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THE EFFECT OF RING STRAIN ON THE ACIDITIES OF FLUORINATED 4-OXAZOLIDINONES

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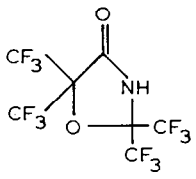
SUMMARY

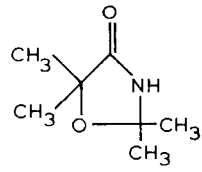
Several new fluorinated 4-oxazolidinones have been prepared by the reaction of cyanide ion with fluoroketones. The acidities of these oxazolidinones are influenced by the amount of ring strain present. For example, 2,2,5,5-tetrakis-(trifluoromethyl)-4-oxazolidinone (I) is an appreciably stronger acid than perfluoro-5-oxa-10-azadispiro[3,1,3,2]-undecan-11-one (IX).

INTRODUCTION

In a previous paper we reported[1] that 2,2,5,5-tetrakis-(trifluoromethyl)-4-oxazolidinone (I) is an unusually acidic lactam with a pK_a of 2.22. This degree of acidity is surprising since 2,2,5,5-tetramethyl-4-oxazolidinone (II)[2], the fluorine-free analog of (I), is too weak an acid to titrate in aqueous systems.



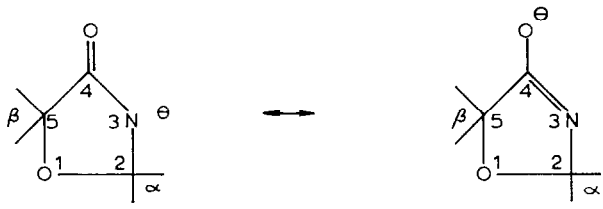
(I)



(II)

The inductive effect of the fluorine atoms in (I) would be expected to cause it to be more acidic than (II). Trifluoroacetic acid (pK_a 0.23) shows almost a 10^5-fold increase in acidity over acetic acid (pK_a 4.75). However, (I) shows more than a 10^{10}-fold increase in acidity over (II). It seems likely that part of this increase is due to effects other than simple induction.

Theoretically, steric effects, including various types of ring strain, could affect the acidity of a substituted 4-oxazolidinone. The relative ease with which a proton could be removed would depend upon how well the resulting anion could be stabilized by charge delocalization, as represented by resonance structures (III a) and (III b).



(IIIa) (IIIb)

If no strain were present, other than that inherent in a five-membered ring, structure (III a) would be favored over (III b), since (III a) contains only one sp^2-bonded atom in the ring, and (III b) contains two. Factors that would decrease the internal angles at ring positions 2 and 5, and therefore increase the internal angles at 3 and 4, would increase the stability of the anion by allowing better delocalization of the charge. Better delocalization would be expected because resonance structure (III b) would become more important as the ease of incorporating two sp^2-bonded atoms in the ring increased.

Since the trifluoromethyl groups attached to the 2 and 5 positions of oxazolidinone (I) are much larger than the corresponding methyl groups attached to oxazolidinone (II), the bond angles (α and β) between the geminal trifluoromethyl groups of (I) should be larger than the corresponding bond angles between the geminal methyl groups of (II). Consequently, the internal angles at ring positions 2 and 5 would be smaller and the angles at 3 and 4 should be larger for (I) than (II). Such an effect would increase the acidity of (I) as compared to (II), even if the inductive effects of the fluorine are ignored.

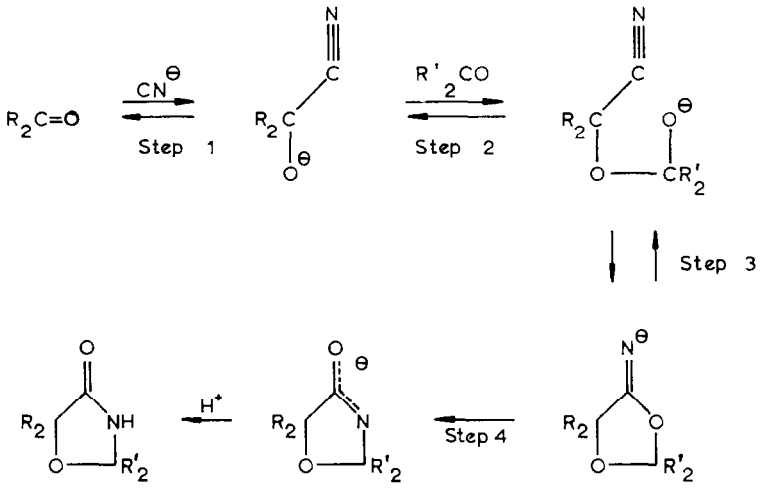
RESULTS

To test this theory, we have prepared and measured the acidities of a number of new fluorinated oxazolidinones that have different strain effects. The size of the internal angle at positions 2 and 5 has been varied by changing the size of the groups attached to these positions, using CF_2H as a small group and CF_2Cl as a larger group, and by replacing the geminal pairs of substituents at the 2 and/or the 5 position with spiro-fused 4- and 5-membered perfluorocycloalkyl rings.

The oxazolidinone (I) was prepared by a previously reported reaction of two equivalents of hexafluoroacetone with sodium cyanide in acetonitrile[3]. This same procedure was successful in preparing oxazolidinones (XIII) and (XV) from

pentafluoroacetone and *s*-tetrafluoroacetone, although a lower reaction temperature was necessary to obtain good yields. However, the reaction of sodium cyanide with chloropentafluoroacetone and hexafluorocyclobutanone failed to give the corresponding oxazolidinones in appreciable yields. By substituting the more soluble tetraethylammonium cyanide for sodium cyanide, these ketones, as well as perfluorocyclopentanone and chlorotetrafluoroacetone, gave the corresponding oxazolidinones (VI), (IX), (X), and (XIV) in satisfactory yields.

The formation of the oxazolidinones by action of cyanide ion on fluoroketones involves several distinct steps, as illustrated below.



The first three steps are believed to be equilibrium reactions, but the fourth step, which is a rearrangement, appears to be irreversible. Use of the more soluble tetraethylammonium cyanide, in place of sodium cyanide, would result in a higher concentration of cyanide ion, and therefore favor products in the equilibrium steps. This, however, does not completely explain the large difference in reactivity between sodium and tetraethylammonium cyanide. A more satisfactory explanation may be that the intermediate product from step 3 will rearrange more easily if the associated cation is large (such as tetraethylammonium). A small cation (such as sodium) would be more tightly bound by coulombic attraction to the charged nitrogen, and therefore would tend to prevent the delocalization of the charge required for the rearranged product.

Since the formation of the oxazolidinones is stepwise, two different ketones can be used in the synthesis. A number of oxazolidinones (IV), (V), (VII), (VIII), and (XI) containing different substituents at the 2 and 5 positions have been prepared by stepwise addition of two different fluoroketones to a cyanide solution in acetonitrile.

Attempts to prepare tetrakis-(chlorodifluoromethyl)-oxazolidinone (XII) by reaction of *s*-dichlorotetrafluoroacetone with either sodium or tetraethylammonium cyanide were unsuccessful. This lactam was prepared instead by an acid-catalyzed condensation of the ketone with its pre-formed cyanohydrin. Oxazolidinone (XVI) was also prepared by an acid-catalyzed condensation of acetone with hexafluorocyclobutanone cyanohydrin.

TABLE 1

ACIDITIES OF OXAZOLIDINONES WITH DIFFERENT RING STRAIN EFFECTS

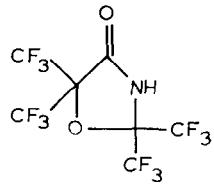
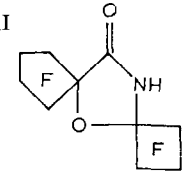
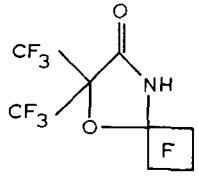
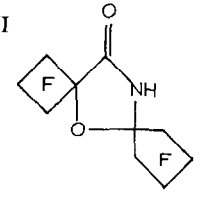
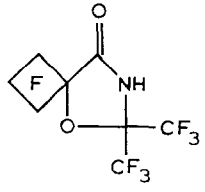
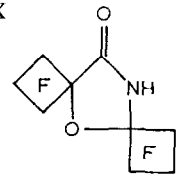
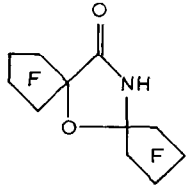
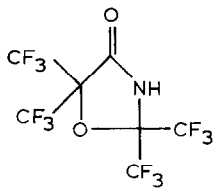
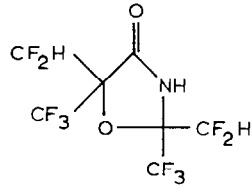
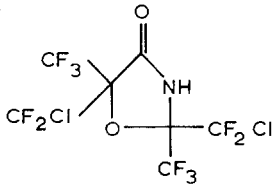
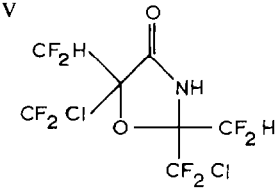
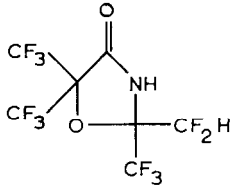
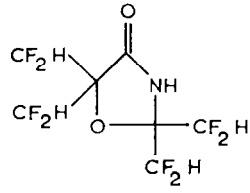
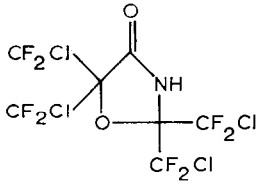
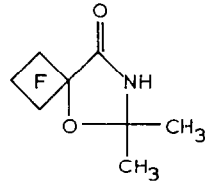
No.	Oxazolidinone	pK_a in 40% EtOH	No.	Oxazolidinone	pK_a in 40% EtOH
I		2.22	VII		3.06
IV		2.46	VIII		3.09
V		2.72	IX		3.54
VI		2.92			

TABLE 2

ACIDITIES OF OXAZOLIDINONES SUBSTITUTED WITH GROUPS OF DIFFERENT ELECTRONEGATIVITIES

No.	Oxazolidinone	pK_a in 40% EtOH	No.	Oxazolidinone	pK_a in 40% EtOH
I		2.22	XIII		4.06
X		3.13	XIV		4.10
XI		3.55	XV		5.90
XII		3.78	XVI		8.83

DISCUSSION

Ring strain has a definite and predictable effect upon the acidities of 4-oxazolidinones, as can be seen from Table 1. Spiro-fusion of a perfluorocyclobutyl ring at either the 2- or the 5-position (as in (IV) and (V)) causes a decrease in

acidity as compared to (I). Spiro-fusion of a four- or five-membered perfluorocycloalkyl ring at both the 2- and the 5-positions (as in (VI), (VII), (VIII) and (IX)) further decreases the acidity, with the most strained compound of this series (IX) showing the lowest acidity. Thus, it appears that spreading the internal angles at the 2 and 5 positions of the oxazolidinone ring does indeed decrease the acidity when the inductive effects of the substituents are approximately equal.

The steric effects of replacing the CF_3 groups of (I) with the smaller CF_2H or the larger CF_2Cl groups are less apparent (see Table 2), for the differences in inductive effects of these groups compared to a CF_3 group apparently overshadow the smaller effects that could be caused by steric repulsion.

EXPERIMENTAL

^{19}F NMR spectra (CCl_3F reference) were obtained for each compound and were consistent with structures. Positions of CF_3 groups adjacent to the carbonyl function (71–75 ppm) were lower field than those adjacent to the nitrogen function (75–81 ppm); $-CF_2$ and $-CF_2H$ groups appeared in the region 121–144 ppm; and $-CF_2Cl$ groups appeared in the 55–66 ppm region. ^1H NMR spectra were obtained where applicable and were consistent with structures. The acidity (pK_a) constants of the oxazolidinones were determined in 40% ethanol–60% water by potentiometric titration with aqueous sodium hydroxide.

Perfluoro-6,6-dimethyl-5-oxa-8-azaspiro[3,4]-octan-7-one (IV) (nc)

This material was prepared by consecutive distillation of 0.1 mole hexafluoroacetone and 0.1 mole perfluorocyclobutanone[4] into a solution of 0.1 mole tetraethylammonium cyanide in 110 ml acetonitrile. The temperature was held at −30 to −20° during the additions. The reaction mixture was stirred at room temperature for several hours and poured into dil. aq. HCl. The organic layer was separated and washed with water until the product solidified. The product was filtered off, washed with water, dried, and purified by recrystallization from pentane and sublimation under reduced pressure to give 16.1 g (43%) of the oxazolidinone as colorless needles: m.p. 75–77°. Calcd. for $C_8HF_{12}NO_2$: C, 25.89; H, 0.27; F, 61.44; N, 3.77; Found: C, 26.06; H, 0.62; F, 61.28; N, 3.75.

Perfluoro-5-oxa-12-azadispiro[3,1,4,2]-11-one (VII) (nc)

This was prepared as for (IV) using perfluorocyclopentanone[5] followed by perfluorocyclobutanone. The product was purified by sublimation under reduced pressure and recrystallized from benzene. It was further purified by dissolving in 5% $NaHCO_3$, filtering, and acidifying the filtrate. The product was again sublimed to give an 8% yield of the oxazolidinone: m.p. 108–110°. Calcd. for $C_{10}HF_{14}NO_2$: C, 27.73; H, 0.23; F, 61.42; N, 3.23; Found: C, 27.03; H, 0.04; F, 61.47; N, 3.07.

Perfluoro-5-oxa-11-azadispiro[3,1,4,2]-12-one (VIII) (nc)

This was prepared as for (IV) using perfluorocyclobutanone, followed by perfluorocyclopentanone. The product was sublimed and further purified by dissolving in 5% $NaHCO_3$, filtering, and acidifying. The product was again sublimed to give a 22% yield of the oxazolidinone: m.p. 123–125°. Calcd. for $C_{10}HF_{14}NO_2$: C, 27.73; H, 0.23; F, 61.42; N, 3.23; Found: C, 27.49; H, 0.17; F, 61.22; N, 3.18.

2-(Difluoromethyl)-2,5,5-tris-(trifluoromethyl)-oxazolidin-4-one (XI) (nc)

This material was prepared as for (IV) using hexafluoroacetone followed by pentafluoroacetone. The product was recrystallized from benzene and sublimed under reduced pressure to give a 40% yield of the oxazolidinone: m.p. 100–101°. Calcd. for $C_7F_{11}H_2NO_2$: C, 24.65; H, 0.59; F, 61.27; N, 4.11; Found: C, 25.38; H, 1.12; F, 60.98; N, 4.88.

Perfluoro-5-oxa-10-azadispiro[3,1,3,2]undecan-11-one (IX) (nc)

Perfluorocyclobutanone, 22 ml (*ca.* 0.2 mole) was distilled into a solution of 15 g (0.096 mole) tetraethylammonium cyanide in 160 ml acetonitrile at −30°. The reaction mixture was worked up as for (IV) and purified by recrystallization from benzene and sublimation under reduced pressure to give 16.8 g (46%) of the oxazolidinone as colorless needles: m.p. 118–119°. Calcd. for $C_9HF_{12}NO_2$: C, 28.22; H, 0.26; F, 59.63; N, 3.66; Found: C, 28.42; H, 0.39; F, 59.41; N, 3.67.

Perfluoro-6-oxa-12-azadispiro[4,1,4,2]tridecane-13-one (VI) (nc)

This material was prepared as for (IX) from pentafluorocyclopentanone in 26% yield: m.p. 145–146°. Calcd. for $C_{11}HF_{16}NO_2$: C, 27.35; H, 0.21; F, 62.93; N, 2.89; Found: C, 27.67; H, 0.77; F, 62.80; N, 2.99.

2,5-Bis-(chlorodifluoromethyl)-2,5-bis-(trifluoromethyl)-4-oxazolidinone (X) (nc)

This was prepared as for (IX) from chloropentafluoroacetone. The crude oily product was purified by extraction with 5% NaOH and reprecipitation of the aqueous layer with 10% HCl. The product was further purified by recrystallization from pentane and sublimation under reduced pressure to give a 33% yield of the oxazolidinone as colorless crystals: m.p. 87–89°; IR (KBr) 5.60 μ (C=O). Calcd. for $C_7HCl_2F_{10}NO_2$: C, 21.45; H, 0.26; Cl, 18.09; F, 48.47; N, 3.57; Found: C, 21.53; H, 0.33; Cl, 17.99; F, 48.43; N, 3.45.

2,5-Bis-(chlorodifluoromethyl)-2,5-bis-(difluoromethyl)-4-oxazolidinone (XIV) (nc)

This was prepared as for (IX) from 1-chloro-1,1,3,3-tetrafluoroacetone[6]. The crude oily product was dried ($MgSO_4$) and distilled (b.p. 88–100° at 1.8 mm) to give a nearly colorless liquid which solidified on cooling, and was further

purified by sublimation to obtain 6.3 g (47%) of the oxazolidinone as a white solid: m.p. 33–36°; IR (melt) 5.68 μ (C=O). Calcd. for $C_7H_3ClF_8NO_2$: C, 23.61; H, 0.85; N, 3.94; Found: C, 23.90; H, 0.90; N, 3.89.

2,5-Bis-(difluoromethyl)-2,5-bis-(trifluoromethyl)-4-oxazolidinone (XIII) (nc)

A 50 ml sample (measured at −78°) of pentafluoroacetone was distilled into a stirred suspension of 13.4 g (0.275 mole) powdered sodium cyanide in 200 ml acetonitrile. The temperature was maintained at −30° during this addition, and the mixture was stirred for 1 h at −30°, then allowed to warm to 25°. The mixture was worked up as for (IV) above and purified by recrystallization from benzene–hexane and sublimation. An 88% yield of the white crystalline oxazolidinone was obtained as a 50:50 mixture of the *cis* and *trans* isomers: m.p. 93–94° (sublimed); 91.5–93° (recryst.); IR (KBr) 5.66 μ (C=O). Pure samples of the *cis* and *trans* isomers were obtained by GLC separation on an 8 ft column of 25% fluorosilicone on "Chromsorb W" at 100°. Spectral data (^{19}F NMR, ^{1}H NMR) were essentially the same for the two isomers. Melting points were also very close: (a) shorter retention time, m.p. 92.2–93°; (b) longer retention time, m.p. 93–94°. Calcd. for $C_7H_3F_{10}NO_2$: C, 26.01; H, 0.94; N, 4.34; F, 58.81; Found: C, 26.03; H, 0.91; N, 4.27; F, 58.81.

2,2,5,5-Tetrakis-(difluoromethyl)-4-oxazolidinone (XV) (nc)

This was prepared as for (XIII) from *s*-tetrafluoroacetone; the temperature was held at 25–40° during the ketone addition step. The reaction mixture was worked up by pouring into dil. aq. HCl, washing the organic layer with water, and dissolving the organic layer in 5% aq. NaOH. The solution was filtered to remove undissolved material, and acidified with aq. 5% HCl. The solid that precipitated was recrystallized from benzene and sublimed under reduced pressure to give a 11.2% yield of the oxazolidinone as colorless needles: m.p. 123–5°; IR (KBr) 5.69 μ (C=O). Calcd. for $C_7H_5F_8NO_2$: C, 29.28; H, 1.76; N, 4.88; F, 52.96; Found: C, 29.80; H, 1.90; N, 4.61; F, 52.46.

Perfluoro-6,6-dimethyl-5-oxa-7-azaspiro[3,4]octan-8-one (V) (nc)

Sodium hydride (0.06 mole, 50% mineral oil dispersion) was added portionwise to a solution of 5.9 g (0.03 mole) perfluorocyclobutanone cyanohydrin [1] and 10 g (0.06 mole) hexafluoroacetone in 50 ml of glyme at −40°. The reaction mixture was stirred at room temperature for several hours and poured into dil. aq. HCl. The organic layer was separated, washed with water, dried ($MgSO_4$), and distilled (b.p. 70–80°, 5 mm) to give a solid which was recrystallized from benzene to give 5.1 g (46%) of the oxazolidinone: m.p. 85–86°; IR (KBr) 5.60 μ (C=O). Calcd. for $C_8HF_{12}NO_2$: C, 25.89; H, 0.27; N, 3.77; Found: C, 25.86; H, 0.11; N, 3.56.

2,2,5,5-Tetrakis-(chlorodifluoromethyl)-4-oxazolidinone (XII) (nc)

A mixture of 11.3 g (0.05 mole) 1,3-dichlorotetrafluoroacetone cyanohydrin[6], 9.9 g (0.05 mole) 1,3-dichlorotetrafluoroacetone, and 1 ml conc. H_2SO_4 was heated 2 h at 175° in an 80 ml Hastelloy-lined bomb to give 18 g of a yellow liquid. The crude product was dissolved in 5% aq. NaOH and the aq. layer precipitated with 10% aq. HCl to give a solid which was filtered off, washed with water, dried, and recrystallized from n-hexane to give 2.7 g (13%) of the oxazolidinone as colorless crystals: m.p. 106–112°; IR (KBr) 5.64 μ (C=O). Calcd. for $C_7HO_2NF_8Cl_4$: C, 19.79; H, 0.24; F, 35.77; N, 3.30; Found: C, 19.87; H, 0.32; N, 3.20; F, 35.73.

1,3-Dichlorotetrafluoroacetone cyanohydrin (nc)[7]

To a solution of (0.1 mole) sodium cyanide in 25 ml water was added 19.9 g (0.1 mole) of 1,3-dichlorotetrafluoroacetone; the temperature was held at less than 10°. The dark reaction mixture was stirred for 30 min, and 33.4 g (0.102 mole) 30% aq. H_2SO_4 added with cooling in ice. The mixture was stirred for 2 h and extracted with methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and distilled to give 10.8 g (48%) of the cyanohydrin as a colorless liquid: b.p. 67–68° (22 mm); n_D^{25} 1.3790. Calcd. for $C_4HCl_2F_4NO$: C, 21.26; H, 0.45; F, 33.63; Found: C, 21.44; H, 0.55; F, 33.56.

1,1,2,2,3,3-Hexafluoro-6,6-dimethyl-5-oxa-7-azaspiro[3,4]-octan-8-one (XVI) (nc)

A solution of 2.5 g (12 mmole) perfluorocyclobutanone cyanohydrin in 20 ml acetone was saturated with dry HCl gas and allowed to stand overnight at 25°. Excess acetone was evaporated, the residue mixed with water and the resultant precipitate filtered off. Recrystallization from benzene gave 0.9 g (34%) of the oxazolidinone as colorless needles: m.p. 121–123°; IR (KBr) 5.77 μ (C=O). Calcd. for $C_8H_7F_6NO_2$: C, 36.51; H, 2.68; F, 43.22; N, 5.32; Found: C, 36.68; H, 2.76; F, 43.39; N, 5.29.

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