Tetrahedron Letters No. 28, pp. 2637-2640, 1971. Pergamon Press. Printed in Great Britain.

CONFORMATIONAL ANALYSIS OF 1-OXASPIRO [4.5] DECANES

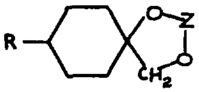
J. J. Uebel, E. L. Nickoloff[1a], W. T. Cole[1b] and C. B. Grant[1c]

Department of Chemistry, University of New Hampshire
Durham, New Hampshire 03824, U.S.A.

(Received in USA 10 June 1971; received in UK for publication 15 June 1971)

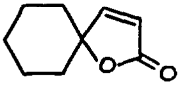
Our interest in 1,1-disubstituted cyclohexanes has been stimulated by the discovery of a dramatic breakdown of the additivity relationship for conformational free energies in 1-methylcyclohexanol.[2,3] The conformational ΔG^o for this material (*ca.* 0.3 kcal/mole) is much smaller than would have been expected [1.7-0.6 (0.9) = 1.1 (0.8) kcal/mole] from a consideration of the conformational free energies of the HO [0.6(0.9)][4] and CH_3 (1.7) groups.[5] Similar observations have been made in other 1,1-disubstituted cyclohexanes.[6] As a natural outgrowth of this work, we were interested in observing the effects produced by linking the substituents together in a second ring. The formation of such a ring would place restrictions on the orientations available to the substituents, and make a ring size effect study possible. A recent communication dealing with the conformational analysis of 1-oxaspiro[4.5]decanes[7] now prompts us to report some startling observations with the same general series of compounds.

1,3-Dioxaspiro [4,5] decanes, 1, 2, and 3 have been prepared by standard techniques. They all exhibit appropriate ir and nmr spectra, and give satisfactory elemental analyses. The related *cis* and *trans*-8-*t*-butyl isomers of known configuration were prepared by hydroxide ion ring opening of the known epoxides,[8] *cis* and *trans*-6-*t*-butyl-1-oxaspiro[2.5]octane. Closure of the resulting diols with formaldehyde, acetone or diethylcarbonate gave 4, 5 and 6, respectively. A related oxaspirene, 1-oxaspiro[4.5]-3-decene-2-one (7) was prepared by the method of Haynes and Jones.[9]



1 ($Z=CH_2$;R=H)
2 ($Z=C(CH_3)_2$;R=H)
3 (Z=C=O;R=H)

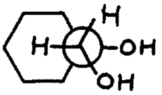
4 ($Z=CH_2$;R=*t*-Bu)
5 ($=C(CH_3)_2$;R=*t*-Bu)
6 (Z=C=O;R=*t*-Bu)



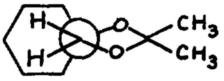
7

The conformational equilibria associated with compounds 1, 2, 3 and 7, were determined with the aid of the corresponding 4-*t*-butyl isomers using various nmr techniques. These results, along with those for some related compounds, are recorded in the table.

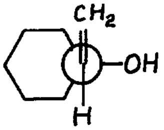
There are several interesting features which emerge from the data. With the exception of ketal 2, all three compound types (spiro[2.5], spiro[4.5], and non-spiro) show the expected preference for an axial oxygen conformation and most possess conformational free energies within the range 0.25 ± 0.2 kcal/mole. The extent of the preference is, however, surprisingly small and unexpectedly constant from one compound to another. We have already called attention to the leveling effect observed in 1-methylcyclohexanol, 1-(hydroxymethyl)cyclohexanol, and related compounds, but did not expect to find a similar effect in the 1-oxaspiro[4.5]decanes.[10] In fact the 1-oxaspiro [4.5]decanes were expected to show an increased preference for the axial oxygen (equatorial CH_2) conformation in comparison to their non-spiro analogues. It was reasoned that tying the substituents together through a five membered ring, as was done in going from 8 to 2, would destabilize the axial-CH_2 conformation, since in doing so the CH_2 (or = CH) group would be twisted into the *syn*-diaxial protons as illustrated below.



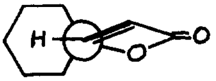
8 $-\Delta G^o$ = 0.46 kcal/mole



2 $-\Delta G^o$ = -0.13 kcal/mole



9 $-\Delta G^o$ = 0.64 kcal/mole

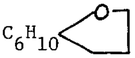
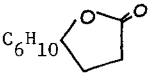
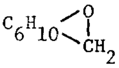


7 $-\Delta G^o$= 0.50 kcal/mole

However, if anything, cyclization led to a decrease, not an increase in the preference for the axial oxygen conformations. The most dramatic example of this is seen in ketal 2, where the equatorial oxygen conformation is in fact more stable than the equatorial CH_2 conformation!

Allinger *et al*. have already suggested an explanation for the leveling effect observed in a number of 1,1-disubstituted cyclohexanes.[11] This may represent a partial explanation for the various 1-oxaspiro[4.5]decanes as well. However, we would like also to suggest that cyclization perhaps forces the atoms directly attached to the cyclohexane ring to bend slightly outward, away from the ring, thereby reducing the axial-CH_2 (or = CH) repulsions and in some cases even converting them into attractions.[15]

Conformational ΔG^o Values for 1-Oxaspiro 4.5 decanes and Related Compounds

Compound	$-\Delta G^o$ [l]	Solvent	Method of Analysis	Reference
1	0.07 (-88°)	acetone	a	this work
2	-0.13 (80°)	$CD_3OD/CDCl_3$(1:9)	a	this work
	-0.28 (35°)	$CD_3OD/CDCl_3$(1:1)	b	this work
3	0.20 (-86°)	acetone	b	this work
7	0.50 (-95°)	acetone	a	this work
	0.47 (38°)	acetone	b	e
9 $C_6H_{10}(OH)CH=CH_2$	0.64 (38°)	CCl_4	b	k
$C_6H_{10}(OH)CH_3$	0.25 (25°)	H_2O/AcOH	c	f,g
$C_6H_{10}(OCH_3)CH_3$	0.3 (55°)	CH_2OH	c	this work
$C_6H_{10}(OH)CH_2OH$ (8)	0.46 (35°)	$CDCl_3$	b	this work
	0.46 (35°)	(CS_2)	d	e
	0.28 (55°)	diglyme	c	e
 $C_6H_{10}\langle{}^{O}_{CH_2}$	0.15 (25°)	H_2O/CH_3OH	j	h
	0.27	CS_2	a	i

[a]Proton nmr using the areas under the CH_2O peaks measured at low temperatures; [b]Proton chemical shift method using the 4-t-butyl compounds as reference models; [c]Equilibration of the 4-t-butyl stereoisomers; [d]IR measurements, applying the molar extinctions for (C-O) obtained for the 4-t-butyl reference models to the unsubstituted compound; [e]P. Picard and M. Moulines, Tetrahedron Lett., 5133 (1970); [f]N. L. Allinger and C. D. Liang, J. Org. Chem., 33, 3319 (1968); [g]J. J. Uebel and H. W. Goodwin, J. Org. Chem., 33, 3317 (1968); [h]J. J. Uebel, Tetrahedron Lett., 4751 (1967); [i]R. G. Carlson and N.S. Behn, Chem. Commun., 339 (1968); [j]kinetic; [k]R. J. Ouellette, K. Liptak, and G. E. Booth, J. Org. Chem., 31, 546 (1966); [l]all values in kcal/mole; a negative value for ΔC^o indicates a preference for an axial oxygen conformation.

Our ΔG^o for lactone 7 of -0.50 kcal/mole, obtained by area measurements taken from the low temperature nmr spectrum agrees very well with that reported by Picard and Moulines (-0.47 kcal/mole). Their value was obtained using the chemical shift method of Eliel *et al.*[12] with the C*H*=CHCO proton serving as the conformational probe. We also observed good agreement between these two methods with ketal 2. It is quite possible that 4-*t*-butyl substituents exert a considerably smaller effect upon the chemical shift of protons attaches to ring substituents, than on protons attached directly to C_1.[14] If this is true, then the chemical shift method would be considerably more accurate in these cases than might be expected. It is interesting to note that the conformational ΔG^o for lactone 7 (-0.5 kcal/mole) is close to that for its non-spiro analogue, 1-vinylcyclohexanol (9; -0.64 kcal/mole), even though the orientation of the vinyl group presumably is considerably different in these two compounds. In the latter compound the vinyl group is assumed to be parallel to the syn-diaxial hydrogens[13] while in the lactone it must be more nearly perpendicular to them (see previous figure).

References

1. (a) Taken in part from the Ph.D. thesis of E.L.N.; (b) Taken in part from the B.S. thesis W.T.C.; (c) National Science Foundation Undergraduate Research Participant, Summer 1970.
2. J.J. Uebel and H.W. Goodwin, J. Org. Chem., 33, 3317 (1968).
3. N.L. Allinger and C.D. Liang, J. Org. Chem., 33, 3319 (1968).
4. The two values cited for the hydroxyl group are for hydrogen bond donating and non-hydrogen bond donating solvents.
5. J.A. Hirsch in "Topics in Stereochemistry," N.L. Allinger and E.L. Eliel, Ed., Interscience Publishers, N.Y., 1967, Vol. 1.
6. N.L. Allinger and C.D. Liang, J. Org. Chem., 32, 2391 (1967).
7. P. Picard and J. Moulines, Tetrahedron Lett., 5133 (1970).
8. E.J. Corey and M. Chaykovsky, J. Amer. Chem Soc., 87, 1353 (1965).
9. L.J. Haynes and E.R.H. Jones, J. Chem. Soc., 954 (1946).
10. J.J. Uebel and E.L. Nickoloff, Abstracts 158th National Meeting of the American Chemical Society, New York, New York, September 1969, p 16 ORGN.
11. N.L. Allinger, J.H. Hirsch, M.A. Miller and I.J. Tyminski, J. Amer. Chem Soc., 91, 337 (1969).
12. E.L. Eliel, Angew. Chem. (Int. Edition). 4, 761 (1965).
13. R.J. Ouellette, K. Liptak and G.E. Booth, J. Org. Chem., 31, 546 (1966).
14. R.A. Ford and N.L. Allinger, J. Org. Chem., 35, 3178 (1970).
15. E.L. Eliel, E. W. Della, and M. Rogic, J. Org. Chem., 30, 855 (1965).