at 25 °C.[3] At physiological pH, captopril is present as the (CO_2^-, SH) form.[3]

Structure–activity studies have shown that captopril has the trans conformation when bound to the enzyme.[4–8] Thus, factors which govern the distribution of captopril between the active trans conformation and the cis conformation, and the kinetics and thermodynamics of interconversion between the trans and cis conformations by rotation around the amide bond, are of interest. An activation energy of 21.3 ± 0.5 kcal/mol has been reported for the cis to trans interconversion of captopril in D_2O solution.[9] Although the solution conditions were not specified, the populations reported for the cis and trans conformations suggest that captopril was present in the low pH (CO_2H, SH) form.[10]

In this paper, we report the results of detailed studies of the kinetics and thermodynamics of interconversion between the cis and trans forms of captopril and the related compounds, glycyl-L-proline (II), glycyl-4-hydroxy-L-proline (III), glycylsarcosine (IV), and glycylglycylsarcosine (V). Rate constants for the interconversion reactions were measured over a range of temperatures using the inversion–transfer NMR method,[11] from which the Gibbs free energies of activation were obtained. Differences in the equilibrium constants $K_{t/c}$ are discussed in terms of the kinetics results.

Experimental Section

The captopril was a gift from the Squibb Institute for Medical Research, Princeton, NJ. The peptides were obtained from Sigma Chemical Co. Solutions were prepared in 99.8% D_2O, and 1,4-dioxane was added as an internal chemical shift reference. Magnetization transfer measurements were made on 0.3 M solutions of captopril at pD 7.36 and 12.06; for the other systems,

(1) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* 1977, *196*, 441–443.

(2) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* 1977, *16*, 5484–5491.

(3) Rabenstein, D. L.; Isab, A. A. *Anal. Chem.* 1982, *54*, 526–529.

(4) Thorsett, E. D.; Harris, E. E.; Aster, S. D.; Peterson, E. R.; Snyder, J. P.; Springer, J. P.; Hirshfield, J.; Tristam, E. W.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* 1986, *29*, 251–260.

(5) Hassall, C. H.; Krohn, A.; Moody, C. J.; Thomas, W. A. *J. Chem. Soc., Perkin Trans. 1* 1984, 155–164.

(6) Andrews, P. R.; Carson, J. M.; Caselli, A.; Spark, M. J.; Woods, R. *J. Med. Chem.* 1985, *28*, 393–399.

(7) Klutchko, S.; Hoefle, M. L.; Smith, R. D.; Essenburg, A. D.; Parker, R. B.; Nemeth, V. L.; Ryan, M. J.; Dugan, D. H.; Kaplan, H. R. *J. Med. Chem.* 1981, *24*, 104–109.

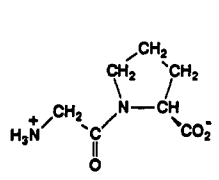
(8) Condon, M. E.; Petrillo, E. W.; Ryono, D. E.; Reid, J. A.; Neubeck, R.; Puar, M.; Heikes, J. E.; Sabo, E. F.; Losee, K. A.; Cushman, D. W.; Ondetti, M. A. *J. Med. Chem.* 1982, *25*, 250–258.

(9) Green, D. V. S.; Hillier, I. H.; Morris, G. A.; Whalley, L. *Magn. Reson. Chem.* 1990, *28*, 820–823.

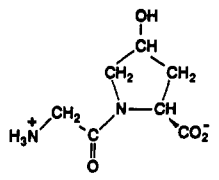
(10) The trans to cis ratio was reported[9] to be ca 6:1, as compared to the equilibrium constant $K_{t/c}$ of 5.9 for the (CO_2H, SH) form.[3]

(11) Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* 1990, *90*, 935–967.

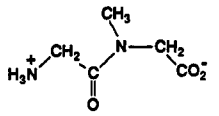
0022-3263/92/1957-6675$03.00/0



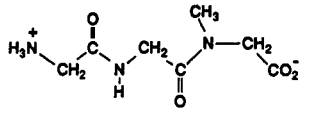
II



III



IV



V

measurements were made on 0.6 M solutions at a pD of 7.03. The equilibrium constants for cis ⇌ trans isomerization were measured by NMR using solutions identical to those used in the kinetics studies. All pH measurements were made at 25 °C and were corrected for deuterium isotope effects with the relation pD = $pH_{meter\ reading}$ + 0.40.[12] To minimize oxidation of the thiolate group, captopril solutions were freshly prepared in D_2O which had been degassed by bubbling with nitrogen.

^{13}C NMR spectra were recorded at 125.7 MHz with WALTZ decoupling. Rate constants were measured over the temperature range 60–85 °C for captopril, glycylsarcosine, and glycylglycylsarcosine and over the temperature range 65–85 °C for glycyl-L-proline and glycyl-4-hydroxy-L-proline. To minimize sample heating from ^1H decoupling, the decoupler was set at the minimum power level which gave complete decoupling of the protons attached to the specific carbons used in the magnetization transfer studies.

Rate constants for trans to cis interconversion, k_{tc}, were determined by the inversion–transfer method. The trans resonance of a given cis/trans pair of resonances was selectively inverted with the pulse sequence:

$$\pi/2(x)-\tau-\pi/2(-x)-t-\pi/2(x,y,-x,-y)-\text{acquisition}$$

where τ is a fixed delay equal to $1/2\Delta$ and $\Delta = |\nu_{cis} - \nu_{trans}|$ in hertz.[13] t is a variable delay, the mixing period, during which transfer of magnetization occurs by exchange between the cis and trans forms. t values ranging from 0.0001 s to 5 times the longest T_1 of the two resonances were used; T_1's were estimated by the inversion–recovery method.[14] Typically, 15 t values were used in each experiment. In all experiments, the trans resonance was inverted by setting the carrier on the cis resonance. For captopril, glycyl-L-proline, and glycyl-4-hydroxy-L-proline, the cis/trans pair of resonances for the δ-CH_2 carbon of the proline ring was used in the inversion–transfer experiment. For glycylsarcosine, the pair of resonances for the CH_2 carbon of the glycyl residue was used, while for glycylglycylsarcosine the pair of resonances for the CH_2 carbon of the internal glycyl residue was used. A typical data set is plotted in Figure 1.

Rate constants were determined from the dependence of the intensity of the cis resonance on mixing time using method one in ref 16. The procedure involved fitting the intensity vs t data by nonlinear least-squares methods to an equation which expresses the resonance intensity in terms of several known parameters and the spin–lattice relaxation times of the cis and trans resonances,[17]

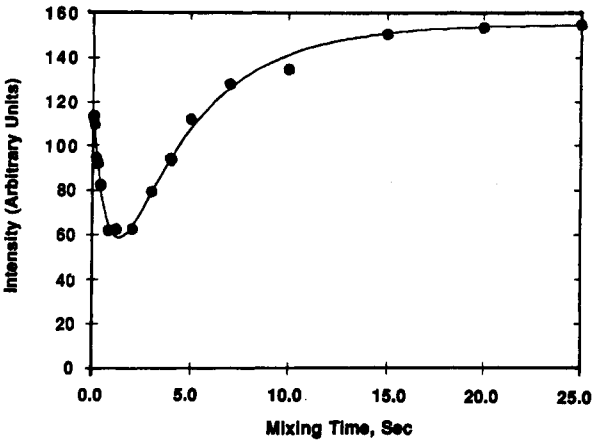


Figure 1. Intensity of the δ-CH_2 carbon resonance of the cis isomer of captopril as a function of the mixing time in the inversion–transfer experiment. The data are for captopril at pD 7.36 and 353 K. The smooth curve through the experimental points was simulated using the parameters obtained by fitting the intensity vs mixing time data, as described in the text.

T_{1c} and T_{1t}, the intensities of the cis and trans resonances at t = 0, and the lifetime of the trans conformation, τ_t. To illustrate, the smooth curve through the points in Figure 1 is the theoretical curve calculated with parameters obtained from the nonlinear least-squares fit to the data. The inverse of τ_t is the first-order rate constant for trans to cis interconversion, k_{tc}.

Equilibrium constants $K_{t/c}$ were determined at 25 °C using the intensities of the same cis/trans pair of ^{13}C resonances as used in the magnetization transfer experiments.

Results and Discussion

The rate of rotation around the imide bond of captopril and the related peptides II–V is slow on the NMR time scale, and separate resonances are observed for the cis and trans isomers. At 25 °C, there was no detectable exchange contribution to resonance line widths for the cis and trans resonances, and there was no evidence of transfer of magnetization by cis ⇌ trans interconversion in inversion–transfer experiments. However, the rate of rotation is sufficiently fast at elevated temperatures to characterize by the inversion–transfer method, as illustrated by the data for captopril in Figure 1.

Rate constants were determined for trans to cis interconversion, k_{tc}, for captopril at pD 7.36 and 12.06 and for glycylsarcosine and glycylglycylsarcosine at pD 7.03 at 5° intervals over the temperature range 60–85 °C using data of the type shown in Figure 1. Rate constants were determined for glycyl-L-proline and glycyl-4-hydroxy-L-proline over the temperature range 65–85 °C. Using these rate constants, the Gibbs free energies of activation for trans to cis interconversion, $\Delta G_{tc}^{\ddagger}$, were calculated using the Eyring equation:[18]

$$\ln (k_{tc}/T) = -\Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R + \ln (k_B/h) \quad (1)$$

where k_B is the Boltzman constant, h is Planck's constant, and R the gas constant. The results obtained for $\Delta H_{tc}^{\ddagger}$ and $\Delta S_{tc}^{\ddagger}$ from plots of ln (k_{tc}/T) vs $1/T$, and the values calculated for $\Delta G_{tc}^{\ddagger}$ at 25 °C using the equation $\Delta G_{tc}^{\ddagger} = \Delta H_{tc}^{\ddagger} - T\Delta S_{tc}^{\ddagger}$, are presented in Table I.

The rate constants listed in Table I for trans to cis interconversion at 25 °C were calculated using eq 1 and the slopes and intercepts of the plots of ln (k_{tc}/T) vs $1/T$.

(12) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.
(13) Robinson, G.; Kuchel, P. W.; Chapman, B. E.; Doddrell, D. M.; Irving, M. G. *J. Magn. Reson.* **1985**, *63*, 314–319.
(14) Because both the cis and trans conformations are simultaneously present, it was not possible to measure directly the actual T_1 values for resonances of the cis and trans conformations in the absence of exchange at the temperatures used in the inversion–transfer experiments. Thus, the T_1 values estimated by the inversion–recovery method for a specific ^{13}C resonance are a function of the T_1's of the resonances for that carbon in both the cis and trans forms.[15]
(15) McLaughlin, A. C.; Leigh, J. S. *J. Magn. Reson.* **1973**, *9*, 296–304.
(16) Mariappan, S. V. S.; Rabenstein, D. L. *J. Magn. Reson.*, in press.
(17) Since T_1 values cannot be measured directly for the cis and trans resonances,[14] it was necessary to treat them as unknown parameters in the fitting procedure.
(18) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107–115.

Table I. Kinetic and Thermodynamic Parameters for Cis–Trans Isomerization of Captopril and Related Compounds

	captopril (pD 7.36)	captopril (pD 12.06)	glycyl-L-proline	glycyl-4-hydroxy-L-proline	glycylsarcosine	glycylglycyl-sarcosine
$\Delta H_{tc}^{\ddagger}$ (kcal/mol)[a]	17.8 ± 1.1	16.9 ± 1.6	17.3 ± 1.0	18.5 ± 1.1	19.2 ± 1.1	15.8 ± 0.6
$\Delta S_{tc}^{\ddagger}$ (cal/mol K)[a]	−10.0 ± 3.1	−12.4 ± 4.6	−11.1 ± 2.8	−7.7 ± 3.0	−4.0 ± 3.1	−12.2 ± 1.8
$\Delta G_{tc}^{\ddagger}$ (kcal/mol)[b]	20.8 ± 1.9	20.6 ± 3.0	20.6 ± 1.8	20.8 ± 2.0	20.4 ± 2.0	19.5 ± 1.1
ΔG°_{tc} (kcal/mol)[b]	0.267	0.763	0.297	0.361	0.203	0.182
$K_{t/c}$[b]	1.57	3.63	1.65	1.84	1.41	1.36
k_{tc} (s^{-1})[a,b]	0.0037 ± 0.0009	0.0051 ± 0.0018	0.0048 ± 0.0011	0.0036 ± 0.0008	0.0073 ± 0.0015	0.033 ± 0.005
k_{ct} (s^{-1})[b]	0.0058	0.019	0.0079	0.0066	0.010	0.045

[a] Uncertainties calculated using the standard errors of the estimates of the slopes and intercepts obtained from linear least-squares fits of the kinetic data to eq 1. [b] 25 °C.

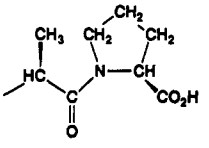
Rate constants for cis to trans interconversion, k_{ct}, at 25 °C were calculated from k_{tc} and the equilibrium constants at 25 °C using the relation $k_{ct} = K_{t/c}k_{tc}$. The free energy differences between the trans and cis conformations, ΔG°_{tc}, were calculated from the values for $K_{t/c}$ at 25 °C.

The equilibrium constant for cis ⇌ trans isomerization, $K_{t/c}$, for captopril is strongly dependent on the protonation states of its carboxylic acid and thiol groups, varying from 5.9 for the (CO_2H, SH) form to 1.45 for the (CO_2^-, SH) form to 3.33 for the (CO_2^-, S^-) form at a captopril concentration of 0.005 M (0.16 M $NaNO_3$ and 25 °C).[3] For the solution conditions used in this work, $K_{t/c}$ is 1.57 for the (CO_2^-, SH) form and 3.63 for the (CO_2^-, S^-) form. For the (CO_2^-, SH) form, this corresponds to a free energy difference between the cis and trans conformations, ΔG°_{tc}, of 0.267 kcal/mol at 25 °C. The cis/trans free energy difference is increased by 0.784 and 0.496 kcal/mol upon protonation of the carboxylate group and deprotonation of the thiol group, respectively.

The equilibrium constant is equal to the ratio of the rate constants for cis to trans and trans to cis interconversion, $K_{t/c} = k_{ct}/k_{tc}$. The results in Table I indicate that, at 25 °C, k_{ct} for the (CO_2^-, S^-) form (pD 12.06) is approximately 3 times larger than k_{ct} for the (CO_2^-, SH) form (pD 7.36), whereas k_{tc} is essentially the same for these two forms. Thus, the larger equilibrium constant $K_{t/c}$ for the (CO_2^-, S^-) form of captopril is the result of a larger rate constant for cis to trans interconversion. $K_{t/c}$ for the (CO_2H, SH) form is also larger than $K_{t/c}$ for the (CO_2^-, SH) form. Using the results of Green et al.[9] it appears that $K_{t/c}$ is larger for the (CO_2H, SH) form as a result of the combined effects of a decrease and increase, respectively, in the rate constants for trans to cis and cis to trans interconversion.[19]

Cis ⇌ trans isomerization involves interchange between two conformations which correspond to the minima of the overall free energy when the amide bond has the cis and trans conformations. Interconversion between these low-energy conformations will involve concerted changes in the torsion angles of numerous single bonds as well as the amide bond.[20] Thus, the differences in k_{ct} for the three different protonated forms of captopril must reflect differences in the combined effects of various intramolecular interactions and other necessary changes in conformation on the rate of rotation around the amide bond. Although it is not clear what the important differences in intramolecular interactions and torsion angles between the cis conformations of the (CO_2H, SH), (CO_2^-, SH), and (CO_2^-, S^-) forms are, molecular models suggest that the cis conformation of the (CO_2^-, SH) form might be stabilized by intramolecular hydrogen bonding between the carboxylate oxygen and the thiol group.[21]

Structure–activity studies have shown that partial structure VI contributes significantly to the high potency of captopril and related compounds as angiotensin converting enzyme inhibitors.[2,22,23] The methyl group is not



VI

required for binding, but its presence adds to their potency as inhibitors. However, the similar kinetic and equilibrium results in Table I for captopril at pD 7.36 and glycyl-L-proline and glycyl-4-hydroxy-L-proline indicate that the methyl group has no major effect on either the equilibrium distribution of captopril between its cis and trans forms or the kinetics of cis ⇌ trans interconversion. Thus, the methyl group must impart increased potency through other interactions, perhaps by influencing conformational equilibria of the trans isomer of captopril or by hydrophobic interaction with the enzyme.[4]

It also is of interest to compare the rate constants for cis ⇌ trans interconversion for glycylsarcosine and glycylglycylsarcosine with those for captopril and the proline-containing peptides in Table I, since proline-containing compounds are more potent inhibitors of angiotensin converting enzyme than are related compounds which incorporate other amino acids.[1] The rate constants k_{tc} and k_{ct} are larger for glycylsarcosine and glycylglycylsarcosine, which suggests that rotation around the amide bond is somewhat restricted in captopril, glycyl-L-proline, and glycyl-4-hydroxy-L-proline as compared to rotation around the sarcosine amide bond. It is also interesting to note that chain elongation at the N-terminus of glycylsarcosine by addition of another glycyl residue increases k_{tc} by a factor of 3.

In summary, the results of this study indicate that the rate constants for interconversion between the cis and trans forms of captopril by rotation around the amide bond are similar to those for simple proline-containing dipeptides, and that the dependence of the equilibrium

(19) Values of 1.84×10^{-3} s^{-1} and 1.31×10^{-2} s^{-1} were obtained for k_{tc} and k_{ct} at 25 °C by extrapolation of Arrhenius plots of rate constant data reported by Green et al.[9] for the (CO_2H, SH) form of captopril.[10]

(20) Grathwohl, C.; Wüthrich, K. *Biopolymers* **1981**, *20*, 2623–2633.

(21) Hydrogen bonds involving thiol groups in proteins have been the subject of a recent review (Gregoret, L. M.; Rader, S. D.; Fletterick, R. J.; Cohen, F. E. *Proteins: Structure, Function and Genetics* **1991**, *9*, 99–107). Also, hydrogen bonds involving the thiol group as donor (S–H···O) have been established in Raman studies of model compounds for cysteine in proteins (Li, H.; Thomas, G. J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 456–462).

(22) Petrillo, E. W.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1–41.

(23) Patchett, A. A.; Harris, E.; Tristam, E. E.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hofsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R. F.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature (London)* **1980**, *288*, 280–283.

constant $K_{t/c}$ for captopril on protonation state of the carboxylic acid and thiol groups is due mainly to differences in rate constants for cis to trans interconversion for the (CO_2^-, SH) and (CO_2^-, S^-) forms. Using rate constants determined in this study, the average lifetimes of the cis and trans conformations are calculated to be approximately 185 and 270 s, respectively, at physiological pH. When the kinetics and equilibria for the binding of captopril by angiotensin converting enzyme have been characterized, these results will be useful for determining if cis to trans interconversion is rate limiting in the binding of captopril by angiotensin converting enzyme.

Acknowledgment. This research was supported by National Institutes of Health Grant GM 37000. The NMR Instrumentation was supported in part by BRSG 2 S07 RR07010-20 awarded by Biomedical Research Resources, National Institutes of Health.

A Highly Selective Synthesis of Monodisperse Oligo(ethylene glycols)

Erik M. D. Keegstra, Jan W. Zwikker, Martin R. Roest, and Leonardus W. Jenneskens*

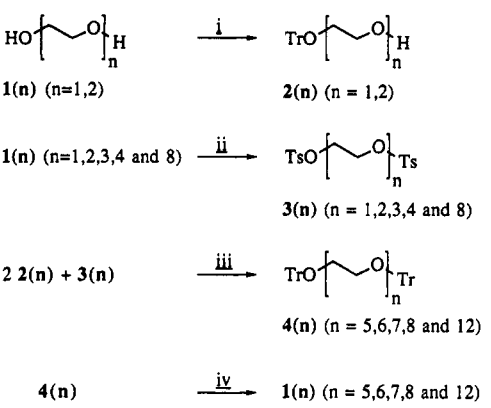
University of Utrecht, Debye Institute, Department of Physical Organic Chemistry, Padualaan 8, 3584 CH Utrecht, The Netherlands

Received June 23, 1992

Although oligo(ethylene glycols) [$H[-OCH_2CH_2]_n-OH$, **1**(***n***); cf. Scheme I] have found widespread application as synthons for crown ether-type derivatives,[1] surfactants,[2] ion-conducting materials,[3] and new materials,[4] the published synthetic methods for commercially unavailable or expensive representatives **1**(***n***) ($n > 4$) are hampered by laborious procedures.[5] Depending on the oligomer, either vacuum distillation or preparative gel permeation chromatography has to be applied for the isolation and purification of the compounds. Since we required easy access to monodisperse **1**(***n***) with n up to 12 for our material research program, we were prompted to address this problem.

We here report a highly selective synthesis, which lacks laborious purification procedures and is very convenient for the preparation of the higher representatives as well. It is based on the quantitative chain extension of α,ω-ditosylated oligo(ethylene glycols) **3**(***n***) (n = 1, 2, 3, and 4) with 2 equiv of the sodium salt of monotritylated mono- or diethylene glycol **2**(***n***) (n = 1 or 2). Hydrogenolysis of the α,ω-ditrityl endcapped homologues **4**(***n***) furnishes the chain-extended monodisperse oligo(ethylene glycols) (Scheme I).

Scheme I[a]



[a] (i) TrCl, C_5H_5N; (ii) TsCl, KOH, CH_2Cl_2; (iii) NaH, THF; (iv) H_2(g), Pd/C, CH_2Cl_2.

Results and Discussion

Pivotal to the approach is our finding of a convenient access to monoprotected ethylene **2**(**1**) and diethylene glycol **2**(**2**), respectively. This was achieved on an 1 molar scale by solvolysis of trityl chloride in a 10-fold excess of glycol **1**(**1**) or **1**(**2**) in the presence of pyridine. The compounds **2**(***n***) (n = 1, 2) were separated from the excess glycol, which can be used again, by extraction with toluene and purified by recrystallization (yield > 75%).

Quantitative chain extension of α,ω-ditosylates **3**(***n***) to the appropriate α,ω-ditritylated oligo(ethylene glycols) **4**(***n***) was achieved by reaction of 2 equiv of the sodium salt of **2**(***n***) (n = 1, 2) with **3**(***n***) (n = 1, 2, 3, 4, and 8 (vide infra), respectively) (Scheme I).

Compounds **3**(***n***) were obtained via an improved procedure involving the addition of small portions of freshly powdered potassium hydroxide to a solution of the appropriate **1**(***n***) (n = 1, 2, 3, 4, and 8) and *p*-toluenesulfonyl chloride in dichloromethane while maintaining the temperature between 0 and 5 °C. The α,ω-ditosylated oligo(ethylene glycols) **3**(***n***) (n = 1, 2, 3, 4, and 8, respectively) were isolated (95–99%) (cf. Experimental Section and ref 6a) without purification.

Following this approach, **4**(***n***) with n = 5, 6, 7, 8, and 12 (vide infra) were conveniently prepared. However, **4**(**5**) could only be prepared by reaction of 2 equiv of the sodium salt of **2**(**1**) with tosylate **3**(**3**). The other approach, i.e. coupling of 2 equiv of the sodium salt of **2**(**2**) with tosylate **3**(**1**), was unsuccessful. ^{1}H NMR spectroscopy revealed that competitive β-elimination[7] occurring with **3**(**1**) thwarted the desired chain extension reaction. In contrast, **4**(**6**) could be prepared in two ways, either from 2 equiv of the sodium salt of **2**(**1**) and **3**(**4**) or from the sodium salt of **2**(**2**) and **3**(**2**). Compounds **4**(**7**) and **4**(**8**) were synthesized by coupling of 2 equiv of the sodium salt of **2**(**2**) with α,ω-ditosylates **3**(**3**) and **3**(**4**), respectively.

Compounds **4**(***n***) were quantitatively converted into the corresponding monodisperse oligo(ethylene glycols) **1**(***n***) (n = 5, 6, 7, 8, and 12) by hydrogenolysis in the presence of 10% palladium on carbon in dichloromethane. The

(1) Huszthy, P.; Bradshaw, J. S.; Zbu, C. Y.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1991**, *56*, 3330–3336.
(2) (a) Binana-Limbelé, W.; van Os, N. M.; Rupert, L. A. M.; Zana, R. *J. Colloid Interface Sci.* **1991**, *144*, 458–467. (b) Craven, J. R.; Hao, Z.; Booth, C. *J. Chem. Soc. Faraday Trans.* **1991**, *87*, 1183–1186.
(3) Armand, M. *Adv. Mater.* **1990**, *2*, 278–286.
(4) (a) Callens, S.; Le Nest, J. F.; Gandini, A.; Armand, M. *Polym. Bull.* **1991**, *25*, 443–450. (b) Bianconi, P. A.; Lin, J.; Strzelecki, A. R. *Nature* **1991**, *349*, 315–317.
(5) (a) Bedells, A. D.; Mobbs, R. H.; Booth, C. *Makromol. Chem.* **1991**, *192*, 2089–2098 and refs cited therein. (b) Coudert, G.; Mpassi, M.; Guillaumet, G.; Selve, C. *Synth. Commun.* **1986**, *16*, 19–26 and refs cited therein. (c) Nakatsuji, Y.; Kameda, N.; Okahara, M. *Synthesis* **1986**, 280–281 and refs cited therein. (d) Bradshaw, J. S.; Reeder, R. A.; Thompson, M. D.; Flanders, E. D.; Carruth, R. L.; Izatt, R. M.; Christensen, J. J. *J. Org. Chem.* **1976**, *41*, 134–136.
(6) (a) Ouchi, M.; Inoue, Y.; Liu, Y.; Nagamune, S.; Nakamura, S.; Wada, K.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1260–1262 and refs cited therein. (b) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571.
(7) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73–80.

0022-3263/92/1957-6678$03.00/0