Table I
Summary of the Effect of Short-Range Interactions on g for Molecules Containing a Trifunctional (Tetrafunctional) Branch Point and Branches of Equal Length[a]

σ	ψ	ω	n, 1%[b]	dg/dn[c]	n, min[d]	g, min[d]	$g_{min}/g_{n=\infty}$[d]
1.00	1	1.000	24 (52)	—	N.O.	N.O.	N.O.
0.54	1	1.000	250 (448)	+	12 (16)	0.716 (0.548)	0.921 (0.877)
0.54	1	0.088	650 (1200)	+	15 (16)	0.659 (0.480)	0.847 (0.768)
10.00	1	1.000	27 (960)	—	N.O.	N.O.	N.O.
10.00	1	0.000	2700 (4200)	+	36 (48)	0.603 (0.428)	0.775 (0.685)

[a] Results obtained with the tetrafunctional branch point are given in parentheses. [b] Number of bonds required for g to be within 1% of its asymptotic limit. [c] Sign of dg/dn on the approach to the asymptotic limit. [d] Results when g experiences a minimum; N.O. = not observed.

Comparison with the results for the corresponding linear molecules (Figures 1, 3, 5, 7 and 9) reveals a correlation between the characteristic ratio for the linear molecule and the sign of dg/dn upon the approach to the asymptotic limit for the branched molecule. Those short-range interactions which lead to a large characteristic ratio for the linear molecule cause dg/dn to be positive upon the approach to the asymptotic limit for the branched molecule. For the cases considered, the minimum experienced by g becomes more pronounced for those short-range interactions which lead to larger characteristic ratios for the linear molecule.

Tonelli[12] has calculated g for certain branched polyethylenes. His approach differs from that used here in that he uses an approximate, rather than the exact, expression for the configuration partition function and certain of his statistical weight matrices were formulated incorrectly.[5] Nevertheless, the results which he obtains for g for the cases where there is a single branch point are generally only slightly larger than those obtained by the present method. The close agreement may be achieved in part because his n in several cases are large enough so that g has nearly attained its asymptotic limit. Tonelli also reports that $g_{mc} < 1$ only if $\Delta\phi \neq 0°$, a conclusion which is contradicted by the results we report in Figure 6.

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Hard Block Length Distribution in Segmented Block Copolymers

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ABSTRACT: Further evidence is presented to show that under ideal conditions and at complete conversion under stoichiometric conditions the sequence length distribution of hard block segments in a segmented block copolymer follows the most probable distribution. A two-stage polymerization results in a narrower distribution of hard blocks than a single-stage polymerization of the same stoichiometry when the first reaction of the low molecular weight difunctional monomer is faster than the second reaction ($\mu > 1$). In the two-stage polymerization, at intermediate extents of conversion the hard block segments can be classified into six types, depending on how the segment is capped. At conversions greater than 0.10, the concentrations of all segment types follow the geometric distribution $N_i = N_1\alpha^{i-1}$, where i is the number of extender molecules in the segment under consideration, N_1 is the concentration of the first member of the series, and α is a function of conversion and is independent of the segment type.

A two-stage polymerization of segmented block copolymers is defined as the polymerization of an excess low molecular weight difunctional monomer, usually a diisocyanate, with a macrodiol to complete reaction of the macrodiol, followed by a second-stage polymerization, with a low molecular weight diol or diamine extender. Many difunctional monomers exhibit different rates of reaction for the two functional units. The reaction rate of the first isocyanate group is usually faster than that of the second; hence, the reactivity ratio μ is greater than unity.[1] The reason for the difference in reaction rates may be due to steric hindrance, alteration of the induction-resonance condition of the molecule when it is partly reacted, or the molecular configuration in the transition state. The resulting polymer consists of blocks of macrodiol separated by various amounts of a diisocyanate-extender alternating copolymer. The first paper in this series[2] was concerned with the sequence length distribution of the diisocyanate-extender copolymer within a segmented polyurethane block copolymer. In order to count the number of units in each se-

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quence, various definitions of a hard block segment were made, then the results of the definitions were compared. From the definitions chosen in ref 2, it was found that the same average length of sequences resulted, independent of the definition of a hard block. This observation led to the conclusion that the sequence length distribution followed the most probable form. In this paper a hard block segment is defined as the sequence contained between two consecutive macrodiol units. Further evidence is presented on the distribution of sequence lengths in polyurethanes which are formed only by condensation of an isocyanate group with a hydroxyl group without side reactions and are prepared under stoichiometric conditions. It will be shown that the concentration of the hard block segments depends on the polymerization recipe and whether a one- or a two-stage reaction is used.

Theoretical Development and Discussion

The same assumptions used in the previous paper are made: (1) the reactivity of one end of a diisocyanate monomer depends only on whether or not the other end has reacted; (2) the reaction between a diisocyanate and a diol is irreversible; (3) if one of the diisocyanate ends has reacted, the reactivity of the unreacted end is independent of the molecular weight of the polymer to which it is attached; (4) the extender is a low molecular weight diol; (5) the reactivity of any hydroxyl group is independent of molecular weight; and (6) no other reactions occur. An additional requirement imposed here is that polymerization occurs under stoichiometric conditions. These assumptions certainly do not apply in practice. Therefore, the examples to be considered refer to ideal situations.

At the end of the first-stage reaction between excess diisocyanate and macrodiol, when the macrodiol has reacted completely, the concentration of diisocyanate monomer X_1^0 is a positive root of the relation[2]

$$\mu(X_1^0/A_1)^{1/2\mu} + (\mu - 1)(X_1^0/A_1) = (2\mu - 1)(A_1 - B_1)/A_1 \quad (1)$$

while the concentration of monomer plus oligomer is $A_1 - B_1$, where A_1 is the initial concentration of diisocyanate and B_1 is the initial concentration of macrodiol. Each oligomer molecule contains two terminal diisocyanate residues and perhaps some internal diisocyanate residues. The total concentration of the internal diisocyanate residues X_1^{int} can be found from the concentration of diisocyanate residues in the oligomer, $A_1 - X_1^0$, less the concentration of oligomer chain ends, $2(A_1 - B_1 - X_1^0)$:

$$X_1^{int} = 2B_1 + X_1^0 - A_1 \quad (2)$$

Now let P_i be the concentration of sequence lengths that contain exactly i extender units, sandwiched between two macro units. It follows that in any sequence of i extender units, there are exactly $i + 1$ diisocyanate units. If the reaction is carried to completion under stoichiometric conditions, then the initial concentration of diisocyanate and of extender, C_1, is given by

$$A_1 = X_1^{int} + \sum_{i=1}^{\infty} (i + 1)P_i \quad (3)$$

$$C_1 = \sum_{i=1}^{\infty} iP_i \quad (4)$$

Under these conditions, each sequence of diisocyanate units is followed by a macro unit, or stated differently, the concentration of X_1^{int} plus the total concentration of sequences containing extender units must equal the concentration of macro units:

$$B_1 = X_1^{int} + \sum_{i=1}^{\infty} P_i \quad (5)$$

This equation also results from A_1 and C_1 by difference.

The number average number of extender units is then

$$\bar{i} = \sum_{i=1}^{\infty} iP_i \Big/ \sum_{i=1}^{\infty} P_i = 1/(1 - p) \quad (6)$$

where

$$p = X_1^0/C_1 \quad (7)$$

In the previous paper, it was inferred that the distribution of sequences followed the most probable form, because it made no difference in the number average number of counted units whether the extender molecules or the diisocyanate monomer units left over from the first stage were counted.[3] Therefore, let

$$P_i = K\alpha^i \quad (8)$$

The parameters, K and α, can be evaluated by substitution into eq 4 and 6 to yield

$$P_i = C_1(1 - p)^2 p^{i-1} \quad (9)$$

On normalization, the Schulz–Flory equation results

$$F(r) = P_i/\sum P_i = (1 - p)p^{i-1} \quad (10)$$

The derivation still makes the assumption given by eq 8, consequently it is not established that eq 9 is unique; other solutions may exist.

The same type of reasoning used in the development of eq 3–5 can be applied to a single stage polymerization where stoichiometric amounts of macrodiol, extender, and diisocyanate are reacted simultaneously to complete conversion. In this case, the number of diisocyanate units will be counted. Let S_j be the number of diisocyanates sandwiched between two macrodiols, and

$$A_1 = \sum_{j=1}^{\infty} jS_j \quad (11)$$

$$B_1 = \sum_{j=1}^{\infty} S_j \quad (12)$$

$$C_1 = \sum_{j=1}^{\infty} (j - 1)S_j \quad (13)$$

and

$$\bar{j} = 1/(1 - C_1/A_1) = 1/(1 - q) \quad (14)$$

Therefore, by assuming the geometrical distribution again

$$S_j = (B_1^2/A_1)q^{j-1} \quad (15)$$

which is independent of μ. When $\mu = 1$, it can be shown that

$$S_j = P_{j-1} \text{ when } j > 1 \quad (16)$$

and

$$S_1 = X_1^{int} \quad (17)$$

The equivalence of a single-stage reaction with a two-stage reaction with $\mu = 1$ follows from chemical logic because of assumption (5), that the reactivity of hydroxyl groups on extender molecules equals that on the macrodiol. If this assumption is relaxed, then another set of parameters needs to be incorporated into the kinetic scheme.

One can then ask about the advantages of a two-stage polymerization over a single-stage polymerization, from a theoretical point of view. Figure 1 shows the weight fraction of sequences containing k diisocyanate residues as a function of k, A_1, and μ. The distribution was calculated

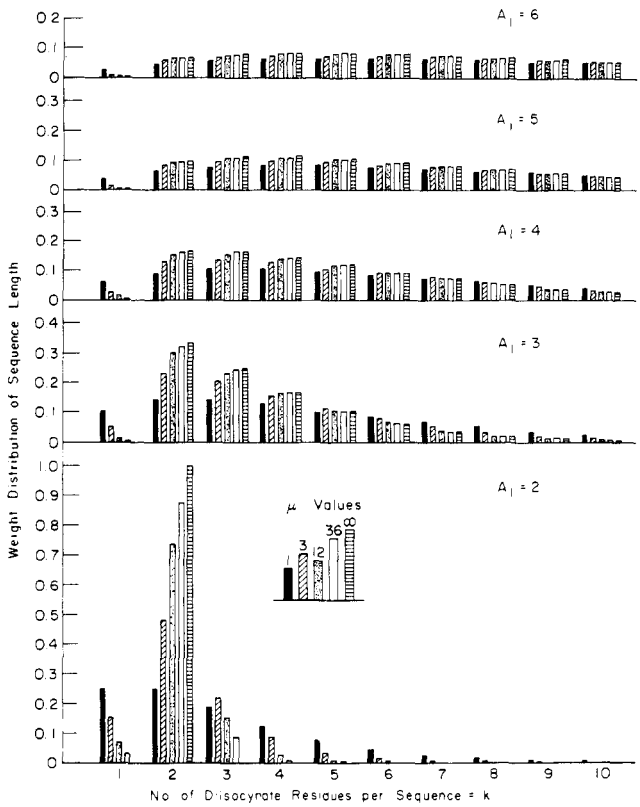

Figure 1. Weight fraction of sequences containing k diisocyanate units between two consecutive macrodiol units. See text for further discussion.

Table I
The Heterogeneity Index, $\bar{k}_w/\bar{k}_n$, of Diisocyanate Sequences for Two-Stage Polymerization as a Function of μ for Various Initial Concentrations of Diisocyanate A_1[a]

Reactivity ratio μ	A_1[b] 2	3	4	5	6
1/3	2.242	2.377	2.377	2.347	2.323
1	1.500	1.668	1.750	1.880	1.833
3	1.220	1.390	1.513	1.591	1.652
12	1.081	1.268	1.411	1.509	1.581
36	1.035	1.238	1.386	1.490	1.564
∞	1.000	1.222	1.375	1.480	1.555

[a] A single-stage polymerization is equivalent to the values of $\mu = 1$. [b] $B_1 = 1$, $C_1 = A_1 - 1$.

from the weight fraction of diisocyanate residues in sequences containing extender units, $(i + 1)P_i/A_1$, and the weight fraction of isolated internal units X_1^{int}/A_1. The figure is complicated because two variables, μ and k, are shown in each section. Consider the portion $A_1 = 3$ and $k = 2$. The five vertical bars represent the weight distribution of sequence lengths for $\mu = 1$, 3, 12, 36, and ∞, respectively. To examine the distribution as a function of k when $\mu = 12$, $A_1 = 3$, look only at the central bar within each set, ignoring the other four bars. Comparison of the $\mu = 12$ vs. $\mu = 1$ distributions for $A_1 = 3$ shows that the two-stage distributions with $\mu = 12$ have higher concentrations of the sequences containing 2, 3, and 4 diisocyanate residues and lower concentrations for all remaining k. When $A_1 = 2$ and $\mu = \infty$ in a two-stage polymerization, the only sequence present is the one containing two diisocyanate residues; under this one condition, an ordered copolymer exists. For all other conditions, a most probable distribution results; but all distributions with $\mu > 1$ are narrower than the one representing a single-stage recipe. The greatest effect between the single vs. the two-stage reaction occurs at low values of A_1. Furthermore, the value of X_1^{int} decreases with increasing μ. These conclusions, of course, are based on the assumptions made; this includes the assumption that the allophonate reaction does not occur at the end of the first stage of the two-stage reaction.

Table II
Values of A_1, μ, and p Used in the Computer Evaluation of P_i with $B_1 = 1$, $C_1 = A_1 - 1$

A_1	μ	p	A_1	μ	p
2	1	0.500	3	1	0.667
	3	0.306		3	0.580
	36	0.066	6	1/3	0.871

Another way of examining the various distributions is to compare the ratio of the weight average number of diisocyanate residues to the number average number, $\bar{k}_w/\bar{k}_n$.

$$\bar{k}_n = A_1/(X_1^{int} + \sum_{i=1}^{\infty} P_i) = A_1/B_1 \quad (18)$$

$$\bar{k}_w = \frac{X_1^{int} + \sum_{i=1}^{\infty} (i+1)^2 P_i}{X_1^{int} + \sum_{i=1}^{\infty} (i+1) P_i} = \left[A_1 + C_1 + C_1\left(\frac{1+p}{1-p}\right)\right]\Big/A_1 \quad (19)$$

Table I gives values of $\bar{k}_w/\bar{k}_n$ as a function of A_1 and μ. Equations 18 and 19 as well as the entries in Table I differ from the results given in ref 2 because different definitions of the hard block segment are being used; here the hard block consists of all diisocyanate sequences. The conclusions remain the same; however, higher values of μ lead to narrower distributions while higher values of A_1/B_1 (which is $\bar{k}_n$) lead to wider distributions. Within the limits of the kinetic assumptions, the polymerization recipe can be adjusted to produce known variations in the sequence length distribution of the hard blocks.

The value of P_i can also be obtained by computer solution of the simultaneous differential equations relating the concentration of the various species that exist as a function of time during the second stage of polymerization. These species are: [~x], the total concentration of oligomer ends which have not reacted during the second stage, u_i = $[X_1(CCX_1)_i]$, v_i = $[(X_1CC)_i]$, w_i = $[CC(X_1CC)_{i-1}]$, R_i = $[\sim xCC(X_1CC)_{i-1}]$, Q_i = $[\sim x(CCX_1)_i]$, and P_i = $[\sim x(CCX_1)_{i-1}CCx\sim]$, where X_1 comes from the monomer remaining at the end of the first stage, x from the oligomer chain ends, and CC represents the extender molecule. The differential kinetic equations for these species can be found by the procedures given in ref 2.[4] The concentration of each species from $i = 1$ to 9 was calculated by Runga-Kutta integration of the equations for values of A_1 and μ given in Table II. The range of p values covered varies from 0.066 to 0.871. When $\mu = 1$, the distribution must be of the most probable form. As there is a small accumulation of error, the values of P_i at complete conversion had to be extrapolated from the values determined at 96, 97, 98, and 99% conversion. These values agreed to within ±0.3% of those calculated from eq 9. As P_i decreases slowly with increasing i, the remaining P_i can be evaluated from the average value of P_{i+1}/P_i. The sum of the P_i agreed with that calculated from eq 9 to within 0.06%. These calculations give further necessary but not sufficient evidence that the actual distribution resulting from the assumptions enumerated in the introductory section follows the most probable distribution.

It is also informative to examine the distribution of the various species as a function of conversion. At zero conversion, only the species w_1 exists, in addition to the oligomer chain ends. As conversion increases, the concentration of w_1 decreases, while the concentrations of u_i, v_i, w_i ($i > 1$), R_i, and Q_i first increase, reach a maximum, and then decrease. The concentration of P_i continually increases with conversion. These results are to be expected. On the other hand, it is observed that the ratio of concentration of each species to that containing one unit less was essentially constant and independent of the species type. Stated mathematically

$$u_{i+1}/u_i \simeq v_{i+1}/v_i \simeq w_{i+1}/w_i \simeq R_{i+1}/R_i \simeq Q_{i+1}/Q_i \simeq P_{i+1}/P_i \simeq p(c)$$

where $p(c)$ is a function of conversion but is independent of i if conversion is greater than 10%. Below 10%, p slowly decreases with increasing i. Therefore, the sequence length distribution of extender units follows a geometric distribution similar to eq 8 for all of the species present at high conversion. One method of testing the results of the calculations would be to selectively hydrolyze the ester groups of a polyester macrodiol while leaving the urethane groups unchanged.[5] The hard block distribution of diisocyanate residues can be determined by gel permeation chromatography.

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Supplementary Material Available: program for computing the various distributions as a function of conversion (5 pages). Ordering information is given on any current masthead page.

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Conformation of *cyclo*-(L-Leu-L-Tyr-δ-Avaler-δ-Avaler), a Synthetic Inhibitor of Chymotrypsin, by X-Ray Analysis

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ABSTRACT: The synthetic cyclic tetrapeptide (L-Leu-L-Tyr-δ-Avaler-δ-Avaler) is an effective inhibitor of chymotrypsin, competitive with linear peptides like Ac-L-Leu-L-Tyr-OMe. An x-ray diffraction analysis of the crystal structure of the cyclic peptide shows that the conformation of the 18-membered ring is very similar to that of one of the four conformers of cyclic hexaglycyl. There is no internal hydrogen bonding. Side chains are located on two "corners" of the approximately rectangular ring. The χ_{i1} angles for Leu and Tyr are −74 and −48°, respectively. The Leu side chain is extended away from the polypeptide ring while the Tyr side chain is folded under an adjacent carbonyl bond. The cell parameters for the space group $P2_1$ are: a = 9.361 (3) Å, b = 19.039 (10) Å, c = 9.603 (3), Å, and β = 116.54 (3)°. A molecule of $(CH_3)_2SO$ (disordered) and a molecule of H_2O cocrystallized with the cyclic peptide.

Chymotrypsin is active in the duodenum, cleaving further the partially digested food (chyme) passing from the stomach. The major sites of action on the substrates are on the peptide bonds of residues containing aromatic or large aliphatic side chains such as Trp, Phe, Tyr, and Leu. Models of effective, irreversible synthetic inhibitors like acetyl-L-Ala-L-Ala-L-Phe-chloromethyl ketone bound to the substrate binding site in chymotrypsin have been proposed by Segal et al.,[1] based on difference maps from x-ray diffraction data. More recently Tsetlin et al.[2,3] have shown that the synthetic *cyclo*-(L-Leu-L-Tyr-δ-Avaler-δ-Avaler), where Avaler ≡ aminovalerate, containing an 18-membered ring is a very effective inhibitor, competitive with linear substrates like Ac-L-Leu-L-Tyr-OMe. The inhibitor does not undergo hydrolysis. The purpose of this investigation was to determine the conformation of *cyclo*-(L-Leu-L-Tyr-δ-Avaler-δ-Avaler) in order to compare the models of the linear inhibitors used by Segal et al.[1] and to compare the known conformations of cyclic hexapeptides.[4,5]

Experimental Section

Intensity data from colorless, well-formed crystals, derived from $(CH_3)_2SO{\cdot}H_2O$ solution, were collected with the θ–2θ scan technique on a four-circle automatic diffractometer using a scan of $2.0° + 2\theta_{(\alpha_2)} - 2\theta_{(\alpha_1)}$ and a scan speed of 2°/min. The intensities of three reflections, monitored every hour, remained constant during the experiment, thus indicating that there was no deterioration of the crystal upon exposure to x rays. Data, collected to $2\theta_{max} = 126°$, were corrected for Lorentz and polarization factors. Normalized structure factors, $|E_h|$, were obtained with the use of a K curve. Cell parameters and other pertinent data are listed in Table I.

The structure was derived with the aid of the direct method for phase determination.[6] Some confusion arose because the strongest peaks formed several triangles sharing common sides, with distances of bonding length. It was determined later that the S atom in $(CH_3)_2SO$, a solvent molecule cocrystallized with the peptide, was disordered between two positions and that one-half S weight in two positions plus full weight for the O atom and two C atoms accounted for the strange configuration. Meanwhile, a fragment of the peptide structure, recognized in an E map from a less probable phase set, was used to derive the structure. The fragment was misplaced with respect to the origin of the cell. Therefore, the symmetry was lowered to $P1$ and the data were doubled by letting $|E_{hkl}| = |E_{\bar{h}\bar{k}l}|$ and $|E_{\bar{h}kl}| = |E_{h\bar{k}\bar{l}}|$, but with $\phi_{hkl} \neq \phi_{\bar{h}\bar{k}l}$ and $\phi_{\bar{h}kl} \neq \phi_{h\bar{k}\bar{l}}$. The fragment of the peptide was then used in the partial structure procedure[7] which yielded the positions of all the atoms in the two peptide molecules in a unit cell. From the relationship of the two