give rise to individual signals in the NMR spectrum. We have not observed such separated resonances, even in spectra acquired at −23 °C. Nevertheless, an exchange process remains an interesting possibility to explain the observed results. We are grateful to Dr. F. A. Bovey for pointing out this idea.

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Proton Magnetic Resonance Study of Linear Sarcosine Oligomers

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ABSTRACT: A high-resolution proton NMR study of a series of monodisperse N- and C-protected sarcosine (*N*-methylglycine) peptides has been carried out. The compounds of the series *t*-Boc(Sar)$_n$OMe, where *t*-Boc is *tert*-butoxycarbonyl, OMe denotes the methyl ester, and n = 1–5, give well-resolved spectra in Me_2SO-d_6. The cis and trans conformers at the peptide bonds (and at the N-terminal urethane bond) are in sufficiently slow exchange that each exhibits separate CO_2CH_3, NCH_2, NCH_3, and *tert*-butyl proton resonances. Their chemical shifts also vary with the amino acid position in the chain. The result is that the spectra become very complex as n increases and cannot be fully interpreted beyond n = 2. The N-terminal urethane bond shows a weak preference for the cis state, while the C-terminal peptide bond exhibits a ca. 3:1 preference for trans. The other peptide bonds appear to have substantial proportions of both conformers. In contrast to the known behavior of L-proline oligomers [and poly(amino acids) generally], the sarcosine oligomers show no tendency to assume a regular structure as the chain is lengthened. Similar behavior is observed in D_2O and $CDCl_3$. Polysarcosine ($\overline{DP} \simeq 68$) is likewise random in conformation.

High-resolution proton magnetic resonance (^{1}H NMR) is a valuable and widely employed technique in the conformational analysis of linear oligopeptides in solution. Local environments of individual NH and α-CH (or α-CH_2) protons can be probed, and from this information one can deduce subtle structural characteristics of oligopeptides. Goodman, Bovey, Toniolo, Pysh (now Stevens), and co-workers have reported ^{1}H NMR studies of several series of monodisperse fully protected homopeptides derived from N-unsubstituted α-amino acids, including those from γ-alkyl esters of L-glutamic acid,[1-4] L-alanine,[5-7] L-norvaline,[8] L-valine,[7] L-isoleucine,[4,6] and L-methionine.[9-11] Jardetzky and co-workers[12] have examined in detail the glycine series and Shoji et al.[13,14] some C-protected L-alanine oligomers.

Less attention has been paid to homopeptides derived from *N*-alkyl α-amino acids, mainly because few are available. Blout and co-workers[15] have analyzed the proton spectra in chloroform of *t*-Boc(L-Pro)$_n$OX, where n = 2–6 and X is H or benzyl (*t*-Boc is *tert*-butyloxycarbonyl). They reported that the lower oligomers contain nearly random distributions of cis and trans peptide bonds but that the peptides abruptly assume an all-trans helical structure when n = 5 in the *O*-benzyl series and n = 6 in the OH series. A ^{1}H NMR study of the α-CH resonances of *t*-Aoc(L-Pro)$_n$OH (n = 2–6, 8; *t*-Aoc is *tert*-amyloxycarbonyl) in acetic acid has indicated that the peptides larger than the tetramer increasingly adopt the trans tertiary amide conformation with increasing chain length.[16] Rothe and co-workers[17] have shown by proton spectroscopy that all members of the series H_2^+(L-Pro)$_n$O$^-$ (with n from 2 to 40) which they examined have the trans conformation in acetic acid and trifluoroacetic acid. A distinct dependence of the cis–trans isomerism on chain length in other solvents—water, methanol, and trifluoroethanol—has been verified, diproline behaving differently from the higher oligomers. Only in methanol solution is the all-cis configuration attained by the higher oligoprolines (n > 10). Chao and Bersohn[18] observed the ^{1}H and ^{13}C spectra of H_2^+(L-Pro)$_n$O$^-$ (n = 2–4, 6) and reported that the percentage of trans peptide bonds increases substantially from dimer (65% trans) to trimer (90% trans), thereafter remaining more or less constant. A high salt concentration was shown to cause conformational randomization.

Only few and scattered ^{1}H NMR results have been described on homopeptides derived from sarcosine (*N*-methylglycine). They include the following: (i) the crystallizable oligomer Z-(Sar)$_3$OMe (Z is benzyloxycarbonyl) at −70 °C in a halogenated hydrocarbon shows only one isomer, each amide bond being in a single conformation, cis or trans.[19] As the temperature is increased, the 100-MHz ^{1}H NMR spectrum becomes more complex due to cis–trans isomerism of the peptide bonds. On the other hand, the noncrystallizable Z-(Sar)$_7$OMe exhibits a complex ^{1}H NMR spectrum even when dissolved at low temperature. (ii) The 220-MHz ^{1}H NMR spectrum of the *N*,*N*-dimethylamide derivative of a *polydisperse* oligosarcosine with $\overline{DP} \simeq 5$ shows that the ratios of trans–cis conformers in $CDCl_3$ and D_2O are similar (about 2:1).[20]

In this paper we discuss the results of a high-resolution ^{1}H NMR investigation of a homologous series of monodisperse linear sarcosine peptides having the general formula *t*-Boc(Sar)$_n$OMe (n = 1–5) as a function of solvent and temperature. The C-deblocked monomer and dimer and the corresponding homopolymer have also been examined for comparison, the two oligomers by changing solvent, concentration, and pH.

Among the vast body of conformational calculations of the sarcosyl residue and poly(Sar)[20-33] it has been reported that (i) in a linear oligosarcosine of at least four residues the cis conformation of the peptide bond is energetically preferred.[28] However, because the effect of solvation was not included in these calculations, these results are most

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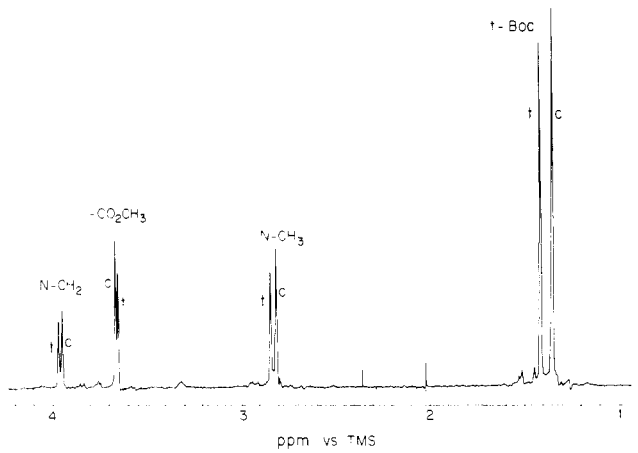


Figure 1. ^{1}H NMR spectrum (360 MHz) of *t*-Boc-Sar-OMe in Me_2SO-d_6 solution at 25 °C. The peak assignments are as indicated, the letters t and c denoting the cis and trans conformers.

applicable to isolated molecules, e.g., to unassociated molecules in an apolar solvent. (ii) A slight but definite increase in the cis–cis sequence and a decrease in the trans–trans sequence were observed in linear oligosarcosines with increasing chain length; the fractions of trans–cis and cis–trans sequences were, however, nearly unchanged.[20]

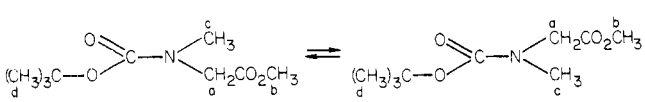
Experimental Section

Materials. The details of the synthesis and characterization of *t*-Boc(Sar)$_n$OMe (n = 1–5) and *t*-Boc(Sar)$_n$OH (n = 1, 2) were reported in ref 34. Poly(Sar) of molecular weight 4800 ($\overline{DP} \simeq 68$) was purchased from Sigma Chemical Co.

Methods. The ^{1}H NMR spectra of the oligosarcosines were recorded on Bruker WH-90 and HX-360 spectrometers. Except where noted, samples were prepared as 10 mg/mL solutions. All spectra were obtained in the FT mode with pulse repetition times of 4–10 s. The WH-90 data were collected in 8K computer locations, using a sweep width of 1000 Hz. For measurements on the HX-360 a sweep width of 3600 Hz was used and the data were collected in 16K computer locations. The number of scans for each spectrum varied between 1 and 100. Chemical shift measurements in $CDCl_3$ and Me_2SO-d_6 were made relative to internal Me_4Si. In D_2O solutions chemical shifts were measured relative to an internal dioxane reference (δ = 3.68). Temperature measurements were made by using a thermocouple and the ^{1}H NMR spectrum of ethylene glycol.

Results and Discussion

(a) Monomers. Since *t*-Boc-Sar-OMe can exist in both cis and trans conformations



cis trans

eight different proton resonances, namely, cis a, b, c, and d and trans a, b, c, and d, are expected if the exchange between the two conformers is slow on the NMR time scale at the observation temperature. The 360-MHz proton spectrum in Me_2SO-d_6 at room temperature is shown in Figure 1. It can be seen that eight peaks are indeed observed and that from the relative intensities of all peaks one conformer is preferred by about 1.2:1.0. If the proton assignments are made according to the NOE results of Anet and Bourn[35] on *N,N*-dimethylformamide, it turns out that the cis conformer is slightly preferred. In $CDCl_3$ solution the cis–trans ratio is very nearly 1:1. (A previous 90-MHz ^{1}H NMR study of *t*-Boc-Sar-OMe in $CDCl_3$ solution failed to reveal doublet splitting in the a–d peaks.[36])

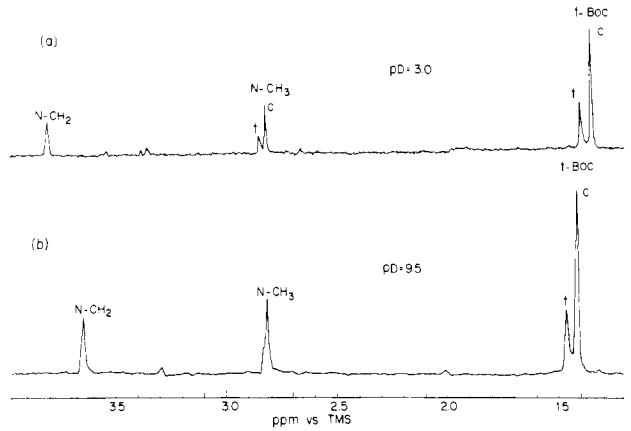


Figure 2. ^{1}H NMR spectra (360 MHz) of *t*-Boc-Sar-OH at 3 × 10^{-2} M in D_2O solution at pD 3.0 (a) and pD 9.5 (b) at 25 °C. The peak assignments are indicated as in Figure 1.

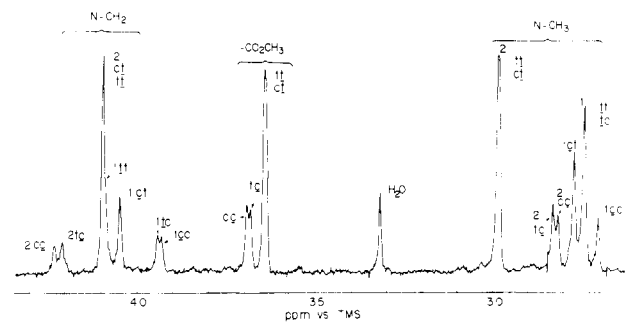


Figure 3. ^{1}H NMR spectrum (360 MHz) of *t*-Boc(Sar)$_2$OMe in Me_2SO-d_6 solution at 25 °C (restricted to the range 2.5–4.5 ppm). The underlined t (trans) or c (cis), together with the number, denotes the residue observed and the other (not underlined) denotes its neighbor. The residues are numbered from the N terminus.

We note that (i) although the cis–trans ratio for the analogous compound Ac-Sar-OMe (Ac is acetyl) varies somewhat as a function of solvent, the trans conformer is always strongly preferred.[37–39] (ii) The resonance of the protons of the methylene group of the cis conformer (a_c) of *t*-Boc-Sar-OMe lies at higher field than that of the protons of the methylene group of the trans conformer (a_t), in contrast to the behavior of Ac-Sar-OMe.[37–39] We attribute these differences to the presence of an additional oxygen atom in the urethane N-blocking group compared to the amide group.[40–42]

We have also examined the spectra of *t*-Boc-Sar-OH in D_2O (at 25 °C) at pD 3.0 and 9.5. The spectra are reported in Figure 2 and show that the urethane group has a strong preference for the cis form (approximately 3:1) which is independent of pD. (The infrared absorption spectrum suggests that the two carbonyl groups are fully solvated in D_2O.[43]) In contrast, previous ^{1}H NMR analyses have indicated that the distribution between the cis and trans isomers of X-Sar-OH (X = Ac, H_2^+-Sar, H_2^+-Gly) is strongly dependent on the state of protonation of the COOH group.[25,44–46]

A ^{1}H NMR investigation of *t*-Boc-Sar-OH at 0.2 M concentration in $CDCl_3$ solution, i.e., in its associated form,[47] has been reported by Branik and Kessler.[48,49] Splitting of the NCH_2 and *t*-Boc resonances was observed at 12 °C but not at room temperature.

(b) Dimers. The 360-MHz spectrum of *t*-Boc-(Sar)$_2$OMe in Me_2SO-d_6 solution, restricted to the range 2.5–4.5 ppm, is shown in Figure 3. The *t*-Boc resonance (not shown in the figure) indicates only the state of the N-terminal urethane group, which has a substantial pro-

portion of both cis and trans conformers; the cis conformer prevails by a 1.2:1.0 ratio as in the lower homologue *t*-Boc-Sar-OMe. The CO_2CH_3 resonance near 3.7 ppm signals the state of the C-terminal peptide bond, with the trans conformer prevailing by a nearly 3:1 ratio. The cis resonance seems to be more sensitive to the state of the next (N terminal) residue than does the trans resonance. The NCH_3 and NCH_2 resonances exhibit both positional and conformational sensitivities. Eight peaks would be expected in each region, assuming the NCH_3 and NCH_2 resonances distinguish all positions and all conformational isomers; not all are resolved. Tentative assignments of all peaks are reported in Figure 3, where for the NCH_2 peaks the assignments of the first (N terminal) residue are based on those of *t*-Boc-Sar-OMe and the assignments of the second (C terminal) residue on those of Ac-Sar-OMe.[37-39] The state of the urethane bond signaled by the *t*-Boc resonance (see above) is consistent with the assignments and intensities of the NCH_2 and NCH_3 resonances.

If these assignments are correct, it is noteworthy that the NCH_2 and NCH_3 protons of the C-terminal residue are insensitive to the state of the urethane bond when the peptide bond is trans. The NCH_3 protons of the N-terminal residue are likewise insensitive to the state of the peptide bond when the urethane bond is trans. But, surprisingly, the NCH_2 protons of the N-terminal residue are much more sensitive to the state of the peptide bond than to that of the urethane bond.

Similar findings were deduced from the 360-MHz spectrum of *t*-Boc$(Sar)_2$OMe in D_2O solution (spectrum not shown). In $CDCl_3$ solution, resolution of conformer resonances is much poorer, but at 360 MHz it is possible to conclude that the trans isomer predominates at the urethane bond. At 90 MHz in $CDCl_3$, each *N*-methyl and *O*-methyl signal is split into two resonances, but the *t*-Boc and NCH_2 resonances show no fine structure, in agreement with the observations of Mauger et al.;[36] these investigators found, however, that at 0 °C the *t*-Boc resonance splits into two singlets of equal intensity.

We have also examined the 90-MHz proton spectra of *t*-Boc$(Sar)_2$OMe in Me_2SO-d_6 solution as a function of temperature (Figure 4). The set of spectra covering the range 25–37 °C show the *t*-Boc cis–trans resonances collapsing to a singlet (at 90 MHz, resolution of the peaks associated with the cis–trans states of the N-terminal group is achieved only for the *t*-Boc resonance). The coalescence of the CO_2CH_3 (C terminal) cis–trans resonances is seen at 63 °C, whereas that of the NCH_3 and NCH_2 (C terminal) cis–trans resonances occurs near 73 °C. The broadening and collapse of the lines makes it difficult to measure the cis–trans ratios accurately as a function of temperature, but qualitatively there appears to be little change. It should be noted that at 73 °C the width of the peak of the N-terminal NCH_3 protons is markedly less than that of the peaks of the N-terminal NCH_2 and C-terminal NCH_2 and NCH_3 protons. These results are consistent with the rotational energy barrier of the urethane group, which is lower than that of amides, ca. 15–16 kcal mol^{-1} vs. ca. 20 kcal mol^{-1}.[41,42] At 133 °C the residual broadening due to conformational sensitivity has been removed and the NCH_2 and NCH_3 protons exhibit only positional sensitivity.

Two of us (C.T. and G.M.B.) have recently demonstrated by infrared absorption that *t*-Boc$(Sar)_2$OH exists as a monomer at about 5×10^{-4} M concentration in $CDCl_3$ solution,[43] whereas intermolecular hydrogen-bond formation, involving exclusively the COOH groups, becomes observable at 3×10^{-3} M concentration[47] and increases with

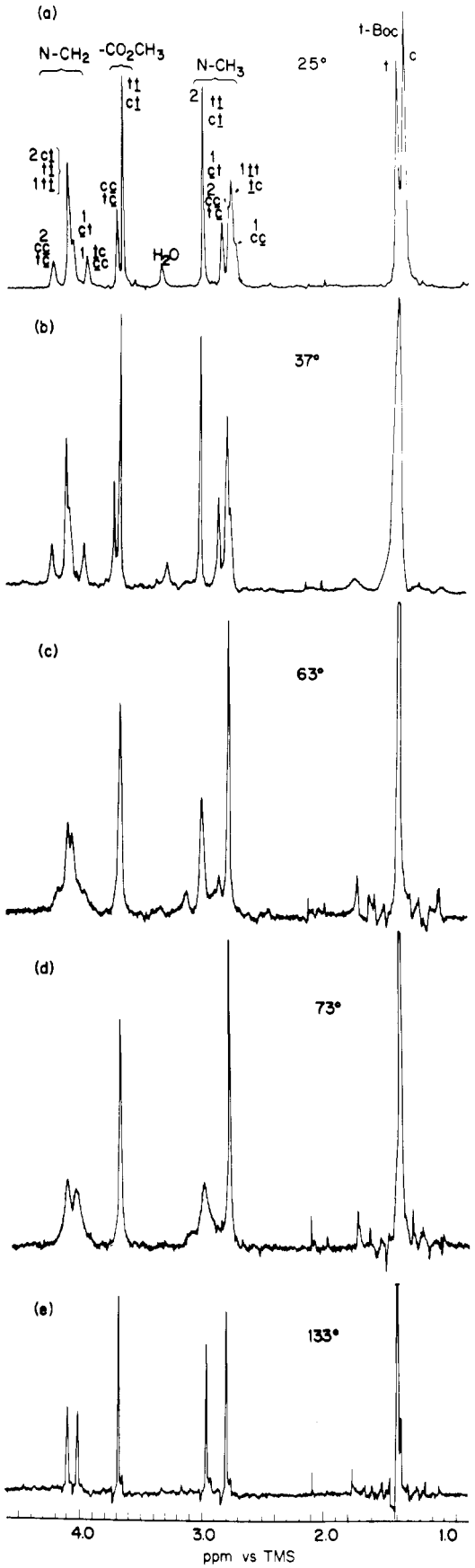


Figure 4. ¹H NMR spectra (90 MHz) of *t*-Boc$(Sar)_2$OMe in Me_2SO-d_6 solution at (a) 25, (b) 37, (c) 63, (d) 73, and (e) 133 °C.

increasing concentrations.[43] We now find that, observed at 90 MHz, the unassociated *t*-Boc$(Sar)_2$OH in $CDCl_3$ (5×10^{-4} M) exhibits cis–trans isomerism at the C-terminal

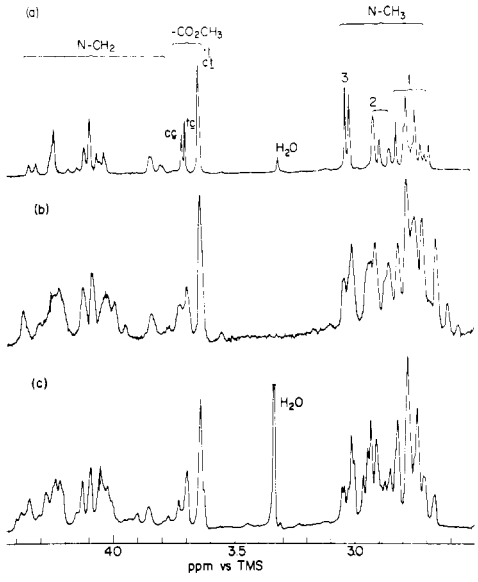


Figure 5. ^{1}H NMR spectra (360 MHz) of t-Boc(Sar)$_n$OMe: (a) n = 3; (b) n = 4; (c) n = 5 [observed in Me_2SO-d_6 at 25 °C (restricted to the range 2.5–4.5 ppm)].

residue with a strong preference for the trans conformer, and the t-Boc and NCH_3 resonances show one singlet each. A sixfold increase in concentration (to 3×10^{-3} M) has no observable effect on the ^{1}H NMR spectrum, strongly suggesting that self-association does not influence the cis–trans isomerism of t-Boc(Sar)$_2$OH. The present results and those of the infrared absorption study[43] do not support the formation of a substantial proportion of intramolecularly hydrogen-bonded forms[50] for t-Boc(Sar)$_2$OH in dilute $CDCl_3$ solution.

In contrast to what is observed in $CDCl_3$, the 90-MHz ^{1}H spectra of t-Boc(Sar)$_2$OH in D_2O (not shown) show two peaks for the t-Boc group and four peaks each for the NCH_2 and NCH_3 protons. Comparison of the spectra at pD 3.0 and 9.5 shows that as the pD is raised, the trans/cis ratio for the urethane bond decreases from 3:1 to 1:1, while that for the amide bond decreases from 4:1 to 2:1. We have seen that the infrared spectrum of t-Boc(Sar)$_2$OH shows that all carbonyl groups are strongly solvated in D_2O solution.[43] It thus appears that the observed variation of the cis/trans ratios for this peptide with pD cannot be readily reconciled with the formation of intramolecularly hydrogen-bonded species at low pD, e.g., of the type proposed for X-Gly-Sar-OH (X = Ac or H_2^+-Sar) peptides from ^{1}H NMR studies.[46,51]

(c) Higher Oligomers and Polysarcosine. The higher sarcosine homopeptides, t-Boc(Sar)$_n$OMe (n = 3–5), have been examined in three solvents, dimethyl sulfoxide, chloroform, and water, with different polarities and hydrogen-bonding properties. The 360-MHz spectra of trimer, tetramer, and pentamer in Me_2SO-d_6 solution are shown in Figure 5; those of the pentamer in D_2O and $CDCl_3$ solutions are illustrated in Figures 6 and 7, respectively. In Me_2SO-d_6 solution the t-Boc resonances of the oligomers with n = 3–5 (not shown in Figure 5) reflect only the state of the N-terminal urethane group, as in the dimer; the trans conformer is somewhat more preferred in the higher oligomers than in the dimer. The C-terminal amide bond exhibits a trans–cis ratio of nearly 3, as reflected in the OCH_3 resonances, and this changes little with chain length.

The NCH_3 and NCH_2 protons of the trimer, tetramer, and pentamer give spectra too complex for interpretation. It appears that all the peptide bonds exist in both cis and

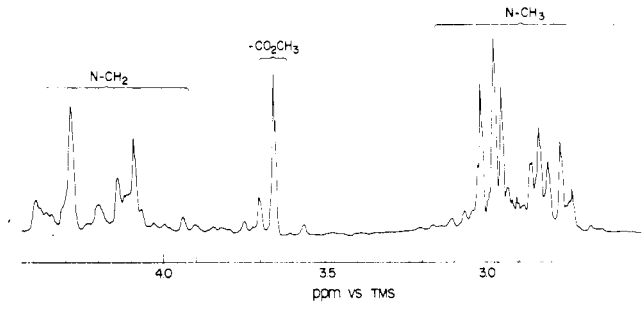


Figure 6. ^{1}H NMR spectrum (360 MHz) of t-Boc(Sar)$_5$OMe in D_2O at 25 °C (restricted to the range 2.5–4.5 ppm).

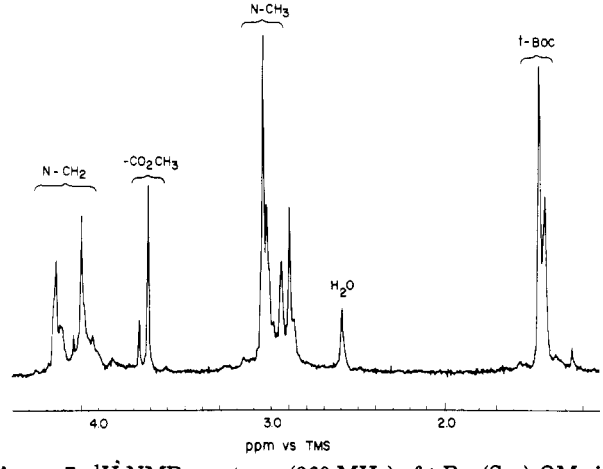


Figure 7. ^{1}H NMR spectrum (360 MHz) of t-Boc(Sar)$_5$OMe in $CDCl_3$ at 25 °C.

trans states, probably in ratios not far from 1:1 (with the exception of the C-terminal unit; see above). The spectra do not show as many resolved peaks as would be expected if all positions and all conformers were distinguishable; if that were the case, the number of peaks to be expected for either the NCH_3 or NCH_2 protons would be 24 for the trimer, 64 for the tetramer, and 160 for the pentamer. If each residue sensed only itself and its immediate neighbors, then the numbers of peaks would be 8, 16, 24, and 32, respectively. The actual numbers of resolved peaks are somewhat smaller than these values.

The spectrum of the pentamer is shown in D_2O in Figure 6. As in Me_2SO-d_6, there is a substantial proportion of both cis and trans conformers at all bonds, with the cis conformer prevailing at the urethane bond (from the t-Boc resonance, not shown) and the trans conformer prevailing at the C-terminal residue (from the OCH_3 resonance). Similar conclusions may be drawn from the spectrum in $CDCl_3$ (Figure 7), which, as for the dimer, shows fewer resolved peaks than observed in the more polar solvents. It appears that positional sensitivity is largely lost but that cis–trans conformers can still be distinguished.

Figure 8 shows the 360-MHz ^{1}H spectrum of polysarcosine in Me_2SO-d_6 at ca. 25 °C. Similar spectra have been previously reported by other investigators.[20,37,38,52-54] Since positional sensitivity can now be ignored, one expects eight resonances, corresponding to discrimination of the cis–trans conformations of each residue and those of its immediate neighbors (i.e., t–t–t, c–t–t, t–t–c, c–t–c, t–c–t, c–c–t, t–c–c, and c–c–c), actually, only four peaks are resolved, but this is sufficient to indicate clearly that the chain conformation is essentially random with respect to the peptide bonds. The present findings for the sarcosine oligomers are entirely in harmony with earlier conclusions concerning the polymer. The absence of ordered structure

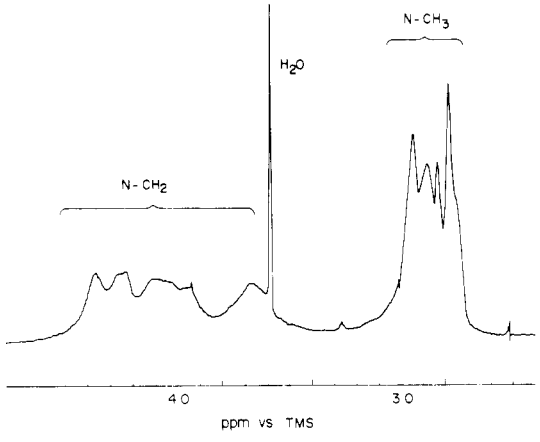


Figure 8. ¹H NMR spectrum (360 MHz) of polysarcosine ($\overline{DP} \simeq 68$) in Me_2SO-d_6 at 25 °C.

in the oligomers is confirmed by the observation that all members of the series *t*-Boc(Sar)$_n$OMe (n = 1–5) are viscous oils or gummy, noncrystallizable solids.[34]

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