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## On the Application of Hamilton's Ratio Test to the Assignment of Absolute Configuration and an Alternative Test

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### Abstract

Examples are given of recent abuses or debatable applications of the  $R$ -factor ratio test ( $\mathcal{R}$ ) for the assignment of absolute configuration, and it is shown that some of the enhanced ratios that have been used do not necessarily imply a statistically significant reduction in  $\alpha$ , the probability of making a wrong assignment. Reasons are given for believing that  $\alpha$  is usually seriously underestimated anyway, and that in marginal situations the weighted ratio,  $\mathcal{R}_w$ , is a safer guide than  $\mathcal{R}$  and can even contradict the assignment based on  $\mathcal{R}$ . Aids are given to facilitate the estimation of  $\alpha$  that are much easier to use than interpolation or extrapolation from Hamilton's tables [Hamilton (1965). *Acta Cryst.* **18**, 502–510]. The misconceptions led to a re-examination of the validity of Hamilton's application of linear-hypothesis testing to this particular problem. A more rigorous justification can be achieved by expressing the atomic scattering factors of all the anomalous scatterers in a crystal in the form  $f_{0j} + f'_j + i\eta f''_j$  and refining  $\eta$ , the chirality/polarity parameter. Its standard deviation offers an alternative and more realistic index of the probability of an assignment. A postscript contributed by Professor G. M. Sheldrick reports very encouraging results for  $\eta$  refinement of three structures.

### Introduction

The assignment of absolute configuration is best based on direct measurement of the intensities of Bijvoet pairs of reflexions. It is, however, more often obtained as a by-product of normal data collection, in which event it usually involves one or other of two comparison procedures: either a comparison of the  $R$  factors of the two enantiomeric models over *all* the measured data, or varied forms of comparison over a limited number of 'sensitive reflexions'. It is usual in the former case to assess the statistical significance of the  $R$ -factor ratio,  $\mathcal{R}$ , by means of Hamilton's (1965) ratio test, but certain abuses and misunderstandings have recently come to my notice, especially while refereeing or being consulted by other referees: they occur often enough to justify the discussion below. In the latter case, a few authors have applied Hamilton's test to the enhanced ratios from 'sensitive reflexions', but apparently without thought as to the legitimacy of doing so. The abuses, together with other considerations which suggested that the ratio test tends to be over-optimistic, prompted me to re-examine the basis of Hamilton's applications of the  $R$ -factor test to this problem and led to the conclusion that his argument does not appear to conform to his definition of a linear hypothesis. An attempt is made to validate this application so that the test can continue to be used, but in doing so a proposal is made for an alternative assignment procedure that yields its own independent confidence index which is expected to be more realistic. The first three trials of this alternative procedure look very encouraging.

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Rothstein, Richardson & Bell (1978) have also recently critically discussed Hamilton's ratio test with special reference to his assumption of linearity and the distribution of errors, and they put forward two alternative tests based on either the statistical 'jack-knife' technique or Kendall's test of independence, both of which appear from tests to be more realistic, but only the briefest passing reference is made to the possibility of using them in the assignment of chirality.

In view of the abuses and misunderstandings, it is regrettably necessary in this paper to devote space to saying what may not be done and explaining why, but numerous positive recommendations are made and these should be read in conjunction with other recommendations of a more practical nature recently published by Rogers & Allen (1979).

### The application of Hamilton's test

First, it is necessary to remind ourselves of the circumstances under which Hamilton's test is usually applied. One solves the structure for a given set of phases and refines it as far as is deemed necessary with real atomic scattering factors and preferably absorption-corrected data. This gives a set of coordinates, the 'working list',  $+x_j$ , referred to right-handed axes together with their thermal parameters and the scale factor. In the absence of dispersion effects the inverse structure ( $-x_j$ , etc.) is an equally acceptable solution and gives the same  $R$  factor. However, when dispersion effects occur the symmetry of  $|F_o|$  in reciprocal space degrades from the Laue symmetry to reveal the true point group. Thus, reflexions  $\{hkl\}$  that are point-group related to  $hkl$  all have the same intensity which may differ from that found for all the reflections  $\{\bar{h}\bar{k}\bar{l}\}$  that are point-group related to  $\bar{h}\bar{k}\bar{l}$ . Any antipodal pair is referred to as a Friedel pair, but more generally any pair, one from  $\{hkl\}$  and the other from  $\{\bar{h}\bar{k}\bar{l}\}$ , constitute a Bijvoet pair and can be used for the assignment.

In order to identify which chirality (and/or polarity in some space groups) is true of the crystal as mounted one can proceed in one of two ways (see Fig. 1).

(A) Calculate two sets of  $F_c$ , one for the coordinate set  $+x_j$  and the other for the antipodal structure,  $-x_j$ . Both sets use the same thermal parameters and scale factor and  $+if_j''$  for each dispersive atom. These sets give different  $R$  values,  $R^+$  and  $R^-$ , defined below. ( $R_w$  is the weighted  $R$  factor defined by Hamilton.)

$$F_c(+x_j, B_{lj}, +if_j'') \Rightarrow R^+ \text{ or } R_w^+$$

$$F_c(-x_j, B_{lj}, +if_j'') \Rightarrow R^- \text{ or } R_w^-$$

It should be noted that inversion of the structure in an enantiomorphous space group changes the space group, and that there are nine other space groups for which inversion is not straightforward (Rogers, 1980).

(B) The same values of  $R^+$ ,  $R^-$ , etc. are obtained much more conveniently and reliably by keeping all the coordinates and the space group intact and merely reversing the sign of all the  $if_j''$ 's. Thus,

$$F_c(+x_j, B_{lj}, +if_j'') \Rightarrow R^+ \text{ or } R_w^+$$

$$F_c(+x_j, B_{lj}, -if_j'') \Rightarrow R^- \text{ or } R_w^-$$

By either route one obtains the ratio  $\mathcal{R} = R^-/R^+$  (or  $\mathcal{R}_w = R_w^-/R_w^+$ ) used in Hamilton's test. It is strictly applicable only to the weighted ratio, but the unweighted ratio  $\mathcal{R}$  is usually quoted and has hitherto been regarded as an acceptable approximation, for, while  $R^-$  and  $R^+$  may differ appreciably from  $R_w^-$  and  $R_w^+$ , the two ratios are more nearly the same. However, I am indebted to Professor T. J. King for recently bringing to my notice two examples where  $\mathcal{R}_w$  (for which the weighting had been re-programmed to conform to Hamilton's definition) and  $\mathcal{R}$  for the same compound indicated *antipodal* assignments. One of them is quoted below. In both cases independent evidence favoured the  $\mathcal{R}_w$  assignment. (It is too soon to offer considered comments on these observations, but readers are advised to check both ratios, especially when the discrimination is marginal.)

For a given value of  $\mathcal{R}$  or  $\mathcal{R}_w$  one looks up Hamilton's tables of  $\mathcal{R}(b, N, a)$  to estimate  $a$ , given  $b$ , the dimension of the hypothesis, and  $N$ , the number of degrees of freedom, i.e.  $(n - m)$ , where  $n$  is the number

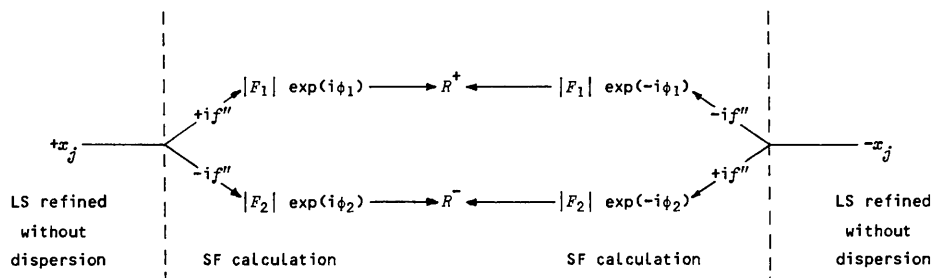


Fig. 1. The two methods of finding the chirality of a crystal by Hamilton's test.

of independent reflexions used for least-squares refinement of the  $m$  variables. The tables cover only  $\mathcal{R} > 1$ . If, for a given problem,  $\mathcal{R}$  proves to be  $< 1$ , the working list of coordinates (which gives  $R^+$ ) defines the 'wrong' chirality/polarity. In that event the coordinate list must be inverted and the space group changed if necessary to invert the ratio and bring  $\mathcal{R}$  within the scope of the tables. A plea was recently made not to publish coordinate lists for a chirality that is known to be wrong: it leads to abstracting difficulties (Rogers & Allen, 1979).

It is usual when following the procedure of Fig. 1 to apply a dispersion correction only for the atoms with the strongest anomalous scattering, but if this is done the value of  $\mathcal{R}$  (and thus of  $\alpha^{-1}$ ) can be considerably too large.

I am indebted to Professor T. J. King and Dr M. J. Begley for the following figures that illustrate both this point and that mentioned above. Compound  $C_{20}H_{24}O_8$ ;  $Z = 4$  in  $P2_12_12_1$ ; 1818 reflexions, 253 variables;  $R = 0.037$ .

Correction applied to	$\mathcal{R}_w (=R_w^-/R_w^+)$	$\alpha_w^{-1}$	$\mathcal{R} (=R^-/R^+)$	$\alpha^{-1}$
O atoms only	1.003	537	0.995	13667
C and O atoms	1.0005	4	0.997	548.

The values of  $\alpha_w^{-1}$ , which were obtained from  $\mathcal{R}_w$  with equation (4) (see later), differ substantially, the first (537) being clearly a serious overestimate, and the second (4) showing that no assignment can safely be made. The values of unweighted  $\mathcal{R}$ , both of which are  $< 1$ , indicate the *opposite* chirality, and the values of  $\alpha^{-1}$  (derived from  $1/\mathcal{R}$  by use of equation 4) suggest that the antipodal assignment is even stronger, whereas subsequent work on a bromo derivative emphatically supported the  $\mathcal{R}_w$  assignment. If these figures prove to be typical, it is clear that the use of  $\mathcal{R}$  in marginal cases seriously overestimates the probability of an assignment and may even get it wrong; that  $\mathcal{R}_w$  provides a much more cautious estimate of the probability and is more likely to get the assignment right; and that  $\mathcal{R}_w$  is much more sensitive than  $\mathcal{R}$  to overestimation if correction is made for only one species of atom.

Several authors have published assignments at about these levels of  $\mathcal{R}$  and regarded them as acceptable. The above figures support the misgivings some of us have had about such assignments, for at these low levels of  $\mathcal{R}$  one is dredging around among the round-off errors in both  $F_o$  and  $F_c$  and the ratio is then of doubtful physical significance.

The origin of the overestimation is readily understood. Thus, if all the atoms in the structure have scattering factors,  $f_j(1 + \delta_j)$ , one can write

$$F(hkl) = \sum_j F_j(1 + i\delta_j) \exp(i\varphi_j)$$

and

$$F(\bar{h}\bar{k}\bar{l}) = \sum_j F_j(1 + i\delta_j) \exp(-i\varphi_j),$$

where  $F_j$  is the resultant scattering for all atoms of type  $j$  present in the structure. If now all  $\delta_j$  were the same regardless of atomic number, these two structure factors would have identical amplitudes but differ in the magnitudes of their phases, *i.e.* the Bijvoet anomaly would vanish for every reflexion. Anomalies are in fact observed only if the values of  $\delta_j$  differ for the different atomic species. If, as is so often done, it is assumed that  $\delta_j = 0$  for most atoms and is non-zero for only a small subset, comparison of the Argand diagrams with and without the full complement of anomalous components shows that, for any combination of  $F_j \exp(\pm i\varphi_j)$  contributions, the corresponding values of  $|F_c(hkl)|$  and  $|F_c(\bar{h}\bar{k}\bar{l})|$  will differ more than they should and so lead to an overestimate of  $\mathcal{R}$ .

For compounds with strong anomalous scatterers the assignment of chirality is not likely to be in doubt, but  $\alpha^{-1}$  is likely to be considerably overoptimistic. For compounds where the assignment is more marginal (especially those where oxygen is the principal scatterer) it is imperative to allow for dispersion of all non-hydrogen atoms and to check whether  $\mathcal{R}$  and  $\mathcal{R}_w$  are concordant. In such cases the only really satisfactory procedure is to make direct measurement of Bijvoet anomalies for a number of sensitive reflexions.

#### Misconceptions associated with the dimension of the hypothesis

For an assignment of absolute configuration based on  $\mathcal{R}$  defined in this way, the hypothesis is said by Hamilton to be one-dimensional. Nevertheless, despite his clear statement in this regard, it has sometimes been argued that  $b$  is greater than unity. Thus, for  $P2_1$ , where inversion can be achieved merely by reversing the signs of  $y$ ,  $U_{12}$  and  $U_{23}$  for every atom, some authors have treated the reversal of these three parameters as independent linear assumptions and so set  $b = 3$ . This is wrong, for mirroring the structure and the thermal ellipsoids in the plane  $y = 0$  necessarily reverses the signs of these three parameters for all atoms *en masse*: it is a single operation in which all parameters dependent on the sign of  $y$  are coupled together. In procedure *B* above, one can attribute the difference in  $|F_c|$  solely to the simultaneous reversal of the signs of all the  $f_j''$  terms: all the  $m$  refinable parameters are common to both sets of  $|F_c|$ .

If one bases the refinement on a unique set of measured data and uses real scattering factors in the refinement prior to making the test, the set of coordinates ( $+x_j$  etc.) will be biased slightly toward the

$|F_o|$ 's in the particular set of data collected. On the other hand, if duplicate data, representing Bijvoet pairs, are recorded and averaged before the refinement, this bias is reduced.

There is, however, a more subtle and widespread misunderstanding concerning the dimension of the hypothesis. Thus, some workers did not derive their ratio in the above way, but nevertheless had no hesitation in using Hamilton's test. Some used a least-squares refinement program (such as *SHELX*) which normally commits them from the start to the use of complex scattering factors. Others, who start refinement with real  $f$ 's, chose to defer the evaluation of  $\mathcal{R}$  till after a few cycles of refinement with complex  $f$ 's in order to obtain an enhanced value of  $\mathcal{R}$ . Two alternative routes are used (see Fig. 2).

(a) Two refinements starting from  $+x_j$  and allowing, separately, for both  $+if_j''$  and  $-if_j''$  yield, as shown in the left-hand half of Fig. 2, two slightly differing sets of parameters,  $+x_j^+$  and  $+x_j^-$ , which will be referred to here as 'dispersion-refined' parameters. The  $B_{ij}$ 's and scale factor will also differ, and, if Gilli & Cruickshank's (1973) experience is in any way typical, these differ more than the coordinates.

(b) Two refinements starting from  $+x_j$  and  $-x_j$  with  $+if_j''$  (allowing for a space-group switch if necessary) yield two sets of 'dispersion-refined' parameters,  $+x_j^+$  and  $-x_j^-$ . Clearly  $|-x_j^-| = |x_j^-|$ , and these two solutions lead, as in Fig. 2, to identical values of  $|F_c|$ , viz.  $|F_4|$  whereas,  $+x_j^+$  and  $-x_j^-$  lead to  $|F_3|$ . During a survey of the literature and while refereeing I found that several authors drew a veil of obscurity over precisely what they did next. In one paper, however, they said explicitly that they compared the  $R$  factor derived from  $|F_3|$  (based on  $+x_j^+$  taken with  $+if_j''$ ) with that derived from the  $|F_c|$  obtained by taking  $-(+x_j^+)$  with  $+if_j''$ . The latter is equivalent (*cf.* Fig. 2) to  $-x_j^-$  taken with  $+if_j''$ : it is a nonsense and any inference drawn from the ratio test in such

a case must be suspect. Fig. 2 shows other nonsensical combinations. Several sets of authors said explicitly that they had compared the  $R$  factors based on  $|F_3|$  and  $|F_4|$  in Fig. 2 and with this there can be no quibble, except that some of them went on to estimate  $\alpha$  with  $b = 1$ . This, however, is indefensible, for it is no longer true that the  $m$  refinable parameters are identical in the two enantiomeric dispersion-refined models ( $+x_j^+$  and  $-x_j^-$ ). The dimension in such a situation is a matter for debate. I have discussed the problem with a number of colleagues. All agreed that it was inadmissible to use  $b = 1$ , but some felt as did I originally that it is analogous to the first example that Hamilton cited, so that  $b = m + 1$ . Others, including now myself, feel that the analogy is not valid and that there is no basis for comparison, so that the ratio test cannot be applied to this procedure. Even if the former view can be sustained the change in  $b$  has a disastrous effect on the estimated probability. For example, consider a structure for which  $n = 1060$  independent reflexions and  $m = 60$  refinable parameters. We can compare the values of  $\mathcal{R}$  as a function of  $\alpha$  for the two cases just discussed where  $b = 1$  or 61 (Table 1).

It is clear from Table 1 that a test based on dispersion-refined parameters has lost most of its discriminatory power and the loss is even more marked for higher values of  $b$ . Consider the following typical values of  $\mathcal{R}$  for the above structure: 1.015 for real- $f$  refinement ( $b = 1$ ,  $N = 1000$ ) gives  $\alpha = 1.3 \times 10^{-7}$ ; 1.045 for dispersion-refined parameters ( $b = 61$ ,  $N = 1000$ ) gives  $\alpha = 5 \times 10^{-3}$ . Thus, a threefold enhancement of  $(\mathcal{R} - 1)$  corresponds to a 38 000-fold reduction in the probability of the assignment.

If this argument is correct then in almost all the cases examined it seemed that the enhancement obtained by dispersion refinement was probably statistically illusory, and the authors might well have been better off with the unenhanced ratio. Even if  $b$  were halved, say, to allow for those of the  $m$  parameters which scarcely

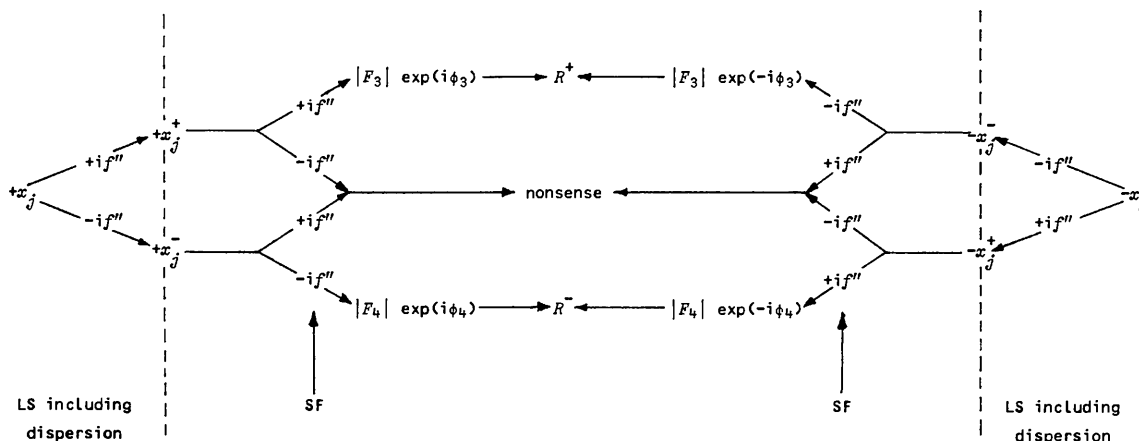


Fig. 2. Correct methods of procedure in Hamilton's  $R$ -factor ratio test.

Table 1. Comparison of the  $\mathcal{R}$  values as a function of  $\alpha$  for  $b = 1$  and 61

The values of  $\mathcal{R}$  quoted here are derived using the interpolation formulae given by Hamilton either from his tables or (for the entries marked \*) from tables given by Fisher & Yates (1963) or Pearson & Hartley (1966). The values quoted in parentheses were calculated by means of equation (4).

$\alpha$	$\mathcal{R}(1, 1060 - 60, \alpha)$	$\mathcal{R}(61, 1060 - 60, \alpha)$
0.5	1.00025 (1.00031)	1.027
0.25	1.00075 (1.00072)	1.031
0.1	1.0014 (1.0014)	1.035
0.05	1.0019 (1.0019)	1.038
0.025	1.0025 (1.0024)	1.040
0.01	1.0034 (1.0032)	1.043
0.005	1.0040 (1.0038)	1.045
0.001	1.0056* (1.0053)	1.050*

differ in the two dispersion-refined models, the general conclusion still stands: the test has been badly blunted and the probability is either seriously weakened or cannot be calculated at all.

#### Varying $N$ , the number of degrees of freedom

For a given value of  $\mathcal{R}$ ,  $\alpha$  decreases with increasing  $n$ , the number of independent intensities used for calculating  $R^+$  and  $R^-$ . Strictly speaking  $n$  should be the number of terms used in the least-squares refinement, but if one were able to base an assignment on a limited random sample of reflexions that gave the same  $\mathcal{R}$ , the value of  $\alpha$  would rise substantially because of the reduction in  $N$ . Many of the reflexions are mere passengers in the calculations of the  $\Delta F$ 's and their contributions to  $R^+$  and  $R^-$  are credited with more significance than is warranted. Hamilton's weighted ratio,  $\mathcal{R}_w$ , discounts weak or unreliable  $|F_o|$ 's, but there is need for another kind of weighting, to discriminate against those Bijvoet pairs for which the interval between  $|F_c^+|$  and  $|F_c^-|$  is not statistically significant compared with the range  $|F_o| \pm k\sigma(F_o)$ , where  $k$  is some suitable confidence limit. My colleague, Dr D. J. Williams, and I have discussed the feasibility of introducing such weights. One could, for example, do it crudely by simply omitting those terms for which both  $|F_c^+|$  and  $|F_c^-|$  lay inside the above range of  $|F_o|$ , but this is arbitrary. Alternatively, one could use a probability-weighted ratio

$$\mathcal{R}_p = R_p^- / R_p^+ = \frac{\sum P^- \Delta F^- / \sum P^- |F_o|}{\sum P^+ \Delta F^+ / \sum P^+ |F_o|} \quad (1)$$

or, perhaps

$$= \frac{\sum P^- \Delta F^-}{\sum P^+ \Delta F^+}, \quad (1a)$$

where

$$\Delta F^\pm = ||F_o| - |F_c^\pm||$$

$$P^\pm = 1 - \exp[-(|F_o^\pm| - |F_o|)^2 / 2\sigma], \quad (2)$$

say. In neither case can we see any way of adapting Hamilton's theory to accept such weights. We are left with the conviction that the values of  $N$  hitherto used are unrealistically large and are unwarrantably inflating the estimate of confidence in the assignment. This is, therefore, a second and quite different reason for regarding the majority of  $\alpha$ 's as too small.

A different sort of problem arises with the use of sensitive reflexions. In the earliest papers, where photographic data were used, a number of such reflexions (rarely exceeding about 25) were cited, but now with diffractometer data the number of sensitive terms has occasionally been substantially larger, and since the advent of Hamilton's test some authors have employed it in this context. This too is inadmissible, for one is selecting a strongly biased and thoroughly atypical set of reflexions, whereas Hamilton's theory is based on the totality of the independent observed data. Again, in this context it is perfectly in order to quote  $R^-$  and  $R^+$ , or their weighted equivalents, but *not* to derive an estimate of  $\alpha$  therefrom.

A special case of selection has, however, been found useful on several occasions in this laboratory, *viz.* the exclusion of all centric reflexions. Such reflexions cannot exhibit Bijvoet anomalies, and, as on average they contribute more to the  $\Delta F$ 's than acentric reflexions (Wilson, 1950; Phillips, Rogers & Wilson, 1950), they contribute the same disproportionate quota to both the numerator and denominator of  $R^-/R^+$  ( $= \sum \Delta F^- / \sum \Delta F^+$ ) and thus weaken the ratio. In some space groups the exclusion of centric reflexions is well worth while, but this is not always the case. Thus, in one recent example, a compound,  $C_{23}H_{23}O_8Br$  in  $P4_22_12$ , gave with Cu  $K\alpha$  radiation the ratio 1.020 for  $\mathcal{R}$ . Of the 863 terms 366 were centric, and these contained the rows  $\{h00\}$ ,  $\{hh0\}$  and  $\{00l\}$  which have enhanced intensity averages and thus larger  $\Delta F$ 's. When the centric terms were removed the ratio became 1.037. In this problem  $m$ , the number of refined parameters (omitting hydrogen) is  $(32 \times 9) + 1 = 289$ , so  $N$  becomes  $863 - 289 = 574$ , or after exclusion only 208. Then,

$$\mathcal{R}(1, 574, \alpha_1) = 1.020 \quad \text{gives} \quad \alpha_1 = 3.0 \times 10^{-6},$$

whereas

$$\mathcal{R}(1, 208, \alpha_2) = 1.037 \quad \text{gives} \quad \alpha_2 = 1.2 \times 10^{-4}.$$

The enhancement in this case did not lead to an improvement in  $\alpha$ , mainly because  $N$  was reduced so drastically. In lower-symmetry problems or where the number of independent observations is larger, the reduction in  $N$  is not so serious and a real advantage is often obtained. This method of enhancing the ratio is believed to be valid, for it embraces *all* the acentric

reflexions unlike the atypical subset discussed above. The first mention of such a limitation so far as we know occurs in a brief note on the assignment of lycopodine ( $P_{2,2,2,1}$ ) by Rogers, Quick & Mazhar-Ul-Haque (1974).

In conclusion it appears that, apart from the exclusion of centric reflexions, all other modes of enhancement give a ratio which is not susceptible to statistical assessment. It was these problems and uncertainties that drove the present author, as described in a later section, to re-examine the basis of Hamilton's application of linear-hypothesis testing to this particular problem.

### Computational aids

It frequently happens, as in several instances above, that  $\mathcal{R}$  falls well outside the range of Hamilton's published tables and, although he gave formulae for interpolating and extrapolating on  $N$  and interpolating on  $b$ , he gave no means of interpolating or extrapolating on  $\alpha$ . His values of  $\mathcal{R}$  were calculated from

$$[\mathcal{R}(\alpha)]^2 - 1 = \frac{F(\alpha)b}{N}, \quad (3)$$

where  $F(\alpha)$  is the Fisher variance-ratio statistic, and this he took from tables published by Merrington & Thompson (1943-6). Freshly computed tables were published by Pearson & Hartley (1966) and included a table for  $\alpha = 0.001$  (taken from Colcord & Deming, 1935-6), which was not included by Hamilton. The remainder of this section is based on these later and additional values.

Fig. 3 gives a rapid means of estimating  $\alpha$  for the one-dimensional hypothesis test. A little experimentation showed that the plot of  $\log\log(\mathcal{R})$  versus  $\log(N)$  is a remarkably good straight line for each value of  $\alpha$ . These lines, which are shown in Fig. 3, all have a slope close to  $-1.02$ . Their intercepts,  $i_\alpha$ , on the quasi-normal shown were plotted in the form of  $\log\log(1/\alpha)$  versus  $i_\alpha$  and, apart from  $\alpha = 0.5$  and  $0.25$  (which are of no value in this context), this too gave a straight line which was considered justification for predicting where the iso- $\alpha$  lines for  $\alpha < 0.001$  will run. Copies of Fig. 3 measuring  $550 \times 380$  mm are available from the author at a small charge for reproduction.

I am indebted to my son, Neil, for the suggestion that it should be possible to eliminate  $i_\alpha$  from these two sets of linear relationships and thus embrace all the one-dimensional hypothesis data in an equation of the form

$$\log\log(\mathcal{R}) = \lambda \log\log(1/\alpha) + \mu \log(N) + \nu.$$

Least-squares calculations, based on the 20 values taken from the *Biometrika Tables for Statisticians*

(Pearson & Hartley, 1966) that correspond to the  $\alpha, N$  combinations enclosed within the rectangle in Table 2, gave

$$\left. \begin{aligned} \log\log(\mathcal{R}) &= 1.239796 \log\log(1/\alpha) \\ &\quad - 1.013506 \log(N) - 0.188892 \\ \text{or} \\ \ln\ln(\mathcal{R}) &= 1.239796 \ln\ln(1/\alpha) \\ &\quad - 1.013506 \ln(N) - 0.634938 \end{aligned} \right\} (4)$$

which has proved to be a good approximation. Table 2 compares the values computed by this equation with the original data: the agreement is good not only over the 20 fitted values, but also for  $N > 120$  as the values agree well with those extrapolated by use of Hamilton's formula (1b). It is believed to be an acceptable approximation for  $\alpha < 0.001$ , especially for large  $N$ . Checks have shown that the constants in equations (4) can be rounded to four decimal places without significant loss of precision in  $\mathcal{R}$ .

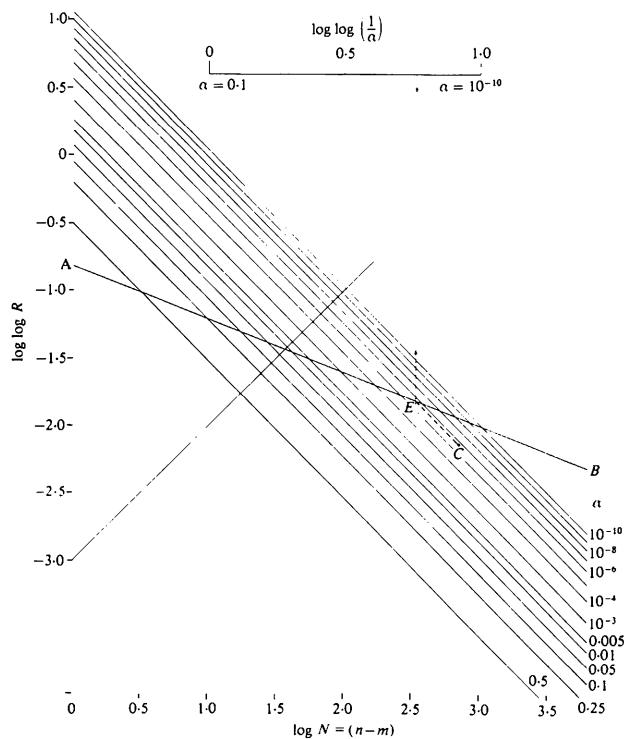


Fig. 3. Chart for estimating the probability,  $\alpha$ , of a one-dimensional hypothesis, given  $\mathcal{R}$ , Hamilton's  $R$ -factor ratio, and  $N$ , the number of degrees of freedom. The line  $AB$  has been drawn to improve the readability of the chart. If one lays a ruler on the chart parallel to the iso- $\alpha$  lines and through the desired point ( $C$  for example) this meets  $AB$  at  $E$  and the horizontal coordinate of  $E$  measured on the upper-edge scale gives the corresponding value of  $\log\log(1/\alpha)$ . The iso- $\alpha$  lines, which correspond to equation (4), are in close accord with Hamilton's data except for the little-used lines,  $\alpha = 0.25$  and  $0.5$ . Each line through the plotted points is a least-squares line for that value of  $\alpha$ , whereas the remainder are derived from equation (4).

Table 2. Comparison of  $\mathcal{R}$  values for a one-dimensional hypothesis

The numbers are derived as follows:

Value quoted by Hamilton (for  $N \leq 120$ ) or derived from his table by his extrapolation formula (1b).

Value calculated from the Biometrika Tables for Statisticians (Pearson & Hartley, 1966) with equation (3).

Value calculated by means of equation (4).

$N \backslash \alpha$	0.25	0.10	0.05	0.025	0.01	0.005	0.001	0.0005	0.0001	$5 \times 10^{-5}$	$1 \times 10^{-5}$	$5 \times 10^{-6}$	$1 \times 10^{-6}$
4	1.205	1.462	1.711	2.014	2.510	2.972							
	1.2052	1.4612	1.7110	2.0137	2.5100	2.9720	4.4198						
	1.2153	1.4415	1.6599	1.9270	2.3718	2.7945	4.1695	4.990	7.69	9.32	14.73	18.03	29.14
8	1.092	1.197	1.290	1.395	1.552	1.684							
	1.0920	1.1969	1.2903	1.3951	1.5516	1.6841	2.0439						
	1.1014	1.1986	1.2854	1.3839	1.5339	1.6637	2.0284	2.217	2.747	3.021	3.790	4.189	5.314
15	1.047	1.098	1.141	1.189	1.257	1.311							
	1.0466	1.0976	1.1413	1.1888	1.2565	1.3115	1.4512						
	1.0524	1.1005	1.1420	1.1875	1.2539	1.3089	1.4535	1.5236	1.7062	1.7942	2.0230	2.1330	2.4188
30	1.023	1.047	1.067	1.089	1.119	1.143							
	1.0227	1.0469	1.0672	1.0889	1.1189	1.1428	1.2012						
	1.0256	1.0486	1.0680	1.0888	1.1186	1.1426	1.2035	1.2319	1.3030	1.3359	1.4177	1.4553	1.5489
60	1.011	1.023	1.033	1.043	1.057	1.068							
	1.0112	1.0230	1.0328	1.0432	1.0574	1.0684	1.0952						
	1.0126	1.0238	1.0331	1.0431	1.0571	1.0683	1.0961	1.1088	1.1401	1.1542	1.1887	1.2043	1.2420
120	1.006	1.011	1.016	1.021	1.028	1.034							
	1.0056	1.0114	1.0162	1.0212	1.0281	1.0335	1.0463						
	1.0062	1.0117	1.0163	1.0211	1.0279	1.0333	1.0465	1.0525	1.0671	1.0736	1.0894	1.0964	1.1133
240	1.0028	1.0057	1.0081	1.0106	1.0141	1.0168	1.0232						
	1.0031	1.0058	1.0080	1.0104	1.0137	1.0163	1.0228	1.0257	1.0327	1.0358	1.0433	1.0467	1.0546
500	1.0013	1.0028	1.0039	1.0051	1.0067	1.0080	1.0111						
	1.0015	1.0027	1.0038	1.0049	1.0065	1.0077	1.0108	1.0121	1.0154	1.0169	1.0204	1.0219	1.0256
1000	1.0007	1.0014	1.0019	1.0025	1.0034	1.0040	1.0056						
	1.0007	1.0014	1.0019	1.0024	1.0032	1.0038	1.0053	1.0060	1.0076	1.0083	1.0100	1.0108	1.0126
1500	1.0005	1.0009	1.0013	1.0017	1.0022	1.0027	1.0037						
	1.0005	1.0009	1.0012	1.0016	1.0021	1.0025	1.0035	1.0040	1.0050	1.0055	1.0066	1.0071	1.0083
2000	1.0004	1.0007	1.0010	1.0013	1.0017	1.0020	1.0028						
	1.0004	1.0007	1.0009	1.0012	1.0016	1.0019	1.0026	1.0030	1.0038	1.0041	1.0050	1.0053	1.0062
2500	1.0003	1.0006	1.0008	1.0010	1.0013	1.0016	1.0022						
	1.0003	1.0005	1.0007	1.0010	1.0013	1.0015	1.0021	1.0024	1.0030	1.0033	1.0040	1.0043	1.0050
3000	1.0002	1.0005	1.0006	1.0008	1.0011	1.0013	1.0019						
	1.0002	1.0004	1.0006	1.0008	1.0011	1.0013	1.0017	1.0020	1.0025	1.0027	1.0033	1.0035	1.0041

### A re-examination of Hamilton's theory

Hamilton defines each dimension of the hypothesis as a distinct linear constraint on the magnitudes of the *refinable variables*, either by imposing a fixed numerical value on one or by imposing linear relationships between others, and he expressed their combined effect as a matrix equation (16). However, he made no attempt in his example 4 to relate his statement – that  $b = 1$  for an assignment of absolute configuration – to his earlier definition, nor to express it in matrix form, though he is at some pains to spell out the derivation of  $b$  in the other five examples. It seems to him to have been self-evident, and in an intuitive sense one can indeed follow him, for, as shown above, if  $\mathcal{R}$  is based on real- $f$ -refined parameters the one hypothesis is that,

if the structure be inverted, *i.e.* the signs of all the  $x, y, z$  parameters are reversed *en masse* but without reversing the sign of the  $f_j''$  terms, the enantiomorph giving the lower of the two  $R$  factors represents the absolute chirality/polarity. But there seems to be no rigorous way of expressing this inversion of the whole structure in terms of Hamilton's defining equation (16).

An alternative is to treat the imaginary terms  $if_j''$  as refinable variables and there are some least-squares programs that allow one to refine each  $f_j''$  term separately and they work reasonably well, but it is doubtful whether the facility existed in any program when Hamilton wrote and he does not mention it.

I have discussed the matter with several individuals who all agreed that a formal inconsistency seems to exist in just this one application of the ratio test. It is

oddy out of keeping with Hamilton's rigorous turn of mind. I am indebted to Professor D. W. J. Cruickshank and Dr D. S. Moss for suggestions which were along lines similar to my own and which I have adapted into the following suggested means of validating Hamilton's argument, namely that a single new least-squares variable,  $\eta$ , be introduced into every dispersion term,  $i\eta f''$ , that contributes in a given crystal structure.  $\eta$  could be kept zero in the early stages of refinement, but later, when allowed to refine, it should converge on a value close to either +1 or -1. Hamilton may well have regarded the sign of the set of  $f''$  terms as a single virtual least-squares variable which is never actually refined, but whose value when it is eventually introduced has a fixed value  $\pm 1$ . However, with the substitution of  $\eta$  as a true least-squares variable it could perhaps be argued that this application of linear-hypothesis testing would be formally validated as one-dimensional, that doubts about past assignments on this score can be dismissed (though the estimates of  $\alpha$  are certainly over-optimistic), and that we can continue to use his test.

However, the introduction of  $\eta$  offers other practical advantages. First, it provides a convenient switch for reversing the chirality or polarity of a set of  $F_c$ 's. Secondly, it automatically excludes centric terms from  $\eta$  refinement and, at a stroke, dismisses all the problems arising over the appropriate values for  $b$  and  $N$ . Thirdly, its precision,  $\sigma(\eta)/|\eta|$ , which is approximately  $\sigma(\eta)$ , is readily computed and is an alternative index of confidence which might well be preferable to  $\alpha$  in many of the difficult situations discussed above. It is likely to be far less optimistic and it should be easy to examine how the values of  $\eta$  and of its e.s.d. depend on weighting schemes and the presence or absence of absorption corrections, how it varies for different ranges of  $\theta$ , and whether it is consistent at different stages in the refinement of the whole structure. It might even be possible to introduce some sort of weighting on the lines of equation (1) above. In addition, the assessment of the dependence of its precision on alternative refinement procedures and weighting schemes would follow lines with which we are all familiar and are much less debatable.

Very shortly after the submission of this paper, on 24 July 1980, I received from Professor G. M. Sheldrick (University of Göttingen, Federal Republic of Germany) the first results of an  $\eta$  refinement which he had incorporated into his *SHELXTL* program for the Eclipse computers. The results are tabulated below.

	Z	n - m	$\mathcal{R}$	$\log_{10} \alpha^{-1}$	$\eta(\sigma(\eta))$	$\frac{(1 +  \eta )}{\sigma(\eta)}$	
(1) $\text{SeC}_{21}\text{H}_{28}\text{O}_2$	$P2_1$	2	2154	1.392	158	+1.056 (42)	49
(2) $\text{Rh}_2(\text{mhp})_8 \cdot 2\text{CH}_2\text{Cl}_2$	$I4_1cd$	8	5189	1.110	128	+0.980 (48)	41
(3) $\text{SC}_{10}\text{H}_{10}\text{O}_3$	$P2_12_1$	4	1340	0.981	10.8	-1.32 (27)	8.6

All three crystals were measured with Mo  $K\alpha$  radiation.

In the first two examples the Friedel opposites had been carefully measured and corrected for absorption, and a decisive  $R$ -factor ratio obtained. The values of  $\eta$  and its e.s.d. for both compounds are equally decisive and the assignments by both methods agree. For the last structure, on the other hand, only one octant of data was available, no special precautions had been taken, and no attempt made to ascertain the absolute configuration prior to  $\eta$  refinement. Nevertheless, the value of  $\eta$  (which had refined from +1.0) clearly indicated that the configuration should be inverted, and this conclusion was subsequently borne out by evaluating  $\mathcal{R}$  and  $\alpha$ , which was calculated from  $1/\mathcal{R}$  with equation (4). The last column expresses the gap between the observed value of  $\eta$  and its value for the enantiomeric structure in terms of  $\sigma(\eta)$ . Even for the third example the value of  $8.6\sigma(\eta)$  is decisive.

These results are most encouraging, but further trials are needed, especially on marginal data such as that referred to earlier which was supplied by Professor King. As this program has recently become operational in this laboratory as well as at Göttingen we look forward to exploring the potential and robustness of  $\eta$  refinement.

I am indebted to a number of individuals for their willingness to discuss these problems. Many, but not all, are cited in the text, but I am especially grateful to Professors Cruickshank and King for stimulating and encouraging correspondence, and particularly to Professor Sheldrick for the enthusiastic way he seized on my suggestion and the speed with which he produced results. I am also indebted to Mrs A. M. Atkinson for use of her data.

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