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Ring-Closure Reactions. 12.[1] gem-Dimethyl Effect in Some Medium and Large Rings[2]

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A quantitative determination of the gem-dimethyl effect on the rate of lactonization of ω-bromoalkanoate ions in 99% aqueous Me₂SO is reported for five representative ring sizes in the common-, medium-, and large-ring regions. The experimental results are tentatively discussed by extension to the many-membered rings of the Allinger and Zalkow approach to the gem-dimethyl effect on common ring formation. More pictorial interpretations as based on preferential conformations to cyclization are critically compared.

Our studies[1,3] on the energetics of the intramolecular reactions of bifunctional chains have shown that structural effects are quite marked up to chain lengths leading to the formation of common and medium rings and become less and less important as the chain length increases. As a consequence, the effective molarity (EM) of the reaction tends to level off toward the formation of large rings and to approach an average value of about -1.6 log EM units.[4]

There is evidence that such a behavior also applies to structural modifications within the chain of a given series, as illustrated by the oxygen atom effect and by the rigid group effect for the formation of benzocyclo ethers.[3a,4] A structural modification of special interest is the geminal substitution of methyl groups at a methylene carbon of the chain to give rise to rate enhancements of varying intensity.[5] The gem-dimethyl effect has been interpreted by Allinger and Zalkow[6] in thermodynamic terms and by other authors[7,8] in terms of profitable rotamers or stereopopulation control.

Quantitative data for the gem-dimethyl effect can be found for three- to six-membered rings.[5] However, little is known for medium- and large-ring formation. Preparative work[9,10] has yielded some evidence of this effect for 8-, 9-, and 16-membered rings.

It seemed of interest to carry out a kinetic study of the gem-dimethyl effect as a function of chain length to cover a broad spectrum of ring sizes (n). Although a systematic investigation of this kind would require a considerable and supposedly tedious effort[11] to test bifunctional substrates of varying lengths and positions of geminal methyl substitution along the chain of any member in a series, the study of a selected group of the more accessible substrates was still expected to provide significant information on the general features of the effect in medium and large rings.

In this paper we wish to report on the kinetics of cyclization

of the ω-bromo derivatives of the 3,3-dimethylalkanoate (C₅, C₈, C₉, C₁₀) ions and of the 9,9-dimethylpentadecanoate (C₁₅) ion leading to 6-, 9-, 10-, 11-, 16-membered macrolides 1–5, respectively, and to compare their reactivity with that of the related unsubstituted ω-bromoalkanoates.[1,3b]

Results and Discussion

The synthesis of ω-bromo acids generally involves long reaction sequences and low to moderate overall yields.[11] Mixed anodic coupling in MeOH of ω-bromo acids and half esters of bicarboxylic acids offers a simple one-step route to long-chain ω-bromo esters.[12] This method was studied in some detail by Woolford,[13] who found that, besides the expected symmetrical and unsymmetrical products, significant amounts of the methyl esters of starting materials were also formed. The presence of these unexpected products lowered the yields, increased the difficulties of purification, and seemed to hamper the general validity of the method.[13c] Although the conditions used in the present work (see, also, Experimental Section) differ from Woolford's but slightly, we obtained better results for all tested compounds. We used electrodes placed 5 mm apart and no more than 80–110 V (1.2–1.4 A). The internal temperature was always kept at 45 °C or less (35 °C for the coupling with 5-bromopentanoic acid, that failed to react under Woolford's conditions[13a]). The total molar concentration was in the range 0.2–0.4 M. Lower concentrations generally led to poor yields of product. In order to in-

Table I. Unsymmetrical Kolbe Syntheses of *gem*-Dimethyl Substituted ω-Bromo Esters

bromo acid	monoester	molar ratio	% yield of unsymm. product,[a]	n_D (°C)
Br(CH₂)₄CO₂H[b] ⎫		2.2/1	40[h]	1.4652 (19)
Br(CH₂)₅CO₂H[c] ⎬	HO₂CCH₂C(CH₃)₂-CH₂CO₂CH₃[f]	2.1/1	36[i]	1.4623 (16)
Br(CH₂)₆CO₂H[d] ⎭		1.8/1	20[j]	1.4596 (26)
Br(CH₂)₆C(CH₃)₂-CH₂CO₂H[e]	HO₂C(CH₂)₆CO₂-CH₃[g]	1/5	39[k]	1.4509 (19)

[a] Yields are based on compound present in lesser molar amount. A 20–40% yield of the dibromoalkane produced by symmetrical anodic coupling of the starting bromo acid was always obtained as a forerun. [b] Registry no. 2067-33-6. [c] Registry no. 4224-70-8. [d] Registry no. 30515-28-7. [e] Registry no. 69120-89-4. [f] Registry no. 27151-66-2. [g] Registry no. 3946-32-5. [h] Registry no. 69120-90-7. [i] Registry no. 69120-91-8. [j] Registry no. 69120-92-9. [k] Registry no. 69120-93-0.

Table II. Physical Data for the *gem*-Dimethyl Bromo Acids

bromo acid		% Br calcd	% Br found
Br(CH₂)₂C(CH₃)₂-CH₂CO₂H	mp 56.5–58 °C	38.22	38.01
Br(CH₂)₅C(CH₃)₂-CH₂CO₂H	bp 137–139 °C (0.4 mm Hg), n^{20}_D 1.4771	31.81	31.33
Br(CH₂)₆C(CH₃)₂-CH₂CO₂H	bp 139–140 °C (0.2–0.3 mm Hg), n^{17}_D 1.4797	30.13	30.05
Br(CH₂)₇C(CH₃)₂-CH₂CO₂H	bp 175 °C (0.9 mm Hg), n^{27}_D 1.4724	28.62	28.54
Br(CH₂)₆C(CH₃)₂-(CH₂)₇CO₂H	n^{16}_D 1.4789[a]	22.87	22.83

[a] Microdistilled with the ball tube under high vacuum.

crease the yield of the unsymmetrically coupled product, the more readily available out of the two reagents was used in excess. Under such conditions we did not find any byproducts, the purification of the crude by means of column chromatography was straightforward, and the yields of unsymmetrical compound were satisfactory. Yields and physical constants of the synthesized compounds are listed in Tables I and II, respectively.

The reactions of the bifunctional chains thus obtained were carried out in 99% (v/v) aqueous dimethyl sulfoxide solution at 50 °C and followed by a micropotentiometric method as described in previous work.[3b] The initial substrate concentrations were about 10^{-4} M, i.e., sufficiently low to let any contribution of the polymerization reaction be negligible. First-order plots were linear up to 75% reaction, and the related rate constants were independent of the initial concentration over fourfold changes. The results are reported in Table III. The log k values obtained in the present work are plotted in the general reactivity diagram[3b] for lactone formation as a function of n (Figure 1). The *gem*-dimethyl effect (k_{rel}) was obtained as the ratio of the rate constant for the *gem*-dimethyl substituted derivative over the corresponding unsubstituted substrate of equal chain length.

gem-Dimethyl effects for six-membered ring formation from the aliphatic bifunctional chain have been found to be of one or two orders of magnitude.[5,14] Accordingly, for the formation of compound 1 we find a factor of 38.5.

Table III. *gem*-Dimethyl Effect on the Rate of Lactone Formation from the Potassium Salts of ω-Bromo Acids in 99% Aqueous Me₂SO at 50.0 °C

ω-bromo acid	n[a]	k, s⁻¹	ref	k_{rel}[b]
Br(CH₂)₂C(CH₃)₂-CH₂CO₂H	6	72.4[c]	this work	38.5
5-bromopentanoic	6	1.88	1	1.0
Br(CH₂)₅C(CH₃)₂-CH₂CO₂H	9	8.21×10^{-4}	this work	6.62
8-bromooctanoic	9	1.24×10^{-4}	3b	1.0
Br(CH₂)₆C(CH₃)₂-CH₂CO₂H	10	4.22×10^{-4}	this work	1.13
9-bromononanoic	10	3.72×10^{-4}	3b	1.0
Br(CH₂)₇C(CH₃)₂-CH₂CO₂H	11	5.75×10^{-4}	this work	0.61
10-bromodecanoic	11	9.45×10^{-4}	3b	1.0
Br(CH₂)₆C(CH₃)₂-(CH₂)₇CO₂H	16	7.06×10^{-3}	this work	1.22
15-bromopentadecanoic	16	5.77×10^{-3}	3b	1.0

[a] Ring size of the ring to be formed. [b] Evaluated from the ratio of the substituted over the unsubstituted bromo acid with the same chain length. [c] See text.
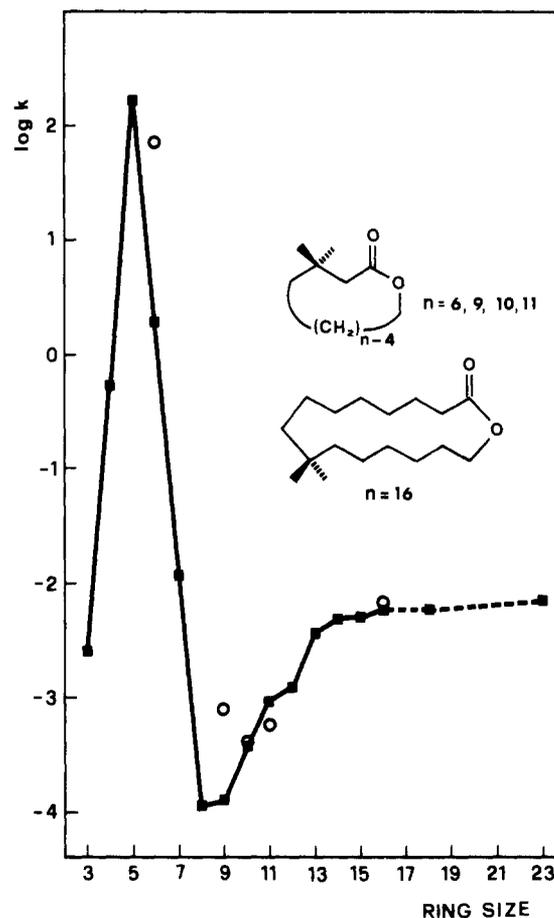
Figure 1. Plot of the *gem*-dimethyl effect on lactone formation from ω-bromoalkanoate ions in 99% aqueous Me₂SO at 50.0 °C: (○) *gem*-dimethyl compounds (this work); (■) unsubstituted compounds (ref 1 and 3b).

The observed effects are particularly significant for compounds 1 to 4 where the *gem*-dimethyl substitution is systematically located at the β-methylene carbon. They tend to decrease as the size of the ring increases. The effect is still appreciable for $n = 9$ (2, rate ratio 6.6), but it becomes negligible for $n = 10$ (3, rate ratio 1.13) and slightly inverse for $n = 11$ (4, rate ratio 0.61). This behavior indicates that the

gem-dimethyl effect may be caused by more than one factor.[5]

Two favorable factors have been clearly identified by Allinger and Zalkow[6] for the formation of cyclohexane and include a ΔH^0 (or $\Delta H^{\ne}$) contribution to the equilibrium (or reaction rate) due to a reduced increase in gauche interactions in the ring to be formed in going from the unsubstituted to the alkyl substituted case and a ΔS^0 (or $\Delta S^{\ne}$) contribution due to reduced internal rotations in the starting alkyl substituted open chain.

No information is available as to the effect on the entropy of many membered rings caused by the introduction of alkyl groups. However, since the looseness of ring structures generally increases on increasing ring size from the rigid six-membered ring up to the large rings,[15] for which the freedom of internal motions should closely resemble that of the open chain precursors, the entropy advantage due to *gem*-dialkyl substitution is likely to become less and less important as the chain becomes longer.

As to the enthalpy effect, presumably either a less favorable or unfavorable ΔH^0 (or $\Delta H^{\ne}$) contribution may originate from increased strain in the transition state of the alkyl-substituted case and is likely to play a role in the medium-ring region where steric crowding is known to be more relevant than in the six-membered lactone.[16] Negligible effects of this kind are expected to arise in the formation of the strainless large rings.

The observed effects for n = 9, 10, and 11 are thought to be the result of the relative intensities of the factors at work in the formation of each ring. The opposing strain factor would more than offset the favorable factors for n = 11, where an inverse effect is observed. In accordance with the expectations, the *gem*-dimethyl effect for the formation of the 16-membered ring 5 is as little as 1.2. The effective molarity for the formation of lactone 5 is ~1.4 log units, that is quite close to the average value (−1.6) obtained from several series.[4]

A more pictorial approach to interpret the *gem*-dialkyl effect is based on the assumption that a *gem*-dialkyl substitution at a methylene position gives rise to preferential conformations resembling the ring to be formed and allowing the reactive ends of the chain to be close to each other.[7-9,17] This view cannot be regarded as an alternative, independent one but, rather, an equivalent description which may be equally correct as long as it is consistent with the necessary thermodynamic requirements (Allinger and Zalkow's approach).[18,19] Although the *gem*-dialkyl effect manifests itself through a rate enhancement, it should not be considered as a sort of special "catalytic" effect since it can be explained by the application of standard thermodynamic concepts as part of the general problem of intramolecular reactivity.[20] This is because alkyl groups by an appropriate structural modification of the chain tend to "restore" part or all of the optimal conditions for a more loosely structured bifunctional chain to react intramolecularly. The maximum rate effect of this kind has been proposed to be in the order of a 10^4-fold factor.[21] Much larger effects[8b] have been assigned to the superposition of steric compression effects.[21]

Evidence for the role of profitable rotamers in the *gem*-dialkyl effect has been critically summarized recently[5] for common rings. The extension of the concept to medium- and large-ring formation is in our opinion less firmly founded although it has been assumed to be valid in a number of instances.[9,17,22] In fact, the increasing looseness in long chains make preferential conformations of the kind referred to above less likely to play an "exclusive" role to facilitate the reaction. The experimental effects seem to be at any rate modest or negligible as the present data indicate and seem to be hardly worth discussing in conformational terms.

In order to obtain a completely reliable test for the existence of specific conformational situations favoring the *gem*-dialkyl effect in long chains, all possible isomeric *gem*-dialkyl derivatives should be examined. Recent preparative work by Borgen[10] provides a partial answer in this direction. Three diverse routes to 16-membered cyclic diynes lead to differently located bis(*gem*-dialkyl) substitutions. Although the highly perturbed nature of the chosen systems favors the appearance of a *gem*-dimethyl effect, the yield data do not show any appreciable difference from one another. This result clearly adds to the examples herein described indicating that the preferential conformation approach is not generally significant in medium- and large-ring formation.

Experimental Section

All techniques and apparatuses were as previously described.[3b] IR and ¹H NMR spectra were taken from CCl₄ solutions.
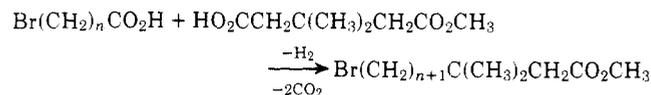
Materials. Methyl hydrogen suberate[23] and 5-bromopentanoic, 6-bromohexanoic, and 7-bromoheptanoic acids[24] were prepared as previously reported. Methyl hydrogen 3,3-dimethylglutarate was synthesized in 91% yield by treatment of 3,3-dimethylglutaric anhydride with sodium methoxide in methanol, followed by acidification and standard workup.[25] This compound had $n^{19}{}_D$ 1.4434 and showed the expected ¹H-NMR spectrum.

All boiling and melting points are uncorrected.

5-Bromo-3,3-dimethylpentanoic Acid. Methyl hydrogen 3,3-dimethylglutarate was reduced with LiAlH₄ in anhydrous diethyl ether and, after acidification, standard workup and distillation; a 40% yield of 3,3-dimethyl-5-pentanolide was isolated: bp 124–126 °C (22 mm Hg); $n^{26}{}_D$ 1.4451; IR $\nu_{C=O}$ 1750 cm⁻¹ (lit.[14] bp 110 °C (10 mm Hg); $n^{25}{}_D$ 1.4480).

The acid was obtained by hydrolysis of the lactone with excess anhydrous HBr in AcOH for 3 days at room temperature: mp 56.5–58 °C (light petroleum) (84% yield); IR $\nu_{C=O}$ 1710 cm⁻¹.

The other compounds were synthesized according to the following general scheme, by means of an unsymmetrical Kolbe synthesis. The cell was as previously reported.[3b]

$$Br(CH_2)_nCO_2H + HO_2CCH_2C(CH_3)_2CH_2CO_2CH_3$$

$$\xrightarrow[-2CO_2]{-H_2} Br(CH_2)_{n+1}C(CH_3)_2CH_2CO_2CH_3$$

The preparation of methyl 9-bromo-3,3-dimethylnonanoate is described in detail.

A solution of 6-bromohexanoic acid (56 g, 0.287 mol) and methyl hydrogen 3,3-dimethylglutarate (25 g, 0.144 mol) in methanol–hexane 3:1[26] (200 mL) was treated with sodium metal (ca. 0.5 g) then electrolyzed at 1.2 A. The temperature of the reaction mixture was kept at 45 ± 5 °C by means of external cooling in order to prevent the oxidation of the –CH₂Br function. The electrolysis was interrupted when the solution turned alkaline (14 h), then the mixture was made acid with AcOH, most of the solvent distilled off, and the residue worked up with diethyl ether. Removal of the solvent left a crude material that was chromatographed on silica gel. Elution with light petroleum gave 1,10-dibromodecane (18 g). Further elution with light petroleum –CHCl₃ 1:1 gave methyl 9-bromo-3,3-dimethylnonanoate (14.4 g; 36% yield): bp 96–100 °C (0.2–0.3 mm Hg); $n^{16}{}_D$ 1.4623; ¹H NMR δ 3.6 (s, 3 H, CO₂CH₃), 3.3 (t, 2 H, CH₂Br), 2.1 (s, 2 H, CH₂CO₂R), 2.0–1.1 (m, 10 H, "central" methylene protons), 0.9 (s, 6 H, CH₃); IR $\nu_{C=O}$ 1745 cm⁻¹. Hydrolysis of the methyl esters with a boiling AcOH–HBr–H₂O mixture afforded the *gem*-dimethyl acids (60–75% yields).

Product Analysis. The lactonization of Br(CH₂)₆C(CH₃)₂-(CH₂)₇CO₂H was carried out according to a previously reported procedure,[23,27] namely, by adding over 2 h a solution of the bromo acid (1.5 g) in Me₂SO (60 mL) to a well-stirred suspension of K₂CO₃ (2.5 g) in Me₂SO (60 mL) at 100 °C. Elution of the crude product with benzene on silica gel gave the pure lactone in 83% yield as a white solid melting at 54.5–56 °C after sublimation.

Anal. Calcd for C₁₇H₃₂O₂: C, 76.06; H, 12.02. Found: C, 76.13; H, 11.99.

Rate Measurements. These were carried out as previously described.[3b] Since the cyclization rate for the six-membered, gem-disubstituted ring was too fast to be followed by conventional techniques, in this case the relative rate was obtained at 50 °C by running the kinetics experiments by the diisopropylethylamine buffer method as previously reported,[3b] employing a buffer ratio, [B]/[BH⁺], equal to 0.146. Under these conditions, the apparent rate constants were 1.23×10^{-2} and 3.19×10^{-4} s⁻¹ for the 5-bromo-3,3-dimethylpenta-

noic acid and the 5-bromopentanoic acid, respectively, the relative rate being 38.5.

From the recently determined rate constant for 5-bromopentanoic acid[1] ($1.88\ s^{-1}$), the rate constant for 5-bromo-3,3-dimethylpentanoic acid was calculated as $72.4\ s^{-1}$.

Registry No.—1, 22791-80-6; **2**, 69120-94-1; **3**, 69120-95-2; **4**, 69120-96-3; **5**, 69120-97-4; 5-bromo-3,3-dimethylpentanoic acid, 69120-98-5.

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Investigating the σ⁺ Resonance Scale Using C-13 Nuclear Magnetic Resonance Shifts. Graphical Representation of the Dual Substituent Parameter Equation[1]

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The advantages of using the dual substituent parameter (DSP) method in preference to the single parameter σ⁺ scale for the analysis of C-13 substituent chemical shift data are discussed. A graphical representation of the DSP equation is presented. This makes possible a fast, qualitative DSP analysis and indicates the best substituents to use for a good linear free energy correlation.

The σ⁺ set of substituent parameters is used to describe the effects of substituents in electron deficient systems where enhanced effects for π donors are observed. The σ⁺ scale was originally derived by Brown and Okomoto[2] from the solvolysis of para-substituted cumyl chlorides and has since been used to study mechanisms involving electron deficient transition states and intermediates.[3] σ⁺ values for strong donors, such as NMe_2 and NH_2, have not been determined accurately in many of these systems because of the extremely short reaction times involved. Accurate measurements for NMe_2 and NH_2 are critical for a good linear free energy correlation because they have large absolute σ⁺ values and ensure a wide substituent range. Recently, attempts have been made to generate new σ⁺ constants from C-13 substituent chemical shifts (SCS).[4-6] C-13 chemical shifts give precise values for all substituents, provided that concentration and solvent effects are minimized, and they are relatively easy to measure. Despite these advantages we caution against the direct estimation of σ⁺ parameters from SCS data.

It has been shown that spectral, and especially NMR substituent effect, data should be analyzed using a two-parameter equation.[7] The dual substituent parameter (DSP) equation (eq 1) separates substituent effects into inductive ($\rho_I\sigma_I$) and

$$\delta = \rho_I\sigma_I + \rho_R\sigma_R \qquad (1)$$

resonance ($\rho_R\sigma_R$) components[3a] and uses one of four different resonance scales ($\sigma_R = \sigma_R^-$, σ_R^0, σ_R^{BA}, or σ_R^+), depending on the electron demand at the reaction or measuring site.[3b] The resonance to inductive blend ($\lambda = \rho_R/\rho_I$) varies markedly both for different systems and for different measuring sites within the same system.[3,8] To analyze the diverse range in data with a single parameter equation which has a fixed λ would require many different σ scales.

Substituent effect data are usually fitted to eq 1 by a standard computer least-squares analysis, and a detailed description of the use of the DSP method is given in ref 3. Additional insight into the DSP method may be gained from a graphical representation where the effective substituent constant, $\bar{\sigma}$, is determined for different resonance to inductive blends. This may be achieved by rearranging eq 1 into eq 2,

$$\delta = (\rho_I{}^2 + \rho_R{}^2)^{1/2}(\sigma_I \cos\theta + \sigma_R \sin\theta) \qquad (2)$$

where the effective ρ and σ values are separated.[9] In Figure 1, the effective σ constant, $\sigma_I \cos\theta + \sigma_R^0 \sin\theta$ (using σ constants from ref 3b), is plotted as a function of θ, which represents all of the possible combinations and proportions of σ_I and σ_R ($\tan\theta = \rho_R/\rho_I = \lambda$). Since the signs of $\cos\theta$ and $\sin\theta$ vary with θ, so does the sign of the contribution from σ_I and σ_R^0. Between 0 and 90° the contributions from σ_I and σ_R^0 are