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Letter to the Editor

Distribution coefficients of atenolol and sotalol

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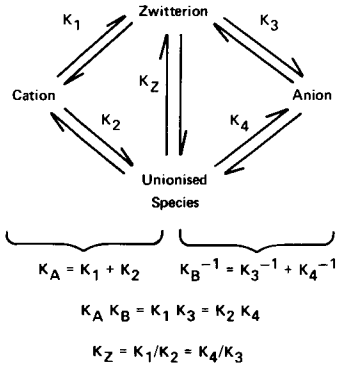
Our original publication (Taylor & Cruickshank 1984) was addressed to one simple specific point: the confusion that has been caused by apparently contradictory data for the same two compounds. It is now criticised on two counts (Day & Parr 1984): that we used a confusing nomenclature; and that our treatment of the data was technically incorrect.

On the first count, we defined P (i.e. IUPAC K_D) and D (i.e. IUPAC D_C) in the form of equations which allow of no ambiguity. It is difficult to see how our definition of 'partition coefficient' P as pertaining to the *same molecular species* (Taylor & Cruickshank 1984) differs in any material sense from that of K_D as pertaining to a *single definite form* (IUPAC 1977; quoted by Day & Parr 1984). We agree in deploring the widespread (undefined) use of 'effective partition coefficient', hence our attempt to define what we believe to be commonly meant by this term; we will be surprised to learn that anyone was actually confused. If it is held by Day and Parr that the use of non-IUPAC symbols such as P and D is confusing *per se*, the same must go for almost the entire literature of medicinal chemistry, including all that by the two principal authorities on this subject in that field (Rekker 1977; Hansch & Leo 1979). Finally, our preference for D over P as the relevant physiological quantity was explicitly tied to context (the pH-partition hypothesis) and based on the quoted sources; the authors offer no evidence to the contrary.

The second count is more important. Our treatment was deliberately simplified in that, to avoid irrelevance, we did not overly consider the zwitterionic nature of sotalol. We now present the full evidence and demonstrate that it makes *no difference* to the conclusions reached, as Day & Parr indeed acknowledge and the reason for which is clarified below.

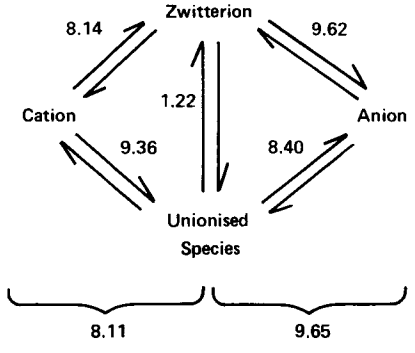
The authors state that the lower pK_a of sotalol is that of 'the acidic sulphanilo group'. *This is incorrect.* The macro-pK_a values for a partially zwitterionic compound, which comprise the lower and upper pK_a values they quote, are neither acidic nor basic pK_a values but some combination of both. The true situation is set out on Scheme 1, where K_A and K_B are the lower and upper titrational or macro-dissociation constants and K_1–K_4 are the corresponding micro-dissociation constants for



Scheme 1. Ionization constant matrix of a zwitterion.

the four individual species. The latter are required for any complete treatment of the various equilibria, such as calculation of the zwitterionic ratio; in a case such as the present, they (in fact pK_4, from which the rest follow) may be obtained by the iterative procedure of Edsall et al. (1958). We have re-determined our (unpublished) data using the computerized techniques that have since become available and the complete set of constants (for 25 °C) appears in Scheme 2. Slight differences result; our new pK_A 8·11 replaces the previous pK_a 8·37 (Taylor & Cruickshank 1984) leading to a revised estimate of 0·026 (from 0·016) for D at pH 7·4 and 25 °C by equation (ii) of that paper.

The picture that results for sotalol is displayed as in Fig. 1. Here the dashed lines passing through pK_4 and pK_2 are the variation in log D with pH calculated for



Scheme 2. pK_a values for sotalol (key as Scheme 1).

* Correspondence.

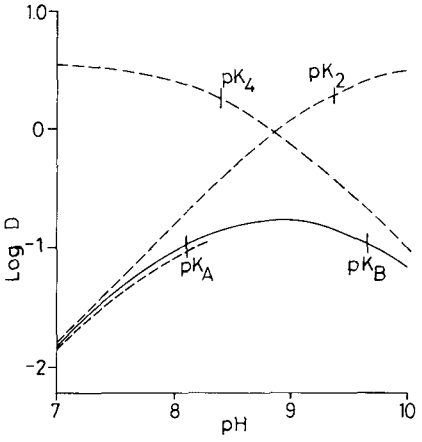


FIG. 1. Log D as a function of pH on various assumptions (see text).

sotalol *for the circumstance that it were solely an acid or a base* respectively. The full line is the resultant of these two: the envelope of the *actual* curve for sotalol as a function of pH. The log *P* value (−0·79) we quote for sotalol is *measured* at the summit of this curve, i.e. the isoelectric point (Day & Parr appear to have misunderstood how this value was obtained even though it is clearly stated to be experimental). Knowledge of the fraction of unionized species as a function of pH, obtained from Scheme 2 making use of the standard equations (Button & Taylor 1973), then enables the full line to be constructed. The dashed line through pK_A is that of equation (ii) (Taylor & Cruickshank 1984); all three lines tend to converge as the pH falls. The near-coincidence of the authors' estimate and our own, noted by Day & Parr (1984) as 'interesting', is somewhat more than that; it lies in the nature of things.

The salient point is that, at pH $\ll pK_A$, either of two simple procedures may be used to approximate log *D*. The one we pursued (Taylor & Cruickshank 1984) uses measured 'log *P*', here a composite quantity, and pK_A; it is *irrelevant*, paradox as this may seem, that the latter is largely (not entirely) that for an acidic group. This procedure is *not* 'mistaken' (Day & Parr 1984), merely approximate. The other is to use the appropriate *micro*-pK_a value, here pK_2, along with the *micro*-partition coefficient for the unionized form, if both can be calculated. This method can be valuable in cases where log *D* is otherwise inaccessible (P. J. Taylor, unpublished observations). Either method may be used but *macro- and micro-quantities must not be mixed.* The procedure of Day & Parr (1984) is just such a mixture, further invalidated by their erroneous assumption as to the species which actually partitions (see below). The rigorous procedure is of course to use the equations from which the full curve of the Figure has been calculated, but as will be seen, very little difference results in the present case.

From Scheme 2, and taking into account the proportion of cation and anion present at the isoelectric point (Button & Taylor 1973), it is possible to calculate the maximum proportion of unionized sotalol as 4·2%. Hence log *P* 0·59 results for this sub-species, somewhat higher than that for atenolol at 0·23. It is interesting that the presently most sophisticated program for octanol log *P* calculation, CLOGP (Hansch & Leo 1984), predicts values for sotalol and atenolol of 0·23 and −0·11 respectively. These are incorrect absolutely but the *difference* is about right. On either basis, log *D* (pH 7·4) or log *P*, atenolol remains more hydrophilic than sotalol.

Finally we consider the assumption of Day & Parr (1984), allegedly based on Garrett & Schnelle (1971), that sotalol partitions as its zwitterion. The above calculation of 'true' log *P* for sotalol assumes *no* extraction of the zwitterion into octanol; if otherwise, the calculated value represents an over-estimate. The extraction of ion-pairs by octanol is typically several orders of magnitude less favourable than that for the neutral form (Hansch & Leo 1979); hence a 16-fold excess of switterion is not likely to contribute much to overall log *P*. Garret & Schnelle (1971) actually state that their partition coefficient (in $CHCl_3$) 'was indicative of some neutral molecules in equilibrium with the zwitterion which, although in low concentration, possessed a sufficiently high coefficient to permit partition into the organic solvent'. This is entirely in line with our own conclusions. Its misreading by Day & Parr (1984) appears to be forced on them by their invalid method of calculation. There is no need on present evidence to postulate any partitioning of the zwitterion.

To summarise: our original treatment (Taylor & Cruckshank 1984) though *simplified* was not *misleading*. Nevertheless the present correspondence may have performed a service in highlighting some common misunderstandings. In view of this, it is hoped that the present fuller treatment of sotalol will prove useful in a more general context.

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