New *Gem*- and *Vic*-Disubstituent Effects on Cyclizations[1]

Michael E. Jung

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, USA
E-mail: jung@chem.ucla.edu

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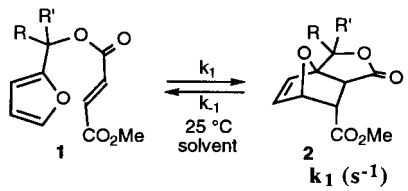
Abstract: Several new *gem*-disubstituent effects on cyclizations - e.g., the *gem*-dialkoxy, -dicarboalkoxy, and -dithioalkoxy effects, have been discovered. In addition we have also observed a new *vicinal* disubstituent effect. A novel ring size effect of ketals on radical cyclizations has been investigated.

Key words: solvent effects on cyclizations, radical cyclizations, intramolecular cycloadditions, oxetane synthesis

Several years ago I wrote one of the first accounts for this journal describing how a research project develops from its inception to its final conclusion.[2] In this account I would like to provide an update of that earlier article, summarizing our recent findings on the effect of substituents on cyclizations.

Table 1 Substituent and Solvent Effects on Cycloaddition of **1** to give **2**



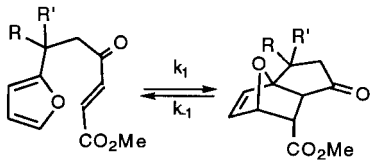
Compound	R	R'	toluene-d_8	CD_3CN	DMSO-d_6
			k_1 (s^{-1})		
1a	H	H	~ 10^{-9} [a]	2 X 10^{-7}	3.2 X 10^{-6}
1b	H	Me	3.0 X 10^{-8}	1.1 X 10^{-6}	6.6 X 10^{-6}
1c	$(CH_2)_2$		2.5 X 10^{-7}	1.3 X 10^{-6}	6.5 X 10^{-6}
1d	$(CH_2)_3$		3.4 X 10^{-6}	3.6 X 10^{-5}	1.3 X 10^{-4}
1e	Me	Me	1.3 X 10^{-4}	3.4 X 10^{-4}	~10^{-3} [b]

a) estimated since K_{eq} ($K_{eq} = k_1/k_{-1}$) too small to determine rate.
b) estimated since K_{eq} too large to determine rate.

Our earlier work (undertaken to explain an unusual rate enhancement observed in our labs in 1984)[3] focused on the source of the rate enhancement seen in cyclizations when alkyl groups were placed on the acyclic chain connecting two reacting centers, the *gem*-dialkyl effect (sometimes erroneously termed the Thorpe-Ingold Effect, which is the angle compression on substitution). After several sets of experiments,[4] we could state confidently that the source of the rate enhancement was due to the 'reactive rotamer effect,' namely the selective destabilization of the ground state conformation and thereby a higher population of the conformation that leads to cyclization,[5] and not the Thorpe-Ingold effect, internal angle compression.[6] We also discovered[4] a new effect on the cyclization of substrates connected by an ester group, namely a polar solvent effect, e.g., for **1** giving **2**. Solvents of higher polarity stabilize the transition state for cyclization (similar to the normally less stable s-cis ester conformation) and therefore give large rate enhancements. The data for both of these effects are summarized in Table 1.

We have since determined that the large rate enhancements seen in the cyclization of **1** are due to the presence of an oxygen atom adjacent to the substituted carbon atom.[7] The rates of cyclization of the keto esters **3abc** to give **4abc** (the carbon analogues of **1** and **2**) were determined and compared to those given above (Table 2).

Table 2 Comparison of Forward Rate Constants in Acetonitrile at 25 °C



3a R= R'= H
3b R= H, R'= Me
3c R= R'= Me

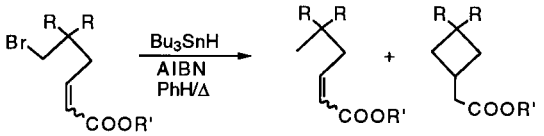
4a R= R'= H
4b R= H, R'= Me
4c R= R'= Me

Substrate	k_1	k_1 (rel)	Substrate	k_1	k_1 (rel)
3a	4.8 x 10^{-9}	1	**1a**	2.0 x 10^{-7}	1
3b	7.5 x 10^{-7}	156	**1b**	1.1 x 10^{-6}	5.5
3c	5.1 x 10^{-6}	1062	**1c**	3.4 x 10^{-4}	1700

As expected, the forward rate constants are larger for the fumarates **1abc** than for the keto esters **3abc**. Because of experimental difficulties, the rate constant measured for **3a** is not reliable; therefore the only fair comparison is the rate increase in going from monomethyl (**1b**/**3b**) to dimethyl (**1c**/**3c**) in both systems. Here the increase in the keto ester series (**3b** to **3c**) is 6.8 while the corresponding increase in the ester series (**1b** to **1c**) is 310. This significant difference led us to postulate again that the presence of the ring oxygen is the major factor responsible for the great rate enhancement observed in the intramolecular Diels-Alder reaction of these furan dienes with *gem*-dimethyl substitution on the tether. We carried out a combination molecular mechanics/continuum reaction field/quantum mechanics study of the intramolecular Diels-Alder reac-tion of the 2-furfuryl fumarates **1** which provided theoretical evidence for both the reactive rotamer effect and for the polar solvent effect on these cycloadditions.[8]

The implication that oxygen substituents should give larger rate increases than carbon substituents led us to examine the *gem*-dialkoxy effect. Cyclization of the 6-bromo-2-hexenoates **5abc** under free radical conditions gave only the acyclic product **6a** in the dihydrido case, a mixture of acyclic and cyclic products **6b** and **7b** in the dimethyl case, and only the cyclic ketal **7c** in the dialkoxy case (Table 3).[9]

Table 3 *Gem*-Dialkoxy Effect in Radical Cyclization of Bromohexenoates

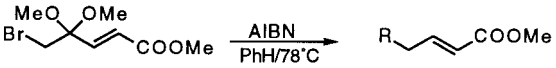


5 6 7

Compound	R	Ratio **6/7**
5a	H	100/0
5b	Me	75/25[a] (12/88)[b]
5c	OEt	0/100
5d	$O(CH_2)_2O$	75/25[c]
5e	$O(CH_2)_3O$	0/100
5f	CO_2Et	20/80

a) The acyclic product **6b** was a 2:1 mixture of the enoate and the saturated analogue. b) Ratio with slow addition of Bu_3SnH (over 8h).

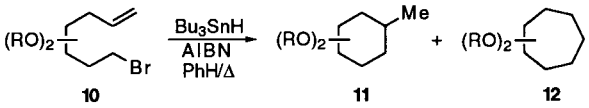
This experiment thus showed that the *gem*-dialkoxy effect was stronger in this system than the *gem*-dialkyl effect, a result seen only once before in a Diels-Alder reaction.[10] We have also detected a novel ketal ring size effect in the cyclization of these 6-bromo-2-hexenoates.[11] Thus cyclization of the substrate having a 6-membered ketal **5e** gave a quantitative yield of the cyclic product **7e** while the substrate having a 5-membered ketal **5d** gave a 3:1 mixture in which the acyclic product **6d** was favored over **7d**. We developed a theoretical force-field method to predict the success of radical cyclizations to give cyclobutane systems of this sort based on the relative activation energy for cyclization.[12] In addition, we discovered a novel oxidation during a cyclization of a ketal to form a cyclopropane ring system.[13] With excess hydride, the 5-bromopent-2-enoate **8** gave only the expected acetal **9a**, formed by cyclization of the initial radical to the cyclopropylcarbinyl radical, opening to the more stable dialkoxyalkyl radical, and hydrogen atom abstraction. However, with 1.5 equiv of hydride, the diester **9b** was formed in 50% yield via final oxidation of the dialkoxyalkyl radical to the ester.



8

10 eq Bu_3SnH 51% **9a** R = $CH(OMe)_2$
1.5 eq Bu_3SnH 50% **9b** R = COOMe

Finally we have examined the effect of the position of the ketal on the rate of cyclization of 7-bromo-1-heptenes **10** to give mainly the methylcyclohexanes **11** (along with small amounts of the cycloheptanes **12**). Our results show essentially no positional effect in these cyclizations.[14]



10 11 12

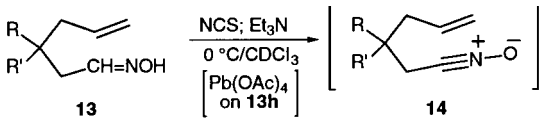
In order to expand the number of different substituents that could be studied, we investigated a different cyclization, namely the intramolecular dipolar cycloaddition of the 5-hexenenitrile oxides with substituents in the 3-position.[15] Treatment of the aldoximes **13** with NCS and base afforded the nitrile oxides **14** which cyclized to the bicyclic oxazolines **15** at 0 °C (Table 4). In this case, the *gem*-dimethyl compound **13c** cyclized more slowly than the monomethyl analogue **13b** which cyclized only slightly faster than the parent **13a** due to the steric interaction of a methyl group with the angular hydrogen atom in the transition state for cyclization. This effect was absent in the Diels-Alder cycloadditions of Tables 1 and 2 and the radical cyclizations of Table 3. The new discovery here was the *gem*-dicarboalkoxy effect, namely that the diester substrate **13f** cyclized more than 20 times faster than the par-

Biographical Sketch

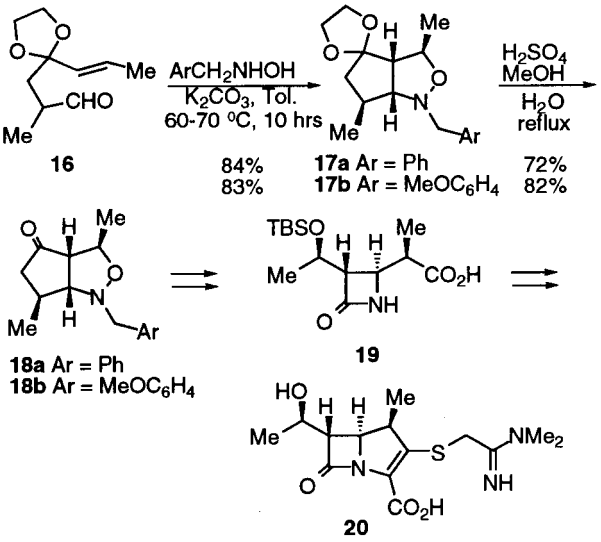
Mike Jung was born and grew up in New Orleans, Louisiana. He received his BA from Rice University in 1969 (working with Richard Turner) and his PhD from Columbia University in 1973 (working as an NSF Predoctoral Fellow with Gilbert Stork). After a one-year NATO Postdoctoral Fellowship at the ETH in Zürich (working with Albert Eschenmoser), he joined the faculty at the University of California, Los Angeles in 1974, where he is currently a full professor.

ent. This is the first case in which a geminal diester group has been shown conclusively to accelerate a cyclization versus the parent, a synthetically useful effect since sequential dialkylation of malonate units is often used to construct molecules quickly. In this series, the dithiane **13h** showed the greatest rate enhancement. It is known from Sternbach's work[10] that the *gem*-dithioalkoxy effect is somewhat smaller than the *gem*-dialkoxy effect, but we were unable to verify that in this case because of synthetic difficulties associated with preparation of the required substrates. This rate acceleration should be of high synthetic utility since cyclization of the dialkylated dithiane followed by reductive desulfurization would generate the unsubstituted compound which is difficult to form by simple cyclizations.

Table 4 Relative Rates of Cyclization of Nitrile Oxides **14**

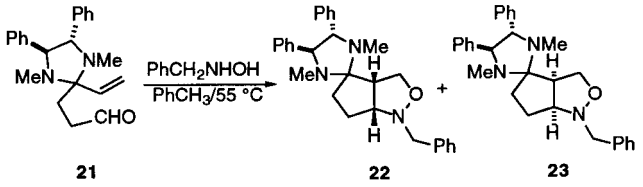


Substrate	Substituents	$t_{1/2}$ (min)	k_{rel}
13a	R = R' = H	990	1.0
13b	R = Me R' = H	624	1.6
13c	R = R' = Me	910	1.1
13d	R = R' = $(CH_2)_4$	338	2.9
13e	R = Ph R' = H	248	4.0
13f	R = R' = COOMe	46	21.5
13g	R = COOMe R' = H	173	5.7
13h	R = R' = $S(CH_2)_3S$	<4	>247

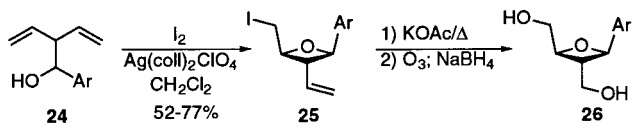


We were able to demonstrate the synthetic utility of these cyclizations in a simple synthesis of the antibacterial agent 1β-methylthiena-mycin **20**.[16] Reaction of the ketal aldehyde **16** with the *N*-benzylic hydroxylamines afforded the oxazolidines **17ab** in good yield. In these reactions, we observed a *gem*-dialkoxy effect, which allowed the reaction to be carried out at lower temperature than the parent system (60-70 °C rather than 110 °C). To our knowledge, the cyclization was completely stereoselective giving only the desired stereochemistry at the four contiguous asymmetric centers. Acidic hydrolysis yielded the ketones **18ab**, the latter of which was converted into the β-lactam **19** and then into **20**.[17]

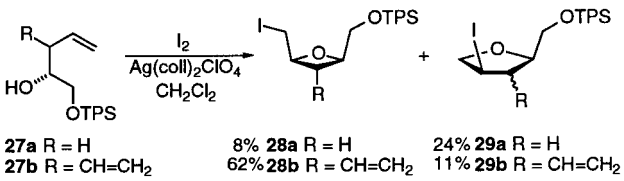
We also have some preliminary evidence for a *gem*-bis(dialkyl-amino) effect on cyclization although it seems to be much smaller than the *gem*-dialkoxy effect. Thus the optically active aminal **21** was converted into the two diastereomeric oxazolidines **22** and **23** under fairly mild conditions. We are currently attempting to increase the asymmetric induction in reactions of this sort.[18]



Since the *gem*-dialkyl effect is mainly a conformational effect in which the normally most stable ground state conformation is selectively destabilized and reactive conformations are favored, we postulated that one might be able to observe a vicinal dialkyl effect. Thus the presence of vicinal alkyl groups might have the same overall effect as *gem*-dialkyl substitution. We have now observed such an effect for the first time in electrophilic cyclizations of substituted homoallylic alcohols.[19] Thus treatment of the α-aryl β-vinyl homoallylic alcohols **24** with bis-(collidine)iodonium perchlorate afforded predominately the desired oxetane **25** which was then taken on to the oxetane-2,3-dimethanols **26** in two steps. Only small amounts of the corresponding tetrahydrofurans were formed in the cyclization which lends evidence to a *vic*-dialkyl effect (because unsubstituted systems give only THF products and *gem*-disubstituted systems afford mainly oxetanes).[20] This reaction sequence was used to prepare trans, trans oxetane-2,3-dimethanols[19] and several isonucleosides which showed good antiviral activity.[21]



As a final example of the usefulness of this *vic*-dialkyl effect, we have shown that the cyclization of the two substrates **27ab** follow completely different paths under identical conditions. Thus cyclization of **27a**, which lacks the vicinal substituents, generates only 8% yield of the oxetane **28a** and 24% of the tetrahydrofuran **29a** while cyclization of the vicinally substituted substrate **27b** under the same conditions affords the desired oxetane **28b** in 62% yield along with 11% of the tetrahydrofuran **29b**. Thus the *vic*-dialkyl effect allows one to form an oxetane which is properly substituted for the synthesis of oxetanocin A in good yield.[22]



27a R = H
27b R = CH=CH$_2$

8% **28a** R = H
62% **28b** R = CH=CH$_2$

24% **29a** R = H
11% **29b** R = CH=CH$_2$

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References and Notes

(1) Dedicated to my teacher and mentor, Albert Eschenmoser, who taught me to think carefully about why reactions occurred and how one could use that knowledge.
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