PRESIDENTIAL ADDRESS.

The Stereochemistry of Labile Compounds.

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THE information yielded by the newer physical methods of investigating molecular configuration relates—for the most part—to molecules in approximately static conditions. In many compounds, however, the molecular configuration is labile and this gives rise to various questions of interest which are most readily investigated by observations of optical activity. Of these compounds some have configurations so unstable that the mere detection of their optical activity lies on—or indeed beyond—the limits of experimental possibility, and many chemists find in problems of this nature no little attraction.

A question that has aroused a good deal of interest in recent years concerns the possibility of demonstrating the optical activity of asymmetric tervalent nitrogen compounds, and I think it might be useful to consider some of the difficulties which this problem involves and the prospects of surmounting them.

Since tervalent nitrogen compounds are derivatives of ammonia, and ammonia is known to have a highly labile configuration, we can only observe optical activity in a compound of this type provided that we can—by appropriate substitution—so far reduce the mobility of the valency system of ammonia as to make the optical activity of an asymmetric derivative sufficiently persistent.

We have therefore first to consider the relevant properties of ammonia and then to examine possible methods of bringing about the requisite increase in its configurational stability.

The molecular configuration of ammonia and its degree of stability are well established. We know from the rotational fine structure in the infra-red absorption spectrum that the $\widehat{HNH}$ intervalency angle is 107° 3′ (Dennison, *Rev. Mod. Phys.*, 1940, **12**, 175). The ammonia molecule therefore has the form of a flattish pyramid and the three valencies need deflections of 21° 48′ only to bring the molecule into the planar form which corresponds with the summit of the potential barrier between the two equilibrium configurations (Fig. 1*a*).

To effect these comparatively small valency deflections no great amount of work is required and the potential barrier is correspondingly low. The height of the potential barrier, which determines the configurational stability, has been found as follows. The potential curve showing the relation of the potential energy of the molecule to the distance of the nitrogen nucleus from the plane of the three hydrogen nuclei must have the general form shown in Fig. 1*b* with two minima corresponding with the two equilibrium configurations. The lower vibrational levels accordingly traverse two allowed regions and in accordance with quantum mechanical principles (symmetrical and antisymmetrical combination of wave functions) are double. The doublet separation * depends on the height of the ammonia pyramid and on the height of the barrier. Since the former is known, the latter can be calculated from the observed splitting.

FIG. 1*a*.

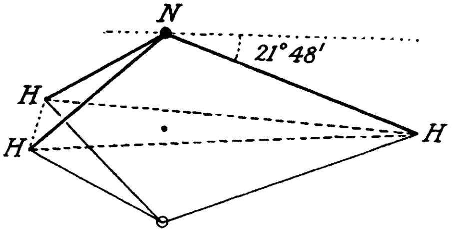
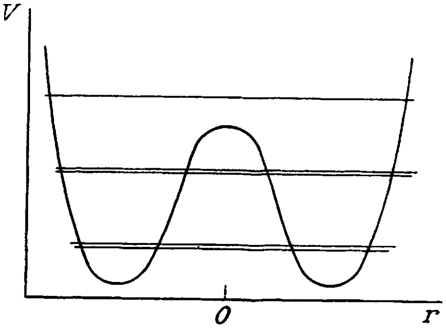


FIG. 1*b*.



Concordant results obtained by different investigators (*inter al.*, Manning, *J. Chem. Phys.*, 1935, **3**, 136) give a value of 5·9 kg.-cals./mol. for the height of the barrier.

When the vibrational energy of the molecule is greater than this (as in the second overtone of the fundamental vibration) it oscillates freely with an exceedingly high frequency between its two equilibrium configurations. The data yielded by the absorption spectrum give the rate of this vibration as $5{\cdot}7 \times 10^{13}$ per second.†

The lowness of the potential barrier is strikingly shown by another consequence of quantum mechanical principles. The barrier is so low that the quantum mechanical "tunnel effect" becomes quite important. In consequence of this effect, ammonia, even when in its ground state, is undergoing inversion at a rate which exceeds 5×10^6 sec. (Sutherland, *Trans. Faraday Soc.*, 1939, **35**, 1373). As this is independent of temperature, the greatest attainable cooling cannot prevent an immeasurably rapid inversion of ammonia.

While the tunnel effect becomes negligible as soon as the hydrogen is replaced by heavier atoms, the rate

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* This is greatly exaggerated in the diagram—it is of the order of 1/1000 of the height of the barrier.

† I am indebted to Dr. G. B. B. M. Sutherland for this figure, and also for helpful discussions.

of the normal inversion (that in which the barrier is surmounted) will remain much too fast for observation until comparatively low temperatures are reached, provided that the height of the barrier is not appreciably raised by the replacement. Reaction velocity at a given temperature is not of course entirely determined by the energy of activation required to surmount the barrier, since the Arrhenius equation contains a " probability factor." If the value 10^{10} is assigned to this factor—and from the values which have been found for other intramolecular changes this would seem to be reasonable, and rather more likely to give too low than too high an inversion rate—then with an ammonia derivative having an energy of activation of 6 kg.-cals./mol. the temperature would have to be lowered to $-163°$ in order to lengthen the half-change period to 1 minute. Unless, therefore, a reasonable chance can be seen of substantially raising the activation energy needed for inversion by introducing appropriate substituents into ammonia, we must conclude that the observation of optical activity due to asymmetric tervalent nitrogen will be exceedingly difficult. We have accordingly to review the different means by which the stability of the nitrogen valency system might be modified.

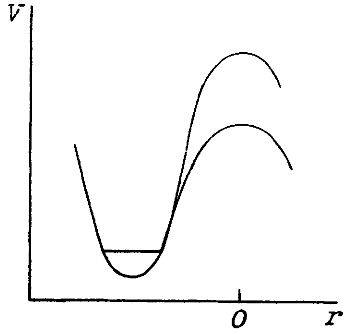
It may perhaps not be superfluous first to consider the effect of the mass and size of the atoms attached to the nitrogen, since in the past many chemists no doubt, on becoming aware of the great configurational instability of ammonia, would have attributed it to the presence of the light mobile hydrogen atoms and would have supposed that the replacement of these by heavier atoms would at once secure greater stability. Such a view would, however, be contrary to the principle of equipartition of energy, which requires the same kinetic energy in each degree of freedom, indpendent of size and mass. If the rigidity of the nitrogen valency system is regarded as constant, *i.e.*, if it is assumed that a given valency deflection calls into play in each case the same restoring couple, then the configurational stability of a compound NR_3 will, to a first approximation, be independent of the size and mass of R.

Many cases are known of course (for example, optically active ketones with the carbonyl group adjacent to the asymmetric centre) in which optical instability is associated with the presence of hydrogen, but in all these the instability can be shown to be due to the ionisation of the hydrogen.

We may next consider how the resistance of a tervalent nitrogen compound to inversion is likely to vary with the chemical nature of the atoms or groups combined with the nitrogen.

The rigidity of the N—R bond in the NR_3 molecule is evidently of much importance in this connexion and a valuable indication of it can be obtained if the angle constant (ratio of a small change in the intervalency angle $R\hat{N}R$ to the restoring couple) can be deduced from the fundamental frequencies of the molecule. What we really want to know, however, is the height of the potential barrier and this cannot be deduced from the angle constant, which depends solely on the small part of the potential curve lying below the energy level of the vibration, as will be clear from the accompanying diagram (Fig. 2).

FIG. 2.



It may therefore be more advantageous to consider the question from a general point of view. From the following table of the principal nitrogen single-bond energies (kg.-cals./mol.) it will be seen that the nitrogen–hydrogen bond is very considerably stronger than any other bond in the list (which probably includes all those of practical importance in the present connexion).

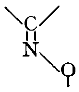
N—H	83·7	N—O	57·9
N—C	48·6	N—F	68·8
N—N	23·6	N—Cl	38·4

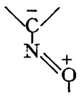
It would appear, therefore, that whenever a hydrogen atom in ammonia is replaced by another atom or group the bond is substantially weakened and it is very difficult to believe that by weakening the nitrogen bonds we could bring about any considerable increase in the resistance of the molecule to inversion.

By employing a substituent group which, like phenyl, resonates with the nitrogen we could increase the strength of the nitrogen–carbon bond, but as this would involve the introduction of a canonical structure in which the nitrogen valencies were flattened out, it could not lead to an increase in the stability of the nitrogen pyramid.

A good deal of encouragement to attack the tervalent nitrogen problem has been derived from consideration of the comparative stability of the oximes. It is doubtful, however, if this is at all closely relevant.

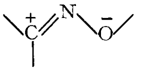
In contrast with the pyramidal configuration of 3-covalent nitrogen derivatives, permitting of inversion by the " dropping through " of the nitrogen nucleus, the nitrogen valencies in the oximes have an angular configuration. Moreover the nitrogen–carbon double bond is of great strength (the C=N bond energy is 94 kg.-cals./mol.) and the stability of the system is still further raised by resonance between the structures :

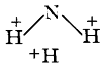




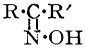
An investigation by Penney and Sutherland (*Proc. Roy. Soc.*, **1936**, *A*, **156**, **654**) is of interest in this connexion. For the angle constants of H_2O and CH_2 they find the values 1·23 and 1·35 and for those of SO_2 and NO_2 the values 3·29 and 3·29 (in units 10^{-11} ergs/radian). Thus the latter two molecules, in which the atoms are linked by strong multiple bonds, have a much greater rigidity than the former two systems, where the linking is by single bonds.

The oximes probably gain additional configurational stability from the attraction of the opposite charges on the carbon and oxygen atoms associated with the different polarities of the nitrogen–carbon and nitrogen–oxygen bonds.

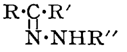




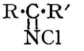
In ammonia and the amines, on the other hand, the repulsion of the positive charges on the atoms attached to the nitrogen would tend to widen the intervalency angle and lower the potential barrier. Some confirmation of the influence of relative polarity on configurational stability may be seen in the different frequency of occurrence of stereoisomerism in the various classes of compounds containing a carbon–nitrogen double bond. The frequency diminishes with decreasing electronegativity of the atom attached to the nitrogen. Thus the oximes show a long series of stereoisomeric forms, the hydrazones a considerable number, the chloroimines a few, and the alkyl imines * none.



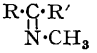
$\begin{array}{c}\mathrm{R{\cdot}C{\cdot}R'}\\ \| \\ \mathrm{N{\cdot}OH}\end{array}$



$\begin{array}{c}\mathrm{R{\cdot}C{\cdot}R'}\\ \| \\ \mathrm{N{\cdot}NHR''}\end{array}$



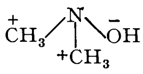
$\begin{array}{c}\mathrm{R{\cdot}C{\cdot}R'}\\ \| \\ \mathrm{NCl}\end{array}$

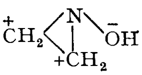


$\begin{array}{c}\mathrm{R{\cdot}C{\cdot}R'}\\ \| \\ \mathrm{N{\cdot}CH_3}\end{array}$

It should accordingly be possible to do something towards increasing the stability of the 3-covalent nitrogen configuration by using substitutents of opposite polarity, as, for example, in dimethylhydroxylamine (IV).

(IV.)





(V.)

Two of the three substituents, however, must necessarily have polarities of the same sign and repel one another. Their repulsion can be abolished if we unite them chemically, as in *N*-hydroxyethyleneimine (V), but then, by including the nitrogen atom in a 3-ring, we impose an unnatural value of about 60° on the intervalency angle. The two carbon atoms are prevented from taking up the directions in which the valency force field is strongest and the nitrogen–carbon bonds accordingly cannot have their normal strength. In the analogous case of *cyclo*propane the heat of combustion shows that the bond energy of each of the three carbon–carbon links is thus reduced by as much as 8·2 kg.-cals./mol.

We have now examined at any rate the more obvious of the methods by which the mobility of the ammonia configuration might be modified. We have seen (1) that increasing the size or mass of the substituents could have little effect; (2) that replacement of the hydrogen by other elements should, if anything, tend to diminish the stability; (3) that, while something might be done towards increasing the stability by introducing substituents of opposite polarity, the full effectiveness of this method would be severely offset by the weakening it requires of two of the three nitrogen bonds on which the stability depends. Considerations of this kind cannot of course yield quantitative comparisons of the relative stability of the configurations of ammonia and its derivatives, but they do, I think, indicate very definitely that it is unlikely that any really considerable increase in stability could be attained.

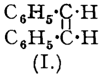
The mobility of the ammonia configuration is, however, so exceedingly great that, even if we doubled the height of the barrier, we should still have a compound of such mobility that it could only be successfully investigated with the aid of an elaborate low-temperatue technique—and it is to be remembered that the lower the heat of activation the smaller the effect of cooling on the inversion velocity.

I cannot help thinking that most of the attempts to solve this problem have been made with an imperfect realisation of the difficulties involved and that, unless some really new method of attack is devised, it can only be solved with an expenditure of effort which would be out of proportion to the value of the result, interesting as this achievement would be.

There is another class of potentially optically active nitrogen compounds which deserves some consideration. Their configurational stability may be too low to allow of their optical activity being actually observed, but a comparison with the class we have just been discussing may help to throw the instability of the latter into stronger relief.

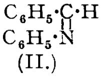
A number of compounds exist containing links, regarded as single on the classical structure theory, to which the modern theory of resonance assigns a certain amount of double bond character. In virtue of this they should acquire torsional rigidity and, introduced into molecules of appropriate structure, should give rise to molecular dissymmetry of corresponding stability.

* Phenylimines will, however, probably be found capable of existence in stereoisomeric forms



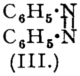
$\begin{array}{c}\mathrm{C_6H_5{\cdot}C{\cdot}H}\\ \| \\ \mathrm{C_6H_5{\cdot}C{\cdot}H}\end{array}$

(I.)



$\begin{array}{c}\mathrm{C_6H_5{\cdot}C{\cdot}H}\\ \| \\ \mathrm{C_6H_5{\cdot}N}\end{array}$

(II.)

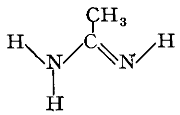


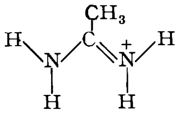
$\begin{array}{c}\mathrm{C_6H_5{\cdot}N}\\ \| \\ \mathrm{C_6H_5{\cdot}N}\end{array}$

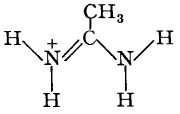
(III.)

Since *iso*stilbene (I.) and *cis*azobenzene (III.) are known, *cis*benzylideneaniline (II.) must surely have considerable stability and should be obtainable by the application of appropriate methods (*e.g.*, ultra-violet radiation of the *trans*-form).

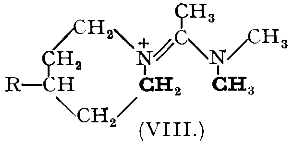
Perhaps the most obvious example is afforded by the salts of the amidines.


(VI.)


(VII*a*.)

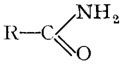

(VII*b*.)

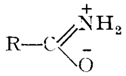
When acetamidine (VI) forms a salt, the cation on the classical structure theory would have been given the formula (VII*a*). Now of course it is considered that formula (VII*b*) is equally justified and the actual structure is envisaged as a resonance hybrid of (VII*a*) and (VII*b*). For full resonance to take place between (VII*a*) and (VII*b*) a planar arrangement of the molecule is necessary. If one NH_2 group is rotated about the C–N axis so that its plane is at right angles to that of the rest of the molecule, all or the greater part of the resonance energy is lost. A corresponding amount of work is therefore required to bring about this rotation and both the carbon–nitrogen links in the salt acquire considerable torsional rigidity. There are, however, serious difficulties in the way of obtaining an optically active amidine salt. Experience with alkylammonium salts would indicate that the hydrogen atoms in the two amino-groups would have to be fully substituted as in the compound (VIII). But in such a compound a co-planar arrangement of the two nitrogen atoms and the five directly attached carbon atoms is scarcely possible on account of the close approach this would require of the CH_2 and the CH_3 group shown in Clarendon type. Both the piperidine ring and the $N(CH_3)_2$ complex would therefore presumably have to set themselves at an angle to the amidine plane and most of the torsional rigidity would be lost.


(VIII.)

Similar considerations apply to the cation of the guanidine salts, $(NH_2)_2C{=}\overset{+}{N}H_2$, where, however, the torsional rigidity to be expected is less, since when one of the three NH_2 groups is rotated through 90° the greater part of the resonance energy would still be supplied by the other two.

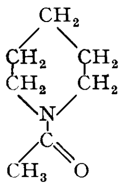
It may be therefore that, in spite of their lower resonance energy, substituted amides offer more promising material for the experimental demonstration of the torsional rigidity of a resonating bond. According to Pauling (" Nature of the Chemical Bond," p. 192) the amides have a resonance energy of about 21 kg.-cals./mol. arising from resonance between the structures

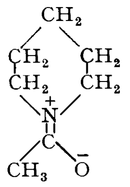


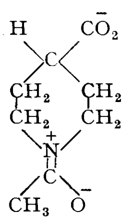


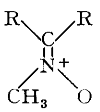
In agreement with this the C–N interatomic distance (1·38 A.) found from the crystal structure of acetamide (Senti and Harker, *J. Amer. Chem. Soc.*, 1940, **62**, 2008) is appreciably less than the normal value for a single bond (1·47 A.). From comparison with the normal C—N, C═N and C≡N bond lengths this length would indicate about 46% double bond character.

Examples of compounds having potential optical activity dependent on the torsional rigidity of the amide C–N bond are to be found in derivatives of acetylpiperidine (IX*a* and *b*).*


(IX*a*.)


(IX*b*.)


(X.)


(XI.)

In this compound the replacement of the hydrogen atoms of the amino-group by the pentamethylene chain would very possibly reduce the resonance by making it more difficult for the nitrogen atom to acquire a positive charge. However, for resolution experiments a substance such as the acetyl derivative of piperidine-4-carboxylic acid (X) would be selected, and in the salts of this compound the inductive action of the anionic charge would tend to promote the acquisition of a positive charge by the nitrogen and counteract this effect.

When the acetyl group is rotated through 90° about the N–Ac axis the electron distribution and the bond-lengths adjust themselves so as to minimise the energy for that orientation. If, as there is some reason to think, the effect of these adjustments would not be very great, a large part of the resonance energy would be lost in the 90° position and a considerable barrier would be interposed between the two equilibrium configurations. If, for example, the effect of the adjustments amounted to $\frac{1}{4}$ of the resonance energy, we should have a barrier of some 16 kg.-cals./mol. and the experimental demonstration of its existence might not be too difficult.

* The relation of (IX*b*) to the formula of the *N*-methyl ethers of the oximes (XI) is to be noted. It consists in an interchange of C and $\overset{+}{N}$.

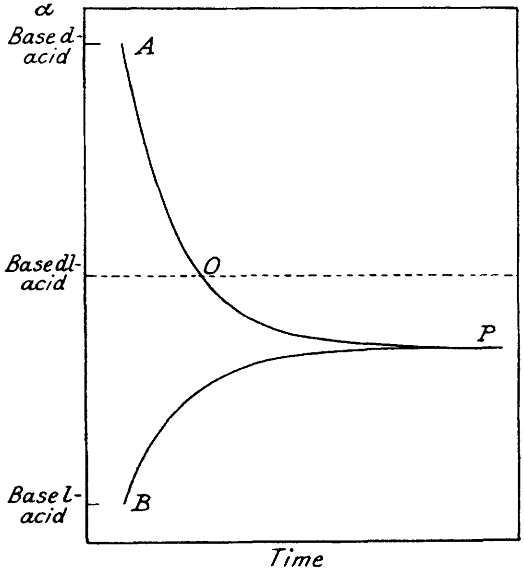
If, however, the effect of the adjustments was more considerable and amounted to as much as, say, one half of the resonance energy, leaving a barrier of about 10 kg.-cals./mol. only, the demonstration of optical activity would need an elaborate low-temperature technique.

A few years ago no one could have suspected the existence of torsional rigidity in the acetyl group of a compound like acetylpiperidine, yet on examination it seems to offer a more promising field for investigation than the potential optical activity of asymmetric tervalent nitrogen.

The standard methods of resolution are likely to present difficulties when all manipulations have to be carried out at low temperatures. There is, however, a general property of labile dissymmetric compounds which may be of use in demonstrating their potential optical activity under these conditions. It is more particularly applicable to acids and bases.

When a labile *dl*-acid interacts with an alkaloid in a non-ionising solvent such as chloroform, the two diastereoisomeric salts which result, *d*A*l*B and *l*A*l*B, must differ in *all* their properties. This is well recognised as regards their solubilities, but it must hold also for their stability and therefore for their rates of mutarotation. Each of the labile salts will be in a state of continuous mutarotation and they will be in equilibrium when their concentrations are inversely proportional to their rates of mutarotation and, since the latter are unequal, the equilibrium mixture will contain unequal proportions of *d*- and *l*-acid. Thus in presence of the alkaloid the normal equilbrium becomes displaced and the acid is activated. Mutarotation under these conditions can only be due to a displacement of a *d*-*l* equilibrium of the acid and its observation therefore demonstrates the optical activity of the acid.

Fig. 3.



This phenomenon was first observed by Read and McMath in **1925**. Two or three years later Elliott and I encountered it in investigating the benzenesulphonyl derivative of 8-nitronaphthylglycine (XIII) and we gave an explanation of its origin. More recently Turner and his collaborators have examined it in considerable detail.

The extent of the activation varies of course from case to case and it may happen that it is too small to be detected. In some cases, however, it is very considerable. Thus Read and McMath found a **4** : **1** ratio (approximately) in the equilibrium

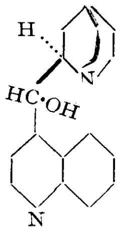
$$\text{base } l\text{-acid} \rightleftharpoons \text{base } d\text{-acid}$$

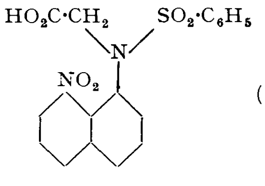
for chlorobromomethanesulphonic acid and *l*-hydroxyhydrindamine in acetone and Turner and Jamison a 2 : 1 ratio for the acid (XIII) and cinchonidine in chloroform.

The nature of the phenomenon is clearly shown when the *d*- and the *l*-form of the acid can both be obtained, since the mutarotation of each of the two salts can then be observed separately, as has been done by Turner and Jamison (J., **1938**, **1653**). Fig. **3** shows the mutarotation curves which would be found for a salt for which the equilibrium proportion of the antimeric forms of the acid (*d*/*l*) was 1 : 2. The slopes of the curves at the points A and B (which give the mutarotation rates for the pure salts, *base* d-*acid* and *base* l-*acid*), are in the ratio **2** : 1. The point O shows the initial rotation observed on combining the base with the inactive *dl*-acid and OP is the activation curve.

The usual causes of the differences in the mutarotation rates of the isomeric salts will probably be found to lie in steric hindrance combined with dipole interactions. For example, in the salts formed from cinchonidine (XII) and the acid (XIII), after salt formation between the carboxyl group of the acid and the quinuclidine nitrogen, the next strongest interaction would be that between the dipoles of the hydroxy-group of the base

(XII.)





(XIII.)

and the nitro-group of the acid. On experimenting with models in which the configuration (XII) is assumed for cinchonidine it is at once found that in one form of the acid these two groups are easily brought into proximity, whereas in the antimeric form their approximation is impossible. Thus one of the two salts should have its configuration stabilised by this dipole attraction but there should be no corresponding effect in the other.

The amount of activation will probably be greatest when the acid and the base contain groups of marked polarity in fairly close proximity to the salt-forming groups. In the above-mentioned case observed by Read and McMath, where the degree of activation was unusually high, it may be noted that the amino-group of the base has a vicinal hydroxy-group and the sulphonic group of the acid has two strongly polar C-Halogen groups in the α-position.

Observations made by Turner and Jamison on the effect of excess of acid on the activation process call for some notice, lest they should be regarded as obscuring its interpretation and lessening its value as a means of demonstrating optical activity in labile systems.

Addition of excess of the acid to the salt alters the equilibrium proportions of the *d*- and the *l*-form. It may either increase or decrease the extent of the activation and even reverse its direction. We have evidently here a separate effect, arising from an interaction between the acid and its salt, superposed on that due to the unequal rates of partial racemisation of the stereoisomeric salts.

There can be little doubt as to the nature of the interaction in question. We know that when an excess of an acid is added to its salt under the conditions of these experiments a very rapid interchange will be taking place between the free and the combined acid and the disturbance attending the replacement of the anion associated with the asymmetric cation would appear likely to promote directed configurational change. The resultant rate of change would be due to the summation of several different effects and would have no direct connexion with the rate of change in the neutral salt. There would seem, therefore, to be no reason to regard these additional observations as affecting the diagnostic value of the activation process.