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Manuscript received January 5, 1976; revision received and accepted March 22, 1976.

The Hydrodynamic Resolution of Optical Isomers

A potentially simple and effective technique is proposed for separating enantiomorphic crystal pairs from each other, or separating individual enantiomorphs from optically active impurities.

This method consists essentially of settling under conditions controlling orientation of the asymmetric particles and taking advantage of the tensorial nature of their friction factors.

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SCOPE

A new and potentially simple method is proposed for resolving racemic mixtures of optically active substances. Separation is achieved purely by hydrodynamic means, without conversion of the components to geometric isomers. The procedure suggested is essentially a means for automating the mechanical sorting technique of Pasteur for separation of enantiomorphic crystals.

CONCLUSIONS AND SIGNIFICANCE

Experiments with a variety of crystals and crystal models demonstrate the effectiveness of hydrodynamic forces for producing such separations. It remains, however, to refine the orientation techniques and to establish effective crystallization procedures

Where the proposed method is feasible, it should substantially facilitate both the resolution of enantiomorphs and the separation of optically active crystals from inactive solids. It is particularly promising for reducing the costs of pharmaceuticals and food or feed additives as an alternate to present resolution procedures.

Resolving racemic mixtures of optically active compounds is important in the synthesis of food or feed additives and pharmaceuticals, and it can be both tedious and expensive. In addition, presently used procedures, all of which involve chemical reactions with one isomer of a second optically active species, are quite complex in comparison with Pasteur's classic mechanical resolutions of tartrate salts (Pasteur, 1847, 1850). His procedure was simply to crystallize a racemic mixture under conditions yielding pure crystals of the individual enantiomorphs and to separate these mechanically under a low-power microscope. His technique is expensive only because of the amount of labor required, and we decided to see if the sorting process could be automated. We proposed to do this by utilizing the peculiar hydrodynamic properties of enantiomorphic crystals, which typically have a pronounced screw sense, or skewness.

The impetus for this project was repeated reports that the right and left shells of bivalves sometimes turn up in significantly different numbers on ocean beaches (Lever, 1958, 1961, 1964; Nagle, 1964, 1967). Many of these shells closely approximate the mirror image asymmetry of enantiomorphic pairs, and they may be considered as crystal analogues. It therefore appeared that effective spontaneous resolution was being achieved in relatively simple flow situations.

We began by seeking suitably asymmetric conditions for the separation either of the optically active molecules themselves or their crystals, which generally show the same type of mirror image asymmetry. As a guide in this search, it was useful to review the transport behavior of skew particles at both the molecular and macroscopic levels.

THEORY

All optically active molecules lack a plane of symmetry, and the mirror image relation of enantiomorphic pairs suggests that, for any given molecular orientation, they will move in different directions when acted on by the same

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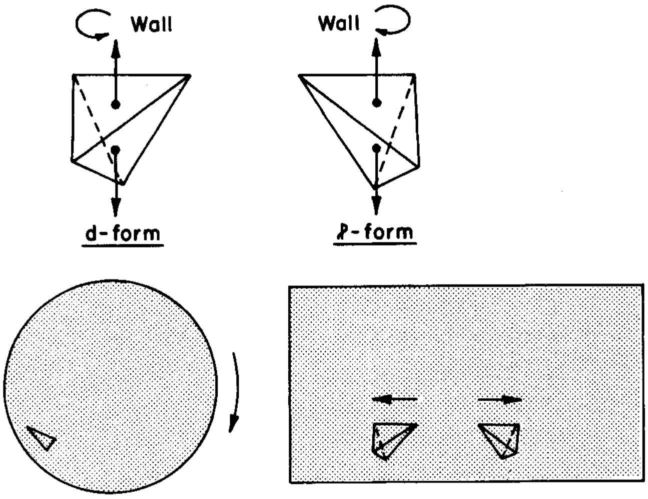

Fig. 1. Hydrodynamic resolution of optical isomers. A pair of crystals with mirror-image asymmetry, shown at the top of the figure, is separated by rotation in a drum filled with a nonsolvent liquid, here less dense than the crystals.

diffusional driving forces.

If diffusion in such a system may be considered pseudobinary, as will frequently be the case, mass transport is described by*

$$x_i(\mathbf{v}_i - \mathbf{v}^\star) = \mathsf{D}_{im} \cdot \mathbf{d}_i$$

where (see Lightfoot, 1974, p. 168):

$$\mathbf{d}_i = \mathbf{d}_i^0 \equiv x_i \nabla_{T,p} \ln a_i + (c_i\overline{V}_i - \omega_i)\nabla p/c\mathcal{R}T + \frac{x_i\nu_i F}{\mathcal{R}T}\nabla\phi \quad (1)$$

Equation (1) is rather powerful in forming the basis for describing concentration, pressure, and electrodiffusion. The nine elements of the diffusion coefficient

$$\mathsf{D}_{im} = \begin{pmatrix} \boldsymbol{\delta}_x\boldsymbol{\delta}_x\mathcal{D}_{xx} & --- & \boldsymbol{\delta}_x\boldsymbol{\delta}_z\mathcal{D}_{xz} \\ | & & \\ & \rule{3em}{0.4pt} & \boldsymbol{\delta}_z\boldsymbol{\delta}_z\mathcal{D}_{zz} \end{pmatrix} \quad (2)$$

depend upon the orientation of the molecules, and this in turn must be obtained from an equation describing rotary diffusion. Such equations are available, for example in Brenner and Cundiff (1974), but they need not concern us here. It is sufficient to note that the degree of orientation in any situation depends upon a Langevin parameter

$$L = \epsilon/KT \quad (3)$$

where ϵ is a measure of molecular alignment energy, and K is Boltzmann's constant. As one example, for a dipolar molecule aligned by an electric field, it is convenient to define

$$\epsilon = \mu_\epsilon\,|\nabla\phi| \quad (4)$$

where μ_ϵ is the molecular dipole moment. When L is small relative to unity, the randomizing effect of Brownian motion dominates system behavior, and D_{im} approaches the usual scalar result

$$\mathsf{D}_{im} \to \mathcal{D}^\circ_{im}\,\boldsymbol{\delta} \;(L \to 0) \quad (5)$$

where $\boldsymbol{\delta}$ is the unit tensor, and the superscript degree indicates the Brownian limiting magnitude. The nondiagonal elements of D_{im} now disappear, and the three diagonal elements become equal. For ellipsoids of revolution, Brenner and Cundiff show that alignment only becomes effective at $L \sim 10$, and this in turn requires very intense fields; these appear impractical at present. Direct molecular separations are therefore not very attractive at the macroscopic level. It may be possible to produce the required fields in systems of suitable geometry at the molecular level by development of specialized charged polymers, for example. We have not yet considered these possibilities in a serious way.

It is, however, well known that the molecular mirror image asymmetry is maintained in macroscopic crystals. This is indicated in Figure 1, where an enantiomorphic crystal pair is shown schematically. For these large bodies, Brownian effects are negligible, and they act as hydrodynamic particles when suspended in a fluid.

For isolated particles moving at low Reynold's number relative to a quiescent fluid, hydrodynamic behavior is particularly simple and can be described by two equations:

$$\mathbf{F} = \mu D[\mathsf{K} \bullet \mathbf{v}] + \underline{\mu D^2[\mathsf{C}_R{}^T \bullet \boldsymbol{\omega}]} \quad (6)$$

$$\mathbf{T} = \mu D^2[\mathsf{C}_R \bullet \mathbf{v}] + \underline{\mu D^3[\boldsymbol{\Omega} \bullet \boldsymbol{\omega}]} \quad (7)$$

Here μ is fluid viscosity, and D is a characteristic particle length. Equation (6) states that the force $\mathbf{F}$ exerted by the particle on the fluid is proportional both to its velocity $\mathbf{v}$ and rate of rotation $\boldsymbol{\omega}$ relative to the fluid. Equation (7) states a similar relation for the torque, applied at an arbitrary but definite point R in the particle. The proportionality factors are tensorial constants characteristic of particle shape, and in the case of C_R, of R: the translational tensor K, the coupling tensor C_R and its transpose $\mathsf{C}_R{}^T$, and rotational tensor $\boldsymbol{\Omega}$. Equation (6) corresponds to Equation (1) and Equation (7) to the rotary diffusion equation.

A macroscopic separation also requires control of rotation, and the simplest procedure is to eliminate it, that is, eliminate the underlined terms in Equations (6) and (7). We see immediately that to do this will require a torque equal to $\mu D^2[\mathsf{C}_R \bullet \mathbf{v}]$. If such a torque can be applied, any force acting on the particle will produce a motion according to the relation

$$\mathbf{F} = \mu D[\mathsf{K} \cdot \mathbf{v}] \quad (\boldsymbol{\omega} = 0) \quad (8)$$

Furthermore, one can readily extend the hydrodynamic theory of diffusion (see, for example, Bird et al., 1960, §16.4, and Lightfoot, 1974, p. 59) to this situation and write, for no rotation:

$$\mathsf{D}_{AB} = (\mathcal{R}T/\mu D)\mathsf{K}^{-1} \quad (9)$$

Thus the asymmetry of K will carry over into D_{AB}.

As a simple example we consider free settling of the particles in the presence of our orienting torque. Then, if we designate a particle as A and the solvent as B, we find the driving force to be that of pressure diffusion, and

$$x_A x_B(\mathbf{v}_B - \mathbf{v}_A) = \left(\frac{\phi_A - \omega_A}{c\mathcal{R}T}\right)\frac{\mathcal{R}T}{\mu D}\mathsf{K}^{-1}\nabla p \quad (10)$$

$$\text{(free settling)} \quad \downarrow \quad (x_B \to 1;\ \nabla p \to \rho\mathbf{g})$$

$$(\mathbf{v}_B - \mathbf{v}_A) = \frac{1}{6}\pi D_E{}^2\left(1 - \frac{\rho_A}{\rho_B}\right)\frac{\mathbf{g}}{\nu}\mathsf{K}^{-1} \quad (11)$$

Here

$$D_E = \left(\frac{6}{\pi}V\right)^{1/3} \quad (12)$$

$$V = \text{particle volume}$$

This is a generalization of Stokes' law to asymmetric particles, as may be seen immediately by recognizing that for a sphere

$$\mathsf{K}\,\text{sphere} = 3\pi\boldsymbol{\delta} \quad (13)$$

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* In the absence of appreciable thermal diffusion. The underlying concepts are discussed in the references made during the discussion.

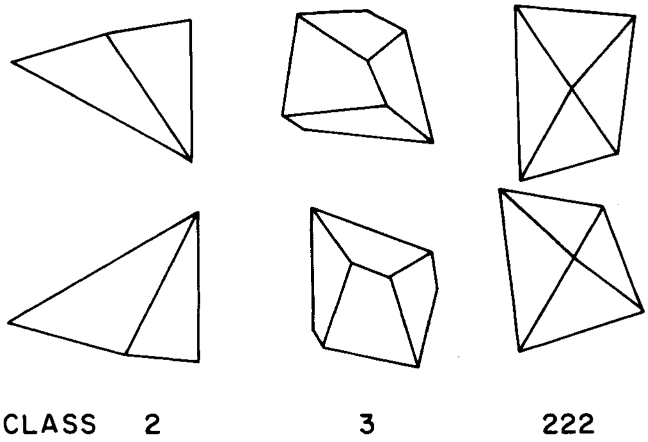

Fig. 2. Crystal models shown to separate effectively in the apparatus of Figure 1. The pair at the right was used to obtain the data presented in Figure 3. The classes indicated are those of Phillips (1946, 1949) and are 2 monoclinic, 3 trigonal, 222 orthorhombic.

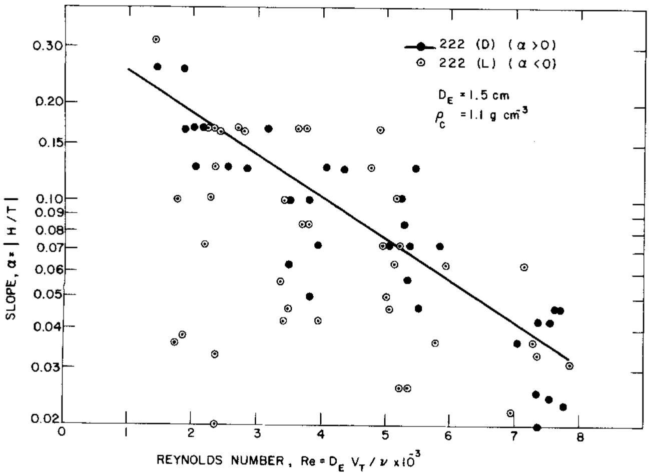

Fig. 3. Tartaric acid crystal used to obtain data shown in Figure 5 (crystal 1).

Putting Equation (8) into (6) we get

$$v_B - v_A = \frac{1}{18} D^2 \left[1 - \frac{\rho_A}{\rho_B} \right] g\mu/\rho$$

which is a well-known relation.

EXPERIMENT

To determine the feasibility of hydrodynamic resolution, a variety of crystals and crystal models were tested in apparatus of the type sketched in Figure 1.

Apparatus and Procedure

This apparatus consists simply of a horizontal cylindrical drum filled with a nonsolvent liquid, and the separation process is just to introduce the crystals to be separated and to rotate the drum about its axis. Rotational speed is chosen to keep the particle well up the side of the drum but not so high that it rotates with the liquid. The prototype used in this study was a water filled 0.0454 m^3 (12 gal) carboy rolled across the laboratory floor. The primary advantages of this system are simplicity of particle alignment and the capacity to utilize relatively slow horizontal motion.

Orientation of the particles is provided by two couples, each with two finite components: that produced by the finite distance between the center of gravity G and of hydrodynamic reaction R, as indicated at the top of Figure 1, and that produced by near contact of one crystal face with the drum wall, induced in turn by gravitational forces. Unfortunately, control of orientation is incomplete in that it is not possible to determine which crystal face contacts the drum. One can attempt to obtain a reproducible distribution of orientation in time by operating at such a high drum speed that continued crystal reorientation occurs, and we normally did this.

Fig. 4. Migration slopes for crystal models.

It may also be noted that the flow situation need not correspond strictly to that for which Equations (6) and (7) were written. $t \rightarrow T$ the qualitative predictions based on these equations are not dependent on geometric detail.*

Test Crystals

Experiments were performed with individual and paired crystal models, with carefully grown large single crystals, and with larger numbers of small crystals.

The crystal models were made of castolite resin (density 1.2 g cm^{-3}) in a variety of crystal habits. Those shown in Figure 2 are representative examples. Water was used as the suspending liquid for all castolite models.

Large single crystals of (natural) d-tartaric acid were grown by free convection of an aqueous solution over a

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* For our situation, the tensorial constants of Equations (6) and (7) must be replaced by tensorial functions of Reynolds number and the additional geometrical factors provided by the wall. It would also be necessary to investigate the use of $C_R{}^T$ as the coefficient of ω in Equation (6). It should, however, be emphasized that the role of Equations (6) and (7) is primarily qualitative, to suggest the kind of behavior we exploit in the experimental section rather than to provide numerical prediction. In this sense Equations (6) and (7) suffice. The hydrodynamics of flow past skew bodies are in any event too complex to warrant attempts at numerical prediction, even for the simplest of geometries and flow conditions. Quantitative hydrodynamic analyses will inevitably involve substantial approximations, and we believe they should be deferred until additional experience with actual skew bodies is obtained.

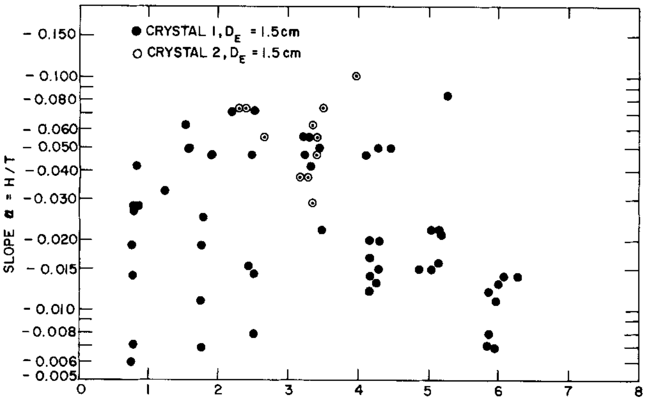

Fig. 5. Migration slopes for single tartaric acid crystals.

heated bed of small crystals. The first such crystal produced is shown in Figure 3.

Smaller crystals were grown by a variety of procedures. Kerosene was used as the suspending medium for both these and the single crystals of tartaric acid.

RESULTS

Results of experiments with the above types of crystals are summarized in Figures 4 and 5 and Examples 1 and 2 below. These suffice to demonstrate the effectiveness of hydrodynamic forces to produce the desired horizontal motion, but, as suggested in the discussion below, much remains to be done.

Studies with Model Crystals

As might be expected, the best separations and most reproducible results were obtained with the castolite crystal models. All, including the six crystals of Figure 2, showed strong qualitatively reproducible horizontal motion. Furthermore, when opposite handed pairs were introduced into the same drum, they always migrated to opposite ends as expected. Results for the orthorhombic crystals (class* 222 Figure 3) are typical, and these are shown in Figure 4. Plotted here are absolute values of the ratios α of horizontal crystal travel H to tangential travel T of the drum surface, as a function of particle Reynolds number:

$$Re = D_E V_T / \nu$$

Here D_E = diameter of sphere with same volume as crystal
V_T = tangential speed of drum surface
ν = kinematic viscosity of supporting liquid.

Note that on a time-average basis α is the ratio of horizontal particle velocity to the relative tangential velocity between it and the adjacent drum surface.

Enantiomorph D gave the more reproducible results and exhibited very large slopes, of about one in five, for the smaller Reynolds numbers. It also showed a marked falloff in the slope α, hence poorer separability, with increasing Reynolds number.† Results for its enantiomorphic peer (L) were similar but showed more scatter. This scatter appears to result from the variability in orientation referred to above, but it is important to note that no reversals in direction were observed for the more than seventy five runs reported; in all cases α, as arbitrarily defined, was greater than zero for the D crystal and less than zero for its L counterpart.

Separations of the D-L pair were also always successful in spite of complex secondary flows when they were close together. These latter appear to have been aggravated by the relatively small size of the drum (about 6.3 cm radius) and could be decreased in second-generation apparatus.

Studies with Single Tartaric Acid Crystals

These were made with two crystals (designated 1 and 2), and all results, except one run, are summarized in Figure 5. The suspending liquid in this case was kerosene. This plot, similar to that in Figure 4, shows lower magnitudes for 2 and more scatter than for the 222 models. There is no discernible effect of Reynolds number, and one run gave a positive α value of 0.05 at the Reynolds number of 2 500. This is, however, only one exception out of more than 65 runs.

The results are generally encouraging, and it may be seen that the maximum values for $|\alpha|$ are both attractive and quite similar for the two crystals.

The reason for the larger scatter observed with tartaric acid is that each crystal has two large faces with near equal probability of facing the drum, and that the crystal moves in opposite directions in these two positions. The observed horizontal travel over a large time interval is thus a relatively small difference in two near equal quantities.

Similar behavior is noted for large masses of small tartaric acid crystals which put on quite an impressive display of large horizontal velocities with frequent changes in direction. Once again the need for firmer control of orientation is evident.

Studies with Small Crystals

A number of studies were made with smaller crystals, and these all gave encouraging but not definitive results. There is no question as to the effectiveness of hydrodynamic forces in any of these cases, but there is a clear need for more uniform crystal habit. All of our small crystals grew resting on solid surfaces and were deformed to some degree as a result. Representative results are given in the following examples.

Example 1. A drum having an inside diameter of 0.1257 m and a length of 0.446 m was filled with Isopar H (aliphatic hydrocarbon from Humble Oil & Refining Company) which had previously been dried by passage through a silica-gel column and saturated with dextro-rotary tartaric acid.

About 1 g of natural (dextro-rotary) granular tartaric acid was introduced through an opening into one end of the drum whereafter the opening was sealed. The drum was tilted so that the crystals congregated at one end, and the drum was then returned to a position with its axis horizontal. The drum was rotated at about 0.05 rev/s so that the bulk of the crystals were continually sliding down the inner surface at an angle of about 45 to 60 deg. from the lowest point. The drum was rotated clockwise as seen from the end at which the crystals were originally congregated.

Within about 1½ hr, the bulk of the crystals had migrated to the other end of the drum. A small fraction, presumably the less perfect crystals, was distributed more or less at random along the length of the drum.

The direction of rotation of the drum was then changed repeatedly, and each time the direction of crystal migration reversed.

Example 2. Eighteen carefully prepared crystals of l-lysine hydrochloride between 1 and 3 mm in diameter were introduced to the center of a drum about 63 mm in diameter and 457 mm in length. The drum was marked in quadrants numbered from one (left end) to four (right end). Crystal distributions were measured after 5 min of rotation. Typical results are:

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* See Phillips (1946, 1949) for description of the classification system.

† This may reflect position on the drum surface rather than Reynolds number as such.

Rotation	Number of crystals in quadrant			
	1	2	3	4
Left	3	1	0	14
Right	13	0	1	4
Left	2	0	0	16
Right	13	1	1	3

In 23 of 25 runs, crystals concentrated in the right end of the cylinder for left rotation or at the left end for right rotation. Normally the degree of separation was high, as indicated in the table, and the bulk of anomalous crystals appeared to be captured by secondary flows, that is, congregated at the extreme ends of the tube. Furthermore, in the two anomalous runs, secondary flow capture appeared unusually strong. Such secondary capture can easily be eliminated in a production unit, as by tapering the ends of the drum.

DISCUSSION

This preliminary survey appears both to establish the effectiveness of hydrodynamic forces for moving asymmetric crystals in directions different from that of the causative force and to pinpoint problems to be overcome in developing practical separations processes based on this principle. In all cases reported, significant horizontal motion was demonstrated, and much better results could be obtained by more effective particle alignment. We are presently planning to replace the drum surface by an electrical induced dipole which will both eliminate wall effects and provide more positive alignment. It will remain then only to produce suitable crystals.

The crystallographic problems are the most difficult and appear to be of two types: formation of pure enantiomorphs rather than racemic crystals or solid solutions, and production of uniform crystals of suitable shape. It is unfortunately not possible to predict success with either of these problems in advance.

In the absence of any strong practical motivation, not a great deal of information has accumulated as to crystallization of racemic mixtures. However, it does appear characteristic (Ricci, 1951) that either racemic or pure enantiomorphic crystals form. It thus remains only to find conditions under which the enantiomorphs are less soluble than the racemate, and these appear not to be rare (Landolt-Böronstein, p3-343). Known examples include such common substances as various tartrate salts, alanine, asparagine, and glutamine.* On balance it appears that enantiomorphic crystals of a great many interesting materials can be obtained with suitable developmental effort.

The remaining problem, that of producing suitable habits, is in the realm of art. In the tartrate system, for example, tartaric acid crystals are promising, whereas those of sodium potassium tartrate are not. These latter tend to form thin plates or short prisms without useful asymmetry. We are currently working on this problem and find that precipitation within sodium silicate gels is promising at the laboratory level. However, scale-up appears to require the type of skill that comes only with experience, and also access to large crystallizers.

Potential practical applications of this technique are easily found simply by noting the characteristically large price differences of pure enantiomorphs and racemic mixtures in any fine chemicals catalog. There are also more humble, but more easily attainable, applications in the separation of enantiomorphs from optically inactive impurities, for example, unwanted inorganic salts. Collectively, these possibilities appear to justify further investigation of the possibilities suggested above.

NOTATION

a_i = $\gamma_i x_i$ = chemical activity of species i
c = total molar concentration
c_i = molar concentration of species i
$\mathbf{D}_{im}$ = effective binary diffusivity tensor
F = Faraday's constant
K = Boltzmann's constant
L = Langevin parameter
p = hydrostatic pressure
$\mathcal{R}$ = the international gas constant
T = absolute temperature
$\mathbf{v}_i$ = observable velocity of species i
$\mathbf{v}^*$ = molar average fluid velocity
$\overline{V}_i$ = partial molal volume of species i

Greek Letters

$\boldsymbol{\delta}$ = unit tensor
ϵ = characteristic energy
μ_ϵ = electrical dipole moment
$\dot{\nu}_i$ = ionic charge on species i, for example, -2 for $SO_4^=$
ϕ = electrostatic potential
ω_i = mass fraction of species i in mixture

$$\nabla_{T,p} \ln a_i = \sum_{j=1}^{N} (\partial \ln a_i/\partial x_j)_{T,p,x_k} \nabla x_k$$

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Manuscript received January 16, 1976; revision received March 15 and accepted March 17, 1976.

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* Found by a cursory inspection of Landolt-Bornstein.