Isoxazolinyldioxepins. Part 2. The Partitioning Characteristics and the Complexing Ability of some Oxazolinyldioxepin Diastereoisomers†

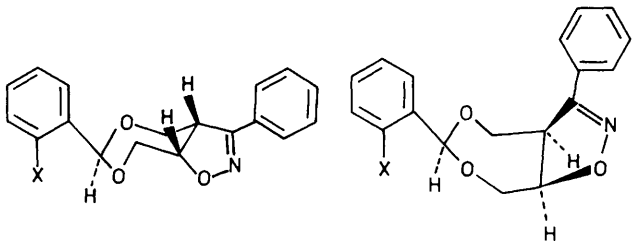
Patrick Camilleri,* David Munro, and Karen Weaver
Shell Research Limited, Sittingbourne Research Centre, Sittingbourne, Kent, ME9 8AG
David J. Williams and Henry S. Rzepa
Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY

The octanol–water partition coefficients (*P*) of pairs of isoxazolinyldioxepin diastereoisomers were measured. It was found that one type of diastereoisomer had a lower partition coefficient than the corresponding analogue from the other type. These differences were attributed to variations in molecular conformation. Quantum-mechanical studies have also shown major differences in the electronic distribution of the two types of diastereoisomers. These findings were finally confirmed by experiments designed to test the ability of the two types of isoxazolinyldioxepin to complex with mono-cations such as Li^+, Na^+, K^+, Cs^+, and Cu^+.

The logarithm of the n-octanol–water partition coefficient (log *P*) has been widely related to biochemical and/or biological activity in a number of quantitative structure–activity relationships. log *P* is usually considered as a measure of hydrophobicity, which is related both to the transport of molecules across biological membranes and to the binding of these molecules at the site of action.

In Part 1, we reported [1] the hydrolytic stability and the crystal structure of pairs of isoxazolinyldioxepin diastereoisomers which can be represented by the two general structures (**Aa**) and (**Ab**) and which we called Type I and Type II, respectively.

We now present a study of the partitioning characteristics of these molecules between octanol and water. We interpret differences in log *P* between molecule Types I and II in terms of the structures and electronic properties of the conformationally defined diastereoisomers and relate these properties to the ability of the two types of isoxazolinyldioxepins to complex with mono-cationic species.



Experimental

Materials.—The synthesis of compounds (**1**)–(**10**) is given in our previous report.[1] Acetonitrile and n-octanol were of h.p.l.c. grade. Water was doubly distilled and deionised. Inorganic salts were 'Analar' grade.

Determination of Partition Coefficients.—The n-octanol–water partition coefficient of the oxazolinyldioxepin derivatives under study were measured either by the 'shake-flask' or the 'h.p.l.c. retention time' method.

For the 'shake-flask' method the following procedure was followed. The compound (10 mg) was dissolved in n-octanol (10 cm^3), presaturated with water. Aliquots (2 cm^3) of these solutions were added to each of four glass centrifuge tubes containing water (15 cm^3), presaturated with n-octanol. The tubes were stoppered and shaken for 1 h at 25 °C, then centrifuged at 5 000 rpm, at the same temperature for 45 min. The separated layers were removed and the n-octanol layer (1 cm^3) diluted with acetonitrile (20 cm^3) for analysis by h.p.l.c.

Table 1. n-Octanol–water partition coefficients (*P*) at 25 °C and chromatographic retention times.

Compd.	Substitutent 'X'	Type	Retention time/min	log *P*
(**1**)	H	I	4.35	3.42[a]
(**2**)	H	II	3.12	2.34
(**3**)	F	I	4.34	3.45
(**4**)	F	II	3.12	2.35
(**5**)	Cl	I	5.48	4.13[a]
(**6**)	Cl	II	3.62	2.92
(**7**)	CF_3	I	5.90	4.31
(**8**)	CF_3	II	3.79	3.00[a]
(**9**)	CH_3	I	5.29	4.00[a]
(**10**)	CH_3	II	3.33	2.72

[a] log *P* values determined from h.p.l.c. retention time measurements.

The water layer was analysed directly by h.p.l.c. The partition coefficient (*P*) was calculated from the ratio of the equilibrium concentration of the dissolved dioxepin derivative in n-octanol and water. Partition coefficients (given in the form of log *P*) are shown in Table 1.

In the 'h.p.l.c. retention time' method a solution of each of compounds (**1**)–(**10**) was analysed by h.p.l.c. and the retention time measured. A plot (Figure 1) of the logarithm (base 10) of retention time against log *P* for compounds previously measured by the 'shake-flask' method was linear (correlation coefficient, $r = 0.995$) and was used to estimate the log *P* of the remaining compounds. The same h.p.l.c. conditions as the ones detailed in our previous report [1] were used in this study.

† This and the preceding paper are reprinted versions of the corresponding articles that appeared in *J. Chem. Soc., Perkin Trans.* 2, 1989, 1265 and 1271. As the result of an oversight in the Editorial Office, some colour plates, which should have appeared in this article, were omitted. The Society apologises for any inconvenience caused.

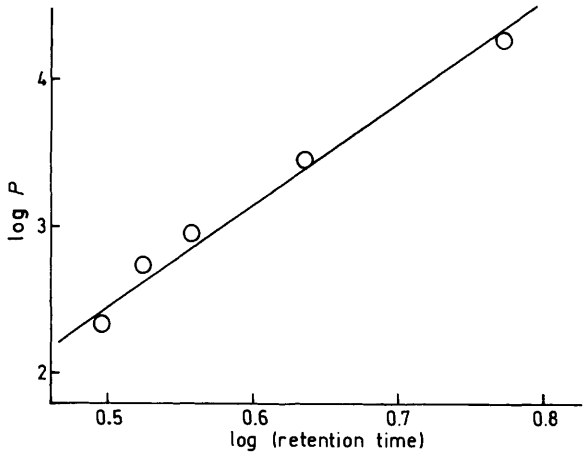


Figure 1. A plot of the logarithms of the octanol–water partition coefficient with the logarithm of the h.p.l.c. retention time.

Chromatography conditions can be summarised as follows: stainless steel column [15 cm × 0.5 cm (i.d.)] packed with Spherisorb ODS2 (0.5 μm); acetonitrile–water (3:2 v/v) eluant at a flow rate of 1 cm^3 min^{-1}; compounds detected at a wavelength of 250 nm. The retention times obtained using these conditions are given in Table 1.

Quantum Mechanical Calculations.—The starting geometries of the oxazolinyldioxepin diastereoisomers (**3**) and (**4**) were based on the *X*-ray structures determined in the previous paper.[1] Molecular electrostatic potentials (MEP) were computed using a VSSPOT procedure of Geesner-Prettre and Pullman.[2] This treats charge distributions as having arisen from ZDO-type valence quantum mechanical calculations and approximates the nuclear charge attraction integrals in terms of spherically symmetric functions. The MEPs were computed on Connolly[3] surfaces using a density of dots of 10 and a water radius of 1.4 Å. Surface areas of molecules (**3**) and (**4**) were derived as part of these computations. Figures 2(*a*) and (*b*) show the MEPs of molecules (**3**) and (**4**). The 'red' and 'blue' dots represent 'positive' and 'negative' potentials, respectively. 'Neutral' areas are represented by 'green' dots. An Evans and Sutherland PS300 was used to extract Figures 2(*a*) and (*b*).

FAB Mass Spectrometry.—Spectra of compounds (**3**) and (**4**) (0.075 mol dm^{-3}) in the presence of various amounts of inorganic salts (see Table 2) were run on a Finnigan MAT 90 mass spectrometer operated at 6 keV using xenon as the collision gas. Glycerol was used as the fluid matrix. The mixture to be analysed was deposited on a copper target operated at about 35 °C.

Results and Discussion

The oxazolinyldioxepin derivatives (**1**), (**3**), (**5**), (**7**), and (**9**) belong to Type I, whereas the remaining compounds have the Type II conformation. The log *P* values of pairs of these diastereoisomers are presented in Table 1, which shows that, without exception, Type I molecules are more hydrophobic than the corresponding Type II diastereoisomers by about an order of magnitude. Within the two types of isomers the variation in hydrophobicity is due to the nature of the *ortho*-substituent 'X'. Substracting the log *P* values in Table 1 from that of the appropriate unsubstituted compound (X = H) gave substituent constants which were related to the corresponding hydrophobicity constants, π, introduced by Hansch and co-workers.[4,5] Deviations from π are observed only for the Type II molecules. In fact the contribution to hydrophobicity made by substituents in Type II diastereoisomers are less than the corresponding π values. This may be explained in terms of a lesser availability of 'X' for hydrophobic interaction in these molecules compared to the Type I conformers.

Table 2. Ratios of DH^+/DM^+ for different salts containing monocation species. D represents either diastereoisomer (**3**) or (**4**).

Salt	Concentration/ mol dm^{-3}	D(**3**)H^+/ D(**3**)M^+	D(**4**)H^+/ D(**4**)M^+
LiCl	0.1	7.34	15.18
LiCl	0.5	1.33	*a*
Lilactate	0.1	2.98	11.73
NaCl	0.1	2.85	9.26
KCl	0.1	1.17	1.17
KNO_3	0.1	5.09	2.19
CsCl	0.1	2.54	2.96
CuCl	Saturated solution about 6×10^{-4}	2.43	23.56

[a] This ratio was not obtained because of much suppression of the FAB signals caused by the high concentration of LiCl.

It is also noticeable from Table 1 that the difference in log *P* values between each pair of diastereoisomers appears to depend on the size of the substituent 'X': the larger the substituent the bigger the difference in log *P*. These changes in log *P* may be due to differences in the orientation of the phenyl moiety (bearing the substituent 'X') with respect to the rest of the molecule.

The higher log *P* values for Type I molecules is undoubtedly due to their having a different conformation than the Type II isomers. Such a variation in conformation may in turn lead to differences in the accessibility to either water (solvation) or octanol (hydrophobic interactions). The Type I isomers are extended in shape whilst the Type II conformers have a 'cradle-like' structure. In Figure 3 the two previously determined *X*-ray structures[1] of molecules (**3**) and (**4**) have been superimposed. From this two dimensional diagram it appears that (**3**) has a bigger surface area than (**4**) indicating a probable reason for the higher hydrophobicity of the former molecule.[6] However, calculating the surface area of the individual isomers, it is found that the difference in surface area is very small and of the order of 1.5 $Å^2$, albeit in the correct direction. Thus it seems unlikely that surface area is a significant factor influencing the partitioning characteristics of the isoxazolinyldioxepin diastereoisomers.

To identify any other causes for the different partition coefficients in Table 1, quantum mechanical calculations were performed on the diastereoisomeric pair (**3**) and (**4**), using starting geometries from the *X*-ray crystal structure of these molecules. Molecular electrostatic potentials (MEPs) were computed on Connolly surfaces as shown in Figures 2(*a*) and (*b*). The colour notation in these figures (see the Experimental section) shows that the negative potential computed for (**3**) is mostly concentrated within the 'cradle' as all four hetero atoms, three oxygens and one nitrogen, are pointing in the same direction. In the case of (**4**) only three of the heteroatoms are pointing in this direction whilst another, an oxygen in the acetal moiety, is pointing in an opposite direction. This latter oxygen appears to be shielded by hydrophobic groups from the adjacent phenyl rings and the methylene groups on the seven-membered ring system so that it is less accessible to solvation by water. As the four hetero atoms in (**3**) are pointing in the same direction, away from hydrophobic centres, solvation is expected to be more possible for this diastereoisomer.

To probe the electronic nature of the isoxazolinyldioxepin moiety in (**3**) and (**4**) further, the binding of these diastereo-

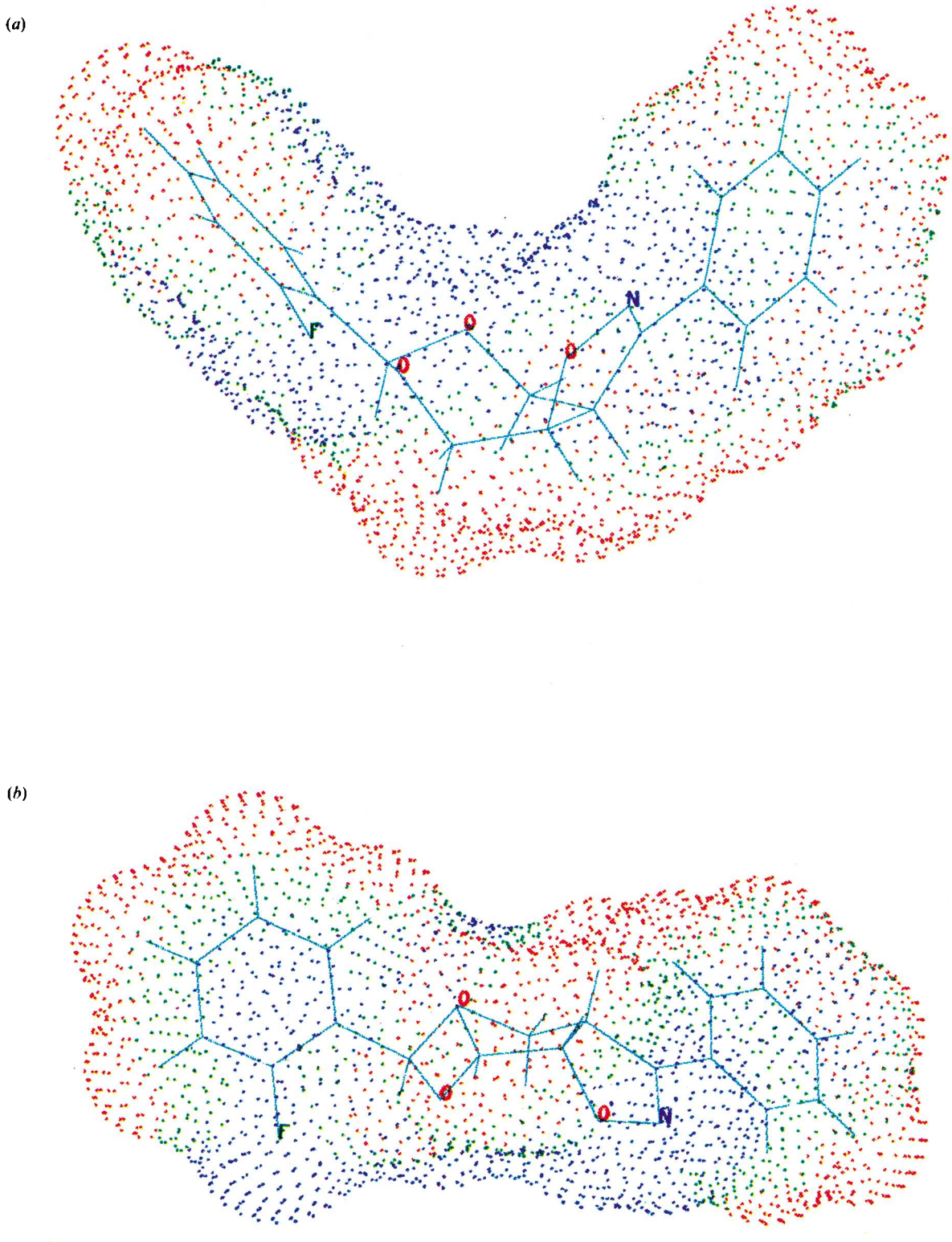


Figure 2. Molecular electrostatic potentials of (*a*) (**3**) and (*b*) (**4**). For colour coding see the Experimental section.

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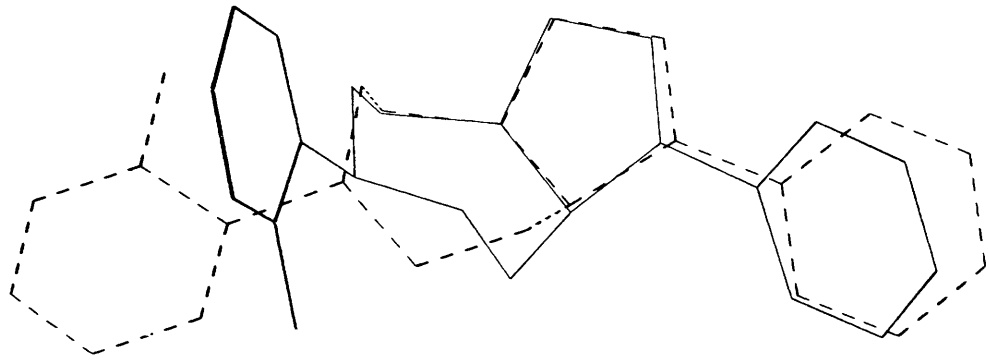

Figure 3. A superimposed view of compounds (**3**) and (**4**) illustrating differences in the geometry of the two molecules.

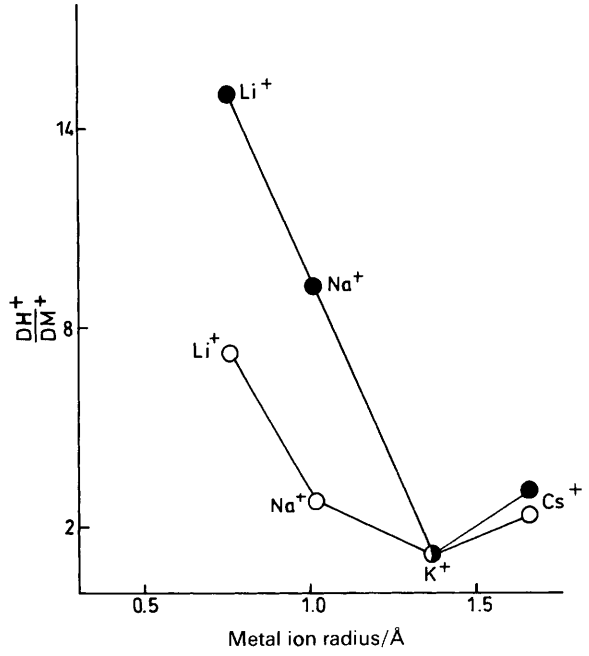

Figure 4. Selectivity of the diastereoisomers (**3**) (○) and (**4**) (●) to monocation complexation. DH^+ and DM^+ are the FAB signals due to the protonated and the cation complexed molecules. The counter-ion was chloride in all cases.

isomers with mono-cations, such as Li^+, Na^+, K^+, Cs^+, and Cu^+, was examined using FAB.[7,8] The ability of a macrocycle to complex with these cations primarily depends on the geometry of both the 'host' molecule and the 'guest' cation. The basicity of the environment on the macrocycle that replaces part or all of the cation's solvation shell[9] also plays an important role in this 'host–guest' interaction.

FAB mass spectrometry has shown that both diastereoisomers (**3**) and (**4**) complex with cations to a varying extent. Results are presented in Table 2. This table gives the ratios DH^+/DM^+ for the complexation of (**3**) and (**4**) with the various cations. DH^+ and DM^+ are the FAB signals observed for the protonated and the metal complexed diastereoisomers, respectively. The lower the DH^+/DM^+ ratio the greater is the complexing ability.

The ability of (**3**) and (**4**) to complex with the cations tested varies between these two conformationally defined molecules, and depends on the size and concentration of the cation and the nature of the counterion, a situation very often encountered in the complexation of other macrocycles, *e.g.* crown ethers, with a variety of cationic species.[9] The results with 0.1 mol dm^{-3} salts containing chloride as the counter ion are shown in Figure 4 which is a plot of DH^+/DM^+ against the ionic radius of the metals involved. This figure shows that both diastereoisomers (**3**) and (**4**) interact with the bigger cations, K^+ and Cs^+ to an equal extent. The smaller cations Li^+ and Na^+ preferably complex to isomer (**4**).

Differences in the complexing ability of (**3**) and (**4**) with monocations can be tentatively explained as follows: the smaller cations may complex within the 'cradle-like' cavity of isomer (**4**), possibly involving both oxygens in the dioxepin rings and the oxygen and the nitrogen atoms in the oxazolinyl ring; cations with the larger ionic radius may not fit in this 'cradle' and will only complex 'sideways' with two oxygens, one from the actual moiety and the others from the oxazolinyl ring. The non-bonding distance between the latter two oxygen atoms is the same for both molecules (**3**) and (**4**).

Acknowledgements

We thank Mr. M. T. Beer for running the FAB mass spectra and Dr. B. Odell for the quantum mechanical calculations.

References

1 P. Camilleri, D. Munro, K. Weaver, D. J. Williams, H. S. Rzepa, and A. M. Z. Slawin, *J. Chem. Soc., Perkin Trans. 2*, previous paper.
2 C. Geesner-Prettre and A. Pullman, *QCPE* Catalog, Indiana Univ., Chem. Dept. Program No. 249.
3 M. Connolly, *QCPE*, Program No. 429.
4 T. Fujita, J. Iwasa, and G. Hansch, *J. Am. Chem. Soc.*, 1964, **86**, 5175.
5 A. Leo, G. Hansch, and D. Elkins, *Chem. Rev.*, 1987, **71**, 525.
6 N. Funasaki, S. Hada, and S. Neya, *J. Chromatogr.*, 1986, **361**, 33.
7 R. A. W. Johnstone and M. E. Rose, *J. Chem. Soc., Chem. Commun.*, 1983, 1268.
8 N. M. Richardson, I. O. Sutherland, P. Camilleri, and J. A. Page, *Tetrahedron*, 1985, **26**, 3739.
9 R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. L. Christensen, and D. Sen, *Chem. Rev.*, 1985, **85**, 271.

Received 3*rd October* 1988; *Paper* 8/03936D