0040-4039(95)02196-5

SUBSTITUENT EFFECTS ON INTRAMOLECULAR DIPOLAR CYCLOADDITIONS: THE *GEM*-DICARBOALKOXY EFFECT

MICHAEL E. JUNG[*1] and BINH T. VU

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Summary: A *gem*-dicarboalkoxy effect (rel. rate >20) has been measured and good diastereoselectivity (~9:1) has been seen for the intramolecular dipolar cycloaddition of 3-substituted 5-hexenyl nitrile oxides.

Recent investigations[2] in our group have shown that the *gem*-dialkyl effect is due to the reactive rotamer effect (selective destabilization of the ground state vs. the transition state)[3] rather than angle compression.[4] We have also shown that the *gem*-dialkoxy effect is even larger than the *gem*-dialkyl and more useful synthetically especially for the preparation of ring systems that are difficult to prepare by other means.[5] We now report the existence of a *gem*-dicarboalkoxy effect, namely the acceleration of a cyclization due to the presence of geminal carbomethoxy groups (Table).

Since the original system for studying these effects - furfuryl methyl fumarates - was not easily adapted to other substituents, we decided to investigate a different system in which a variety of substituents could be introduced. We prepared a series of 5-hexenal oximes **1** with substituents at C3 by standard routes.[6] All but one of these oximes were converted to the nitrile oxides[7] by chlorination to the hydroxamoyl chloride and then elimination of HCl with Et₃N at 0°C in CDCl₃.[8] The dithiane compound **1h** underwent decomposition (presumably due to sulfur oxidation) under these conditions. The nitrile oxide **2h** could be prepared by lead tetraacetate oxidation of the oxime **1h**, a rarely used method
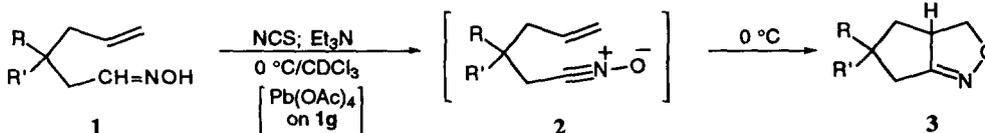
Table: Relative Rates of Cyclization of Nitrile Oxides

Substrate		$t_{1/2}$ (min)	k_{rel}
2a	R=R'=H	990	1.0
2b	R=Me R'=H	624	1.6
2c	R=R'=Me	910	1.1
2d	R=R'=(CH₂)₄	338	2.9
2e	R=Ph R'=H	248	4.0
2f	R=R'=COOMe	46	21.5
2g	R=COOMe R'=H	173	5.7
2h	R=R'=S(CH₂)₃S	<4	>247

for nitrile oxide formation.[9] Measurement of the rates of cyclization were done by integration over time of the vinyl absorptions in 2 and the three protons in the isoxazoline ring of 3. The half-lives for the cyclizations and the relative rates are shown in the Table.

Several important points can be made from the data in the Table. Because of the steric interaction of a methyl group with the angular hydrogen atom in the transition state for cyclization,[10] the *gem*-dimethyl compound **1c** cyclized more slowly than the monomethyl analogue **1b** which cyclized only slightly faster than the parent **1a**. The new exciting discovery is the existence of a *gem*-dicarboalkoxy effect, namely the diester substrate **1f** cyclized more than 20 times faster than the parent. This is, as far as we can tell, the first case in which a geminal diester group has been shown to actually speed up a cyclization versus the parent.[11] Even the mono-carboalkoxy derivative **1g** cyclizes about 6 times faster than the parent (about 4 times faster than the monomethyl compound **1b**). This could be a very useful effect in synthesis since malonate units are often used to build up chains quickly by sequential dialkylation. The greatest rate enhancement is seen with the dithiane **1h**. The *gem*-dithioalkoxy effect is generally somewhat smaller than the *gem*-dialkoxy effect[12] and may also be of high synthetic utility since sequential alkylation of dithiane anions would generate the substrate for cyclization and after cyclization, reductive desulfurization would generate the unsubstituted compound which is difficult to form by simple cyclization.

When C-3 was monosubstituted, we observed good diastereoselectivity in the cyclizations. The results are in agreement with the relative size of the substituents (Ph>Me>COOMe). The monomethyl compound **1b** gave mainly (87:13) the diastereomer with the methyl anti to the angular hydrogen **3b** rather than **3b'** This is in direct contrast to the results of Kurth who reported a 1:1 ratio.[13,14] Calculations of the transition state energies for this cyclization[15]

Substrate		cis/trans
1b	R=Me	87:13
1e	R=Ph	90:10
1g	R=COOMe	70:30
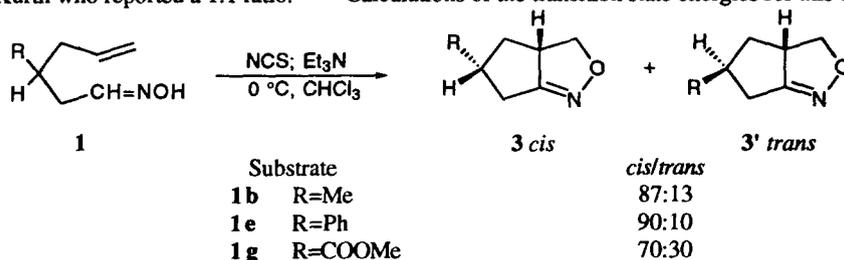
predict an 83:17 ratio of **3b** and **3b'**. We proved the structures of **3b** and **3b'** by converting them to the corresponding hydroxy ketones **4b** and **4b'** using Kozikowski's procedure.[16] The structures of **4b** and **4b'** were then proven by nOe experiments and by the position of the peaks in the ^{13}C NMR spectra of both compounds.[17]

3b	α-methyl		**4b**	α-methyl
3b'	β-methyl		**4b'**	β-methyl
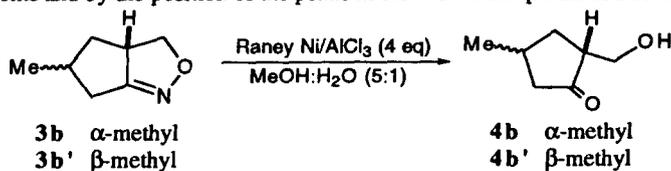
To determine the solvent effect on these cyclizations, the rate of cyclization of **1f** was measured in several different solvent systems. A small solvent effect was observed, with more polar solvents decreasing the rate of cyclization. This suggests that there is slightly less charge buildup in the transition state of cyclization versus the ground state, as might have been expected. In an attempt to understand the reasons behind the *gem*-dicarboalkoxy effect, we carried out the cyclization of the *gem*-dicyano and the *gem*-bis(phenylsulfonyl) analogues, but these two compounds failed to give the normal cyclization products under the reaction conditions described above.[18]

Solvent	$t_{1/2}$ (min)	k_{rel}
$CDCl_3$	248	1.00
50% $CDCl_3$-50% Freon-113	192	1.29
CD_2Cl_2	400	0.62
CD_3CN	467	0.53
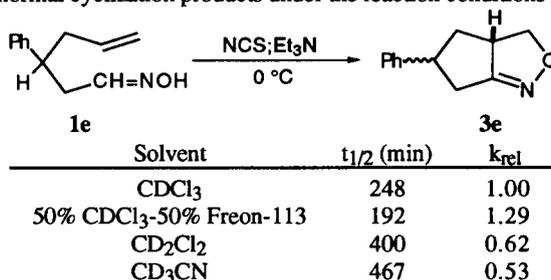
In summary, investigation of the rates of cyclizations of a series of nitrile oxides prepared from 3-substituted 5-hexenal oximes indicates the existence of a *gem*-dicarboalkoxy effect. Further experiments, especially the use of these results in the synthesis of biologically active compounds, are in progress.

References and Notes

1) American Chemical Society Arthur C. Cope Scholar, 1995.

2) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

3) There is some confusion about the meaning of the term "reactive rotamer effect." For an explanation of what we mean by the term, see: Jung, M. E. *Synlett* **1990**, 186.

4) For another interpretation of the reasons behind the *gem*-dialkyl effect, see: Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319.

5) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719.

6) Copper-catalyzed addition of allylmagnesium halide to ethylidene, isopropylidene, cyclopentylidene, or benzyl-idene malonate followed by decarbomethoxylation and reduction furnished **1b-e**. Alkylation of dimethyl allylmalonate with chloroacetaldehyde oxime afforded **1f**. The monoester **1g** was prepared by allylation of γ-butyrolactone, opening with methoxide and conversion of the alcohol to the aldoxime via the aldehyde. Alkylation of allyldithiane with bromoacetal followed by conversion of the acetal to the aldoxime via the aldehyde gave **1h**.

7) Conversion of hexanal oxime to the saturated nitrile oxide showed that the formation of the nitrile oxide is fast

454

with respect to dimerization so that the calculated half-lives accurately measure the relative rates of cyclizations.

8) a) Grundmann, C.; Grünanger, P. *The Nitrile Oxides.* **1971**, Springer-Verlag, New York. b) Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition.* **1984**, Vol. 1, Padwa, A., Ed.; John Wiley & Sons, New York, pp. 291-392. c) Curran, D. P. *Advances in Cycloaddition.* **1988**, JAI Press, Greenwich, CT, Vol. 1, p. 150.

9) Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251.

10) Brown, F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405.

11) This effect may well have been seen before but not measured. For example, Parker reported the intramolecular Diels-Alder reaction of an olefinic furan having a *gem*-dicarboalkoxy group but does not mention whether the simple hydrocarbon (without the ester groups) cyclized or not. Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689.

12) For an early example of the *gem*-dialkoxy and *gem*-dithioalkoxy effects, see: Sternbach, D. D.; Rosanna, D. M; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591.

13) Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259.

14) Kurth and coworkers carried out the cyclization at 25 °C. In our hands, the diastereoselectivity does not change at this temperature, still favoring **3b** over **3b'** by about 6.5:1.

15) Private communication. Houk, K. N.; Raimondi, L. For a description of the force field used in these calculations of transition structures for nitrile oxide cyclizations, see: Brown, F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405.

16) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.

17) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308. In the cis isomer **4b**, the peaks assigned to the methyl and hydroxymethyl carbons were both upfield by ~ 0.65 ppm of the corresponding peaks in the trans isomer **4b'** due to the shielding effect. The structures of the isomeric pairs **3e/3e'** and **3g/3g'** were assigned by analogy.

18) The *gem*-bis(phenylsulfonyl) analogue gave **5** in 50-60% yield under the normal reaction conditions. We assumed that this compound is formed via cyclization of the bis-sulfonyl nitrile oxide which then loses an equivalent of phenylsulfinic acid in the presence of base to give **5**.

5