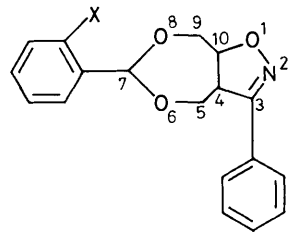
Isoxazolinyldioxepins. Part 1. Structure–Reactivity Studies of the Hydrolysis of Oxazolinyldioxepin Derivatives

Patrick Camilleri,* David Munro, and Karen Weaver
Shell Research Limited, Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG
David J. Williams, Henry S. Rzepa, and Alexandra M. Z. Slawin
Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY

The preparation and acid catalysed hydrolysis of a number of isoxazolinyldioxepins is reported. Individual diastereoisomer pairs were isolated by column chromatography and shown to differ significantly in their hydrolytic stability at acidic pH. The crystal structures of one diastereoisomer pair reveal that conformational differences induce a selective stereoelectronic effect at the acetal centre of the more hydrolytically labile isomer, while the less labile isomer shows no such selectivity.

In our search for biologically active molecules we came across a number of isoxazolinyldioxepin derivatives of general structure (**A**), which differed in the nature of the substituent 'X'. We were



(A)

able to isolate two diastereoisomers differing in configuration at the acetal carbon. Each pair of diastereoisomers could be separated by column chromatography because of their different partitioning characteristics. The five pairs of isomers studied are shown in Table 1 and have been denoted as Type I and Type II.† To provide useful data for structure activity studies and for the design of novel molecules it was necessary to study the hydrolytic stability of these five pairs of oxazolinyldioxepins. Type I molecules were found to be less stable than the corresponding Type II molecules in aqueous media at acidic pH. In order to explain this difference in the ease of the acid catalysed hydrolysis of the acetal linkage in the diastereoisomers in terms of structural and stereoelectronic effects, we have carried out a detailed study of the *X*-ray crystal structure of the diastereoisomeric pair (**3**) and (**4**) corresponding to Types I and II respectively.

Experimental

Materials.—The compounds (**1**)–(**10**) were prepared according to the general procedure shown below. Buffer components were of analytical grade. 1,4-Dioxane was 'Analar' grade whilst acetonitrile was of h.p.l.c. grade. Water was doubly distilled and deionised.

General Synthesis.—A solution of triethylamine (13 mmol dm^{-3}) in diethyl ether (20 cm^3) was added to a solution of benzenehydroximic acid chloride (10 mmol dm^{-3}) and 2-aryl-1,3-dioxepin-5-ene (10 mmol dm^{-3}) over 1 h with stirring and cooling at 0–5 °C. The mixture was stored at room temperature overnight, the separated triethylamine hydrochloride removed by filtration and the residue chromatographed on a silica column, using chloroform as the eluant. A forerun consisting of unchanged dioxepin and nitrile oxide dimer (4,5-diarylfuroxan) was always eluted first followed by the Type I and then the Type II isomer. All isoxazolinyldioxepins were recrystallised from ethylacetate–hexane. Table 1 gives the melting points and the elemental analyses of the ten isoxazolinyldioxepins reported in this study.

Table 1. Melting points and elemental analyses of the isoxazolinyldioxepin derivatives (**1**)–(**10**).

				Analysis					
				Found (%)			Calculated (%)		
Compd.	X	Type	M.p./°C	C	H	N	C	H	N
(**1**)	H	I	134	73.0	5.8	5.2	73.2	5.8	4.7
(**2**)	H	II	174	73.1	5.7	4.7			
(**3**)	F	I	115	68.7	5.2	4.5	69.0	5.1	4.5
(**4**)	F	II	151	68.9	5.1	4.3			
(**5**)	Cl	I	126	65.4	4.9	4.1	65.6	4.9	4.2
(**6**)	Cl	II	170	65.6	5.1	3.9			
(**7**)	CF_3	I	117	62.7	4.3	4.1	62.8	4.4	3.9
(**8**)	CF_3	II	162	62.7	4.4	4.1			
(**9**)	CH_3	I	157	73.5	6.2	4.7	73.8	6.1	4.5
(**10**)	CH_3	II	164	73.2	6.3	4.9			

Kinetic Measurements.—The hydrolysis of the compounds (**1**)–(**10**) was carried out in a reaction medium which consisted of buffer (15 cm^3) and 1,4-dioxane (4.5 cm^3), equilibrated at 39 °C. The following buffers were used: pH 1.99 (0.01 mol dm^{-3} hydrochloric acid); pH 3.02 (0.01 mol dm^{-3} formate); pH 3.97 (0.01 mol dm^{-3} acetate). The pH values shown in Table 2 are those recorded after the addition of dioxane. Stock solutions of the isoxazolinyldioxepins were prepared by dissolving each compound (1.8 mg) in 1,4-dioxane (1.5 cm^3). A portion of this stock solution (0.5 cm^3) was added to the buffer solution and the progress of the hydrolysis was followed by analysing the solution at regular intervals by h.p.l.c. First-order kinetics were obtained over at least three half-lives of reaction.

Method of Analysis.—The h.p.l.c. column consisted of a stainless steel column [150 mm × 5 mm (i.d.)] packed with Spherisorb ODS (2.5 μm). The isoxazolinyldioxepins and their

† See following paper.

Table 2. Hydrolysis data for compounds (**1**)–(**10**) in 25% dioxane–buffer at 39 °C.

Compd.	X	Type	k_{obs}/s^{-1} pH[a] 2.25	pH 3.70	pH 4.52
(**1**)	H	I	2.56×10^{-4}	2.75×10^{-5}	2.08×10^{-6}
(**2**)	H	II	4.94×10^{-5}	5.07×10^{-6}	2.00×10^{-7}
(**3**)	F	I	2.83×10^{-5}	2.60×10^{-6}	1.88×10^{-7}
(**4**)	F	II	4.79×10^{-6}	5.21×10^{-7}	1.32×10^{-7}
(**5**)	Cl	I	1.52×10^{-5}	1.78×10^{-6}	1.31×10^{-7}
(**6**)	Cl	II	2.33×10^{-6}	3.63×10^{-7}	—
(**7**)	CF_3	I	2.32×10^{-6}	4.30×10^{-7}	—
(**8**)	CF_3	II	3.10×10^{-7}	8.99×10^{-8}	—
(**9**)	CH_3	I	8.75×10^{-4}	9.17×10^{-5}	6.78×10^{-6}
(**10**)	CH_3	II	3.50×10^{-4}	1.43×10^{-5}	8.59×10^{-7}

[a] These pH values were obtained after addition of dioxane to the appropriate buffer (see the Experimental section).

products of hydrolysis were eluted from this column using acetonitrile–water (3:2, v/v) at a flow rate of 1 cm^3 min^{-1}. Compounds were detected at 250 nm. Under these h.p.l.c. conditions compounds (**1**)–(**10**) had the following retention times: (**1**), 4.35 min; (**2**), 3.12 min; (**3**), 4.34 min; (**4**), 3.12 min; (**5**), 5.48 min; (**6**), 3.62 min; (**7**), 5.90 min; (**8**), 3.79 min; (**9**), 5.29 min; (**10**), 3.33 min.

X-Ray Crystal Data.—Compound (**3**) $C_{18}H_{16}NO_3F$, M = 313.3, monoclinic, a = 6.450(3), b = 26.802(14), c = 9.263(4) Å, β = 103.14(3)°, U = 1 559 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.33 g cm^{-3}, λ = 1.541 78 Å, μ(Cu-K_α) = 8 cm^{-1}, $F(000)$ = 656. Approximate crystal dimensions 0.07 × 0.13 × 0.50 mm. Compound (**4**)* $C_{18}H_{16}NO_3F$, M = 313.3, monoclinic, a = 22.825(9), b = 5.792(2), c = 12.037(4) Å, β = 105.69(3)°, U = 1 532 Å^3, space group Cc, Z = 4, D_c = 1.36 g cm^{-3}, μ(Cu-K_α) = 8 cm^{-1}, λ = 1.541 78 Å, $F(000)$ = 656. Approximate crystal dimensions 0.10 × 0.33 × 0.50 mm.

Crystal Data Collection and Processing.—Compound (**3**) 2 084 independent measured reflections (θ ≤ 58°) 1 782 observed [$|F_o| > 3\sigma(|F_o|)$]; compound (**4**) 1 048 independent measured reflections [θ ≤ 58°], 1 031 observed. All data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using the ω-scan measuring routine, and corrected for Lorentz and polarisation factors. No absorption corrections were applied.

Structure Analyses and Refinement.—Both structures were solved by direct methods and their non-hydrogen atoms were refined anisotropically. In (**4**), a ΔF map revealed two sites for the fluorine atom, of weight 0.65 and 0.35 on C(18) and C(22) respectively, associated with a rotation of the phenyl group by 180° about the C(7)–C(17) bond. Idealised fixed protons of weight 0.35 and 0.65 respectively on C(18) and C(22) were also allowed for in refinement. The protons on the ring fusion points C(4) and C(10) in (**3**) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. Refinement was by block-cascade, full-matrix least-squares to give for (**3**), R = 0.047, R_w = 0.048 [$w^{-1} = \sigma^2(F) + 0.001\,39F^2$], and for (**4**) R = 0.040, R_w = 0.048 [$w^{-1} = \sigma^2(F) + 0.000\,60F^2$]. Computations were carried

Table 3. Atom co-ordinates (× 10^4) with estimated standard deviations in parentheses for (**3**).

Atom	x	y	z
O(1)	2 331(2)	2 520(1)	6 338(2)
N(2)	2 210(3)	3 043(1)	6 275(2)
C(3)	1 109(3)	3 201(1)	7 178(2)
C(4)	202(3)	2 785(1)	7 940(2)
C(5)	−2 191(4)	2 728(1)	7 298(3)
O(6)	−2 927(2)	2 268(1)	7 758(2)
C(7)	−3 142(3)	1 904(1)	6 665(2)
O(8)	−1 216(2)	1 848(1)	6 156(1)
C(9)	664(3)	1 847(1)	7 321(2)
C(10)	1 599(3)	2 356(1)	7 633(2)
C(11)	728(4)	3 735(1)	7 321(2)
C(12)	−288(4)	3 912(1)	8 384(3)
C(13)	−583(5)	4 416(1)	8 548(4)
C(14)	120(5)	4 754(1)	7 648(4)
C(15)	1 133(5)	4 579(1)	6 581(4)
C(16)	1 426(4)	4 080(1)	6 417(3)
C(17)	−3 821(3)	1 423(1)	7 245(2)
C(18)	−4 654(4)	1 043(1)	6 272(3)
F(18)	−4 820(3)	1 128(1)	4 809(2)
C(19)	−5 345(5)	597(1)	6 721(5)
C(20)	−5 146(5)	518(1)	8 198(4)
C(21)	−4 302(4)	876(1)	9 216(3)
C(22)	−3 659(4)	1 328(1)	8 723(3)

Table 4. Atom co-ordinates (× 10^4) with estimated standard deviations in parentheses for (**4**).

Atom	x	y	z
O(1)	677	1 499(4)	1 026
N(2)	304(1)	1 543(5)	1 775(3)
C(3)	295(1)	3 589(5)	2 181(3)
C(4)	675(2)	5 322(5)	1 749(3)
C(5)	1 111(2)	6 693(5)	2 695(3)
O(6)	1 495(1)	5 295(4)	3 556(2)
C(7)	2 020(1)	4 511(6)	3 271(3)
O(8)	1 890(1)	2 727(5)	2 446(2)
C(9)	1 627(2)	3 512(9)	1 298(3)
C(10)	941(2)	3 754(7)	988(3)
C(11)	−79(1)	4 067(5)	2 973(3)
C(12)	−372(2)	6 186(5)	2 946(3)
C(13)	−737(2)	6 574(6)	3 660(4)
C(14)	−822(2)	4 892(7)	4 413(4)
C(15)	−525(2)	2 807(7)	4 454(3)
C(16)	−154(2)	2 392(6)	3 753(3)
C(17)	2 450(2)	3 651(6)	4 363(3)
C(18)	2 952(2)	4 860(7)	4 927(4)
F(18)	3 018(3)	6 895(9)	4 429(5)
C(19)	3 330(2)	4 279(9)	5 969(4)
C(20)	3 217(2)	2 392(8)	6 492(4)
C(21)	2 724(3)	1 081(9)	5 986(5)
C(22)	2 364(2)	1 730(8)	4 917(4)
F(22)	1 805(3)	779(14)	4 546(9)

* The first crystals of compound (**4**) investigated were of very poor quality and the accuracy of the C–O bond lengths was not adequate to permit definitive conclusions to be drawn. A second batch of crystals from a different solvent system were very much better and the data from these form the basis for the conclusions drawn in this paper. This first batch, however, although containing molecules of virtually identical conformation, were of a different polymorphic form.

Crystal data: $C_{18}H_{16}NO_3F$, M = 313.3, monoclinic, a = 11.880(14), b = 10.581(17), c = 12.446(13) Å, β = 102.07(9)°, U = 1 530 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.36 g cm^{-3}, μ(Cu-K_α) = 8 cm^{-1}, $F(000)$ = 656. 1 027 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$; (θ ≤ 50°)]. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using the ω-scan measuring routine. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically to give R = 0.090, R_w = 0.092 [$w^{-1} = \sigma^2(F) + 0.000\,20F^2$].

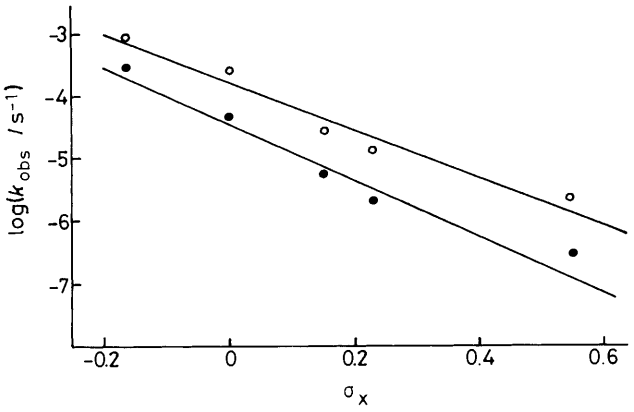
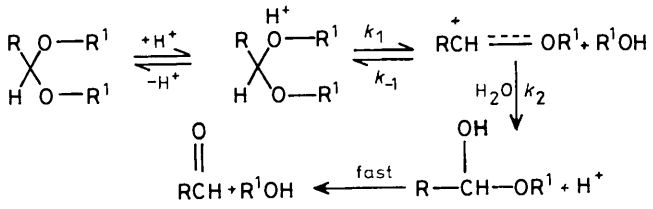
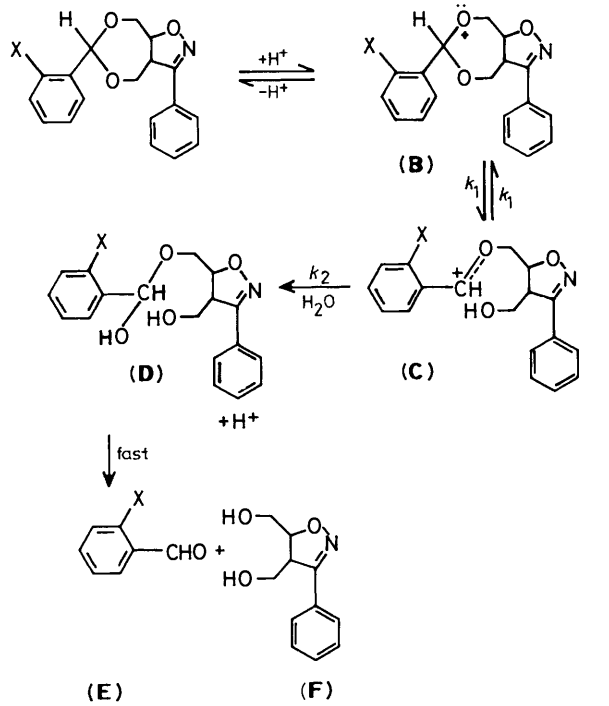


Figure 1. Hammett plots for compounds (**1**)–(**10**) using k_{obs} at pH 2; (○) Type I and (●) Type II.



Scheme 1.



Scheme 2.

out on an Eclipse S140 computer using the SHELXTL program system.

Fractional co-ordinates for compounds (**3**) and (**4**) are given in Tables 3 and 4. The fractional co-ordinates of the hydrogen atoms, their isotropic thermal parameters, and the anisotropic thermal parameters of the non-hydrogen atoms have been deposited.*

* For details see 'Instructions for Authors' (1989), *Perkin Trans. 2*, 1989, Issue 1.

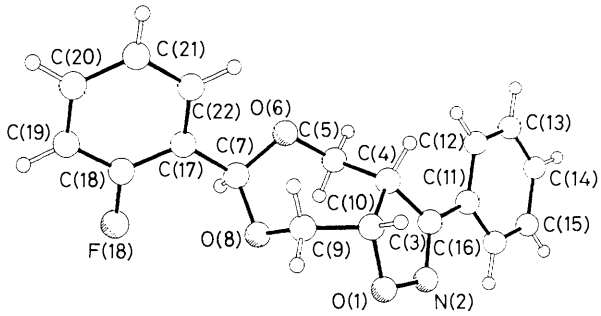


Figure 2. 'Ball-and-stick' representation of the structure of compound (**3**) showing the atomic numbering scheme.

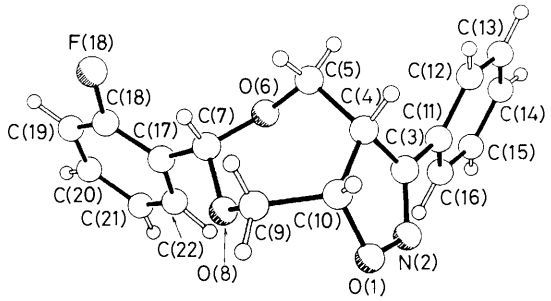


Figure 3. 'Ball-and-stick' representation of the structure of compound (**4**) with the same numbering scheme as that used for compound (**3**).

Results and Discussion

Table 2 is a summary of the hydrolysis data of compounds (**1**)–(**10**) at the pH values shown. Type I molecules are hydrolysed faster than the corresponding Type II analogues. In the case of all compounds log k_{obs} is a linear function of pH and the slope of plots of log k_{obs} *vs.* pH is close to unity (average slope for the ten compounds is equal to -0.95 ± 0.25) indicative that the mechanism of hydrolysis is *via* specific acid catalysis.

The electronic nature of the *ortho* substituent 'X' on the phenyl ring attached to the 1,3-dioxepin moiety has a marked influence on the rate of hydrolysis. Electron-withdrawing substituents slow down the rate of hydrolysis considerably. Using k_{obs} values at pH 1.99 Hammett plots were constructed for both the Type I and Type II compounds: σ_{para} values were used for the *ortho* substituents 'X.' These plots were linear with slopes of -5.0 ($r^2 = 0.981$) and -5.8 ($r^2 = 0.994$) respectively, with no significant deviations (Figure 1). The linear behaviour of log k_{obs} with the nature of the substituent 'X' suggests that the mechanism of hydrolysis of these two classes of 1,3-dioxepin derivatives is electronically rather than sterically demanding.

Non-cyclic acetals are usually hydrolysed quite rapidly at acidic pH. Under these conditions hydrolysis occurs *via* both specific acid and water catalysed pathways.[1] The initial C–O bond breaking in the case of such molecules results in the separation of the alcohol moiety from the remainder of the molecule (Scheme 1). (As no intramolecular catalysis is possible the reaction of these acetals with water is not usually rate determining, that is $k_2 > k_1$). In the case of cyclic acetals C–O bond breaking does not result in the departure of the alcohol moiety so that there is a much higher possibility that the intermediate oxacarbonium ion intermediate reverts back to the protonated cyclic acetal, rather than reacting with water. Under these conditions k_{-1} is greater than either k_1 or k_2. Thus the rate-determining step is either C–O bond cleavage (k_1) or reaction with water (k_2), provided that the intermediate hemiacetal breaks down fast.[2–6]

The hydrolysis of the cyclic acetals under study can be represented by Scheme 2. In the case of all the compounds

Table 5. Comparative bond lengths/Å for (**3**) and (**4**) with e.s.d.s in parentheses.

	(3)	(4)		(3)	(4)
O(1)–N(2)	1.405(3)	1.398(4)	O(1)–C(10)	1.452(3)	1.445(5)
N(2)–C(3)	1.286(3)	1.284(4)	C(3)–C(4)	1.506(3)	1.509(5)
C(3)–C(11)	1.463(4)	1.467(5)	C(4)–C(5)	1.531(3)	1.518(4)
C(4)–C(10)	1.527(3)	1.528(5)	C(5)–O(6)	1.420(3)	1.416(4)
O(6)–C(7)	1.390(3)	1.409(4)	C(7)–O(8)	1.433(3)	1.408(4)
C(7)–C(17)	1.501(3)	1.497(4)	O(8)–C(9)	1.428(2)	1.424(4)
C(9)–C(10)	1.494(3)	1.514(6)	C(11)–C(12)	1.385(4)	1.394(4)
C(11)–C(16)	1.389(4)	1.392(5)	C(12)–C(13)	1.377(4)	1.367(6)
C(13)–C(14)	1.375(5)	1.380(6)	C(14)–C(15)	1.386(5)	1.380(5)
C(15)–C(16)	1.362(5)	1.368(6)	C(17)–C(18)	1.384(3)	1.357(5)
C(17)–C(22)	1.374(3)	1.338(6)	C(18)–F(18)	1.354(3)	1.349(7)
C(18)–C(19)	1.374(5)	1.358(6)	C(19)–C(20)	1.362(6)	1.321(7)
C(20)–C(21)	1.369(4)	1.357(7)	C(21)–C(22)	1.390(4)	1.379(7)

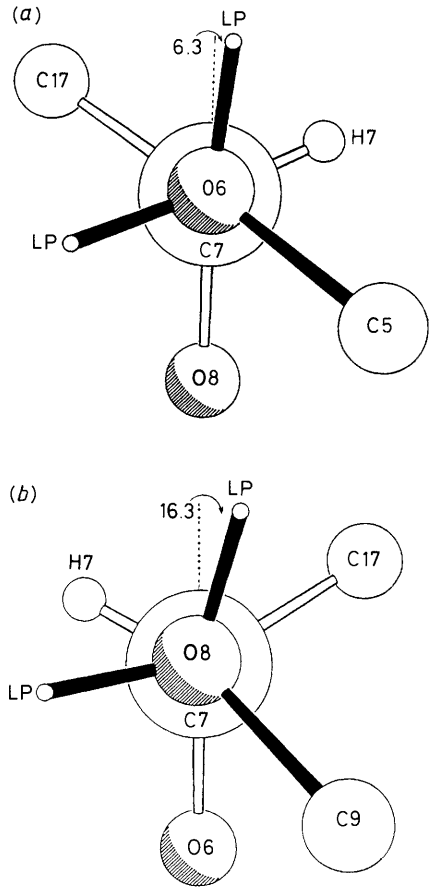


Figure 4. Newman projections along (*a*) C(7)–O(6) and (*b*) C(7)–O(8) bonds of molecule (**3**).

the appropriate *ortho* substituted benzaldehyde (**E**) and the dihydroxy compound (**F**) were found to be the only products of hydrolysis.

The reaction steps shown in Scheme 2 are similar to those delineated by Bender and Silver in their mechanistic study of the acid hydrolysis of (2,6-dioxacyclohexyl)arene derivatives.[7] The rate limiting step is C–O bond cleavage (k_1) in the protonated acetal (**B**) to give the oxonium ion (**C**). The electronic nature of the substituent 'X' affects the basicity and therefore also the extent of protonation of the acetal oxygen prior to the rate-limiting step, and hence the observed rate constant, which is given by the steady state expression $k_{obs} = Kk_1$ where K is the equilibrium constant for protonation.

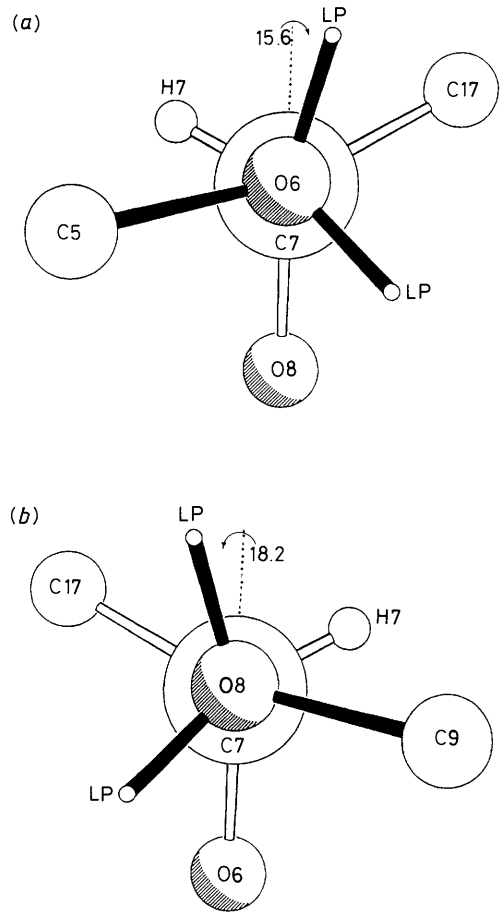


Figure 5. Newman projections along (*a*) C(7)–O(6) and (*b*) C(7)–O(8) bonds of molecule (**4**).

X-Ray crystallography has been used successfully in recent years to explain the stereoelectronic and orientation effects in molecules that break down catalytically in solution.[8–10] To correlate the ease of hydrolysis of the isoxazolinyldioxepin derivatives under study with any variations in the geometrical properties of pairs of diastereoisomers, we have compared the crystal structures of molecules (**3**) and (**4**) (X = F).

The molecular structures of (**3**) and (**4**) are shown in Figures 2 and 3. Selected bond lengths and angles are given in Tables 5 and 6. Both structures show a number of similarities: the *cis* configuration at C(4) and C(10) is retained, the dioxepin moiety is in a chair-like conformation, and the phenyl group attached to C(7) is equatorial. Differences in the geometries of the two stereoisomers arise mainly from an inversion of the configuration at C(7) and a flipping of the C(5) methylene group relative to the remainder of the dioxepin ring system. The molecule (**4**) has approximate local C_s symmetry extending from C(7) to the bisector of the C(4)–C(10) bond. However, the flipping at C(5) in (**3**) destroys this local molecular symmetry and results in changes in the O(8)–C(7)–C(17)–C(22) and O(6)–C(7)–C(17)–C(18) torsion angles.

The C(7)–O(8) and C(7)–O(6) bond lengths at the acetal centre in (**4**) are equivalent (Table 3). In (**3**), however, the C(7)–O(8) bond is significantly longer (by 0.043 Å) than C(7)–O(6). This difference is larger than that reported[11] for a number of (2,6-dioxacyclohexyl)arenes.

The orientation of the phenyl ring attached to the acetal centre, with respect to either C(7)–O(8) or C(7)–O(6) is different for molecules (**3**) and (**4**). In (**3**), O(6) lies close to the plane of the phenyl ring whereas O(8) is approximately orthogonal to this

Table 6. Comparative bond angles/° for (**3**) and (**4**) with e.s.d.s in parentheses.

	(3)	(4)		(3)	(4)
N(2)–O(1)–C(10)	108.0(2)	109.7(2)	O(1)–N(2)–C(3)	109.6(2)	109.7(3)
N(2)–C(3)–C(4)	113.0(2)	114.4(3)	N(2)–C(3)–C(11)	120.7(2)	119.6(3)
C(4)–C(3)–C(11)	126.2(2)	126.0(3)	C(3)–C(4)–C(5)	110.9(2)	114.3(3)
C(3)–C(4)–C(10)	99.3(2)	99.8(3)	C(5)–C(4)–C(10)	116.0(2)	118.3(3)
C(4)–C(5)–O(6)	110.3(2)	113.6(2)	C(5)–O(6)–C(7)	112.1(2)	113.9(3)
O(6)–C(7)–O(8)	111.3(2)	112.1(3)	O(6)–C(7)–C(17)	109.4(2)	107.0(3)
O(8)–C(7)–C(17)	111.8(2)	109.8(3)	C(7)–O(8)–C(9)	113.7(2)	113.8(3)
O(8)–C(9)–C(10)	112.4(2)	113.9(4)	O(1)–C(10)–C(4)	104.1(2)	106.3(3)
O(1)–C(10)–C(9)	107.9(2)	108.7(3)	C(4)–C(10)–C(9)	119.6(2)	117.4(3)
C(3)–C(11)–C(12)	121.1(2)	120.7(3)	C(3)–C(11)–C(16)	120.9(2)	120.4(3)
C(12)–C(11)–C(16)	118.0(3)	118.9(3)	C(11)–C(12)–C(13)	121.0(3)	120.0(3)
C(12)–C(13)–C(14)	120.4(3)	121.0(4)	C(13)–C(14)–C(15)	118.9(3)	119.1(4)
C(14)–C(15)–C(16)	120.8(3)	120.8(4)	C(11)–C(16)–C(15)	121.0(3)	120.2(3)
C(7)–C(17)–C(18)	120.1(2)	122.1(3)	C(7)–C(17)–C(22)	123.6(2)	124.4(3)
C(18)–C(17)–C(22)	116.3(2)	113.4(3)	C(17)–C(18)–F(18)	117.4(2)	114.2(4)
C(17)–C(18)–C(19)	123.2(3)	125.0(4)	F(18)–C(18)–C(19)	119.4(3)	120.4(4)
C(18)–C(19)–C(20)	118.5(3)	119.2(4)	C(19)–C(20)–C(21)	121.0(3)	119.6(4)
C(20)–C(21)–C(22)	119.1(3)	118.6(5)	C(17)–C(22)–C(21)	121.9(2)	124.1(5)

plane; the O(6)–C(7)–C(17)–C(22) and O(8)–C(7)–C(17)–C(22) torsion angles are −16.7(3) and 107.1(2)° respectively. In (**4**), however, the phenyl and dioxepin rings are approximately orthogonal with C(7)–O(8) and C(7)–O(6) bonds, both lying well out of the phenyl ring plane [the O(8)–C(7)–C(17)–C(22) and O(6)–C(7)–C(17)–C(22) torsion angles are 51.7(6) and 70.2(5)° respectively]. Also, it is noteworthy that the sum of the three non-hydrogen angles at C(7) are nearer to 360° by *ca.* 5° for (**3**) indicating a slight increase in the sp^2 character of C(7) in (**3**) relative to (**4**). The packing of molecules (**3**) and (**4**) is normal van der Waals with no significant short intermolecular contacts.

To assess the extent to which stereoelectronic effects may influence the hydrolysis of the two stereoisomeric dioxepins.* Newman projections down the two acetal C–O bonds in (**3**) and (**4**) were studied (Figures 4 and 5). The two lone pairs on each acetal oxygen were calculated in idealised tetrahedral positions and are represented by solid bonds. Figure 4 shows that one of the lone pairs on O(6) in (**3**) is unique in being almost perfectly transantiperiplanar to the longer C–O bond, C(7)–O(8). In contrast, Figure 5 shows that the corresponding lone pairs on either O(6) or O(8) in (**4**) are rotated to the same extent relative to their respective C–O bond, C(7)–O(6) and C(7)–O(8).

The greater ease of hydrolysis of (**3**) relative to (**4**) may be inferred from these observations and the greater planarity of C(7) in compound (**3**). It appears that the ground state in (**3**) is well along the reaction co-ordinate for acetal cleavage, being closer in energy and geometry to the intermediate (**C**) in Scheme 2. Moreover, it may be deduced that it is O(8) in preference to O(6) in (**3**) that is protonated in the equilibrium step prior to C–O bond cleavage, *i.e.* O(8) is more basic than O(6) as a consequence of the selective stereoelectronic interactions.

The bond lengths C(7)–O(6) and C(7)–O(8) in (**4**) are equivalent and intermediate in length to the corresponding values in (**3**), hence the basicity of the two oxygen atoms in (**4**) is also expected to be equivalent and intermediate between that of O(6) and O(8) in (**3**).

* The following conclusions are based upon the assumption that the intramolecular interactions are the same in solution as in the solid state.

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