selective removal of these agents by the cellulose acetate filter which contains plasticizers [Table 2; (*16*)]. The ratio of *m*- and *p*-ethylphenol to 2,4- and 2,5-dimethylphenol is significantly greater in little cigar smoke than in cigarette smoke. At present, we do not know the importance of this observation. The concentration of benz[*a*]anthracene and benzo[*a*]pyrene in the smoke of little cigar tobacco is relatively low (Table 2). This result was expected for tobacco products which are made up largely of cigar type or air-cured tobacco and reconstituted tobacco sheets (*7, 17*).

Our preliminary data indicate that, on a per puff basis (Table 3), the reduced levels of "tar," nicotine, and carbon monoxide may permit the tobacco user to inhale the smoke of some little cigars even though it is otherwise just as toxic as the "uninhalable" smoke of conventional cigars.

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References and Notes

1. E. L. Wynder and E. A. Graham, *J. Amer. Med. Ass.* **143**, 329 (1950); M. L. Levin, H. Goldstein, P. R. Gerhardt, *ibid.*, p. 336; Royal College of Physicians, London, *Smoking and Health* (Pitman Medical, London, 1962); *U.S. Public Health Rep. No. 1103* (1964); *U.S. Public Health Rep. No. 1696* (1967); *U.S. Public Health Rep. 1696-Suppl.* (1968); *U.S. Public Health Rep. 1696-2* (1969); Royal College of Physicians, London, *Smoking and Health Now* (Pitman Medical, London, 1971); *U.S. Dep. Health Educ. Welfare Publ. No. (Health Serv. Mental Health Adm.) 71-7513* (1971); *U.S. Dep. Health Educ. Welfare (Health Serv. Mental Health Adm.) Publ. No. 72-1516* (1972).
2. U.S. Department of Treasury, Internal Revenue Service, "Code of Federal Regulations 26," part 270, "Manufacture of Cigars and Cigarettes" (1972), p. 759.
3. The Kentucky standard cigarettes are manufactured for research purposes only. Their "tar" yield is rather high as compared to commercial U.S. cigarettes of the same length and without filter tips.
4. J. C. Maxwell, Jr., *Tob. Rep.* **98** (No. 10), 20 (1971).
5. *U.S. Dep. Agr. Tech. Bull. 1225* (1969), p. 117, method 34.
6. D. Hoffmann and E. L. Wynder, *Cancer Res.* **27**, 172 (1967).
7. E. L. Wynder and D. Hoffmann, *Tabacco and Tobacco Smoke* (Academic Press, New York, 1968).
8. H. C. Pillsbury, C. C. Bright, K. J. O'Connor, F. W. Irish, *J. Ass. Offic. Agr. Chem.* **52**, 458 (1969) (official method of the Federal Trade Commission).
9. F. J. Schultz and A. W. Spears, *Tob. Sci.* **10**, 75 (1966).
10. A. J. Sensabaugh, Jr., and R. H. Cundiff, *Tob. Sci.* **11**, 25 (1967).
11. D. Hoffman, K. Brunnemann, G. Rathkamp, unpublished data.
12. A. Artho and R. Koch, *Beitr. Tabakforsch.* **5**, 58 (1969).
13. D. Hoffmann and E. L. Wynder, *ibid.* **1**, 101 (1961) ([^{14}C]phenol was the internal standard).
14. G. Rathkamp and D. Hoffmann, *ibid.* **5**, 302 (1970).
15. In general, air-cured tobaccos, freeze-dried (puffed) tobaccos, and reconstituted tobaccos deliver less "tar" than flue-cured tobaccos. The freeze-drying process results in a tobacco leaf with modified structural properties and increased specific volume. Reconstituted tobacco sheets are made of a mixture of tobacco fines, tobacco midribs, and opened tobacco stems. To this mixture certain cellulose derivatives are sometimes added.
16. D. Hoffmann and E. L. Wynder, *J. Nat. Cancer Inst.* **30**, 67 (1963).
17. ———, *Nat. Cancer Inst. Monogr.* **28**, 151 (1968).
18. Supported in part by American Cancer Society grant BC 56P and by National Cancer Institute grant NIH-NCI-70-2087. This is report number XVIII in a series of papers entitled "Chemical Studies on Tobacco Smoke" by D.H. and E.L.W.

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Gravitational Effects on Concentrations and Partial Pressures in Solutions: A Thermodynamic Analysis

Abstract. *Thermodynamic analysis establishes the equilibrium relationships between the concentrations and partial pressures of the components of liquid and gaseous solutions in the presence of a gravitational field. The conditions of equilibrium between a column of gas and gas-saturated water and the conditions of equilibrium governing a model of the distribution of radioactive heat sources in surface rocks are deduced from the theory.*

In a recent report, Fenn (*1*) discussed a series of experiments by Enns *et al.* (*2*), in which the equilibrium through a semipermeable membrane between a gas column and a gas-saturated liquid was studied as a function of depth. In another report, Turcotte and Oxburgh (*3*) suggested that the exponential dependence of the concentration of radioactive heat sources on depth observed in near-surface rocks by Lachenbruch (*4*) could be explained simply in terms of the Boltzmann factor of equilibrium statistical mechanics. I develop here the equilibrium criteria for solutions in the presence of a gravitational field so that both sets of phenomena are described.

The logical structure of equilibrium thermodynamics in the presence of gravitational fields is based on the addition of a term ψdm to the usual Gibbs expression for the differential of the internal energy. Here, ψ is the gravitational potential and dm the change in mass in the region considered. The inclusion of this term assures proper bookkeeping of the total energy when mass dm is moved from one region to another, with the resulting energy change, $(\psi_2 - \psi_1) dm$, in accordance with the definition of gravitational potential. Since dm for a mixture is the sum of terms $M_i dn_i$ over all components i, where M_i is the molecular weight and n_i is the number of moles of i, the Gibbs equation with gravity is identical to the Gibbs equation without gravity, except that with gravity $\mu_i + M_i\psi$ replaces the chemical potential, μ_i. It is a straightforward consequence of the second law of thermodynamics that at equilibrium in the absence of a gravitational field μ_i is the same in all regions of the system which can interchange components i (*5*, p. 93). The identical proof with gravity therefore shows

$$\mu_i + M_i\psi = \text{constant} \qquad (1)$$

to be the generalized equilibrium criterion, along with the usual constancy of the temperature, T.

From Eq. 1 the criterion for hydrodynamic equilibrium follows if we insert the derivative of Eq. 1

$$d\mu_i = -M_i d\psi$$

into the Gibbs-Duhem equation

$$Vdp - \sum_i n_i d\mu_i = 0$$

for a small region V centered on the point of interest. Division of the result by V yields

$$dp + \rho d\psi = 0 \qquad (2)$$

(where p is the pressure and ρ is the density of the medium at any depth), the criterion for lack of bulk fluid flow. This criterion can be integrated for gases if we substitute

$$\rho = m/V = pM(y)/z(y)RT$$

where z is the compressibility factor for the gas at the point y, M is the weight of an Avogadro number of molecules taken about the point y, R is the gas constant, and T is the absolute temperature. If $\psi = -gy$, where y is the depth, g is the magnitude of the gravitational field, and in the ideal gas approximation where $z = 1$, the barometric formula results:

$$p_{\text{gas}}(y) = p_{\text{gas}}(0) \exp(Mgy/RT) \qquad (3)$$

where M is the average molecular weight of the gas between 0 and y. The criterion, Eq. 2, may also be integrated for liquids if one knows how ρ changes with pressure and such concentration changes as occur. For dilute, incompressible solutions, ρ is constant, and

$$p_{\mathrm{liq}}(y) = p_{\mathrm{liq}}(0) + \rho g y \tag{4}$$

is the familar result of the integration.

In order to find the concentrations of the various species as functions of depth, one writes

$$d\mu_i = v_i dp + \sum_{j=2}^{r} \left(\frac{\partial \mu_i}{\partial X_j} \right)_{T,p,X_k,k = 1,j} dX_j \tag{5}$$

at constant T, where v_i is the partial molar volume of the gas and r is the number of components. We take X_1 to be the mole fraction fixed by $\Sigma_i X_i = 1$. Equation 5 can be integrated to find $\mu_i(y) - \mu_i(0)$ over any path between [$p(0)$, conc 0] and [$p(y)$, conc y] along which the integrand is known. If we choose the path [$p(0)$, conc 0]$\rightarrow$[$p(0)$, conc y]$\rightarrow$[$p(y)$, conc y], and equate the result to $M_i[\psi(y) - \psi(0)]$ from Eq. 1, the result is

$$-M_i\,[\psi(y) - \psi(0)] = \int_{p(0)}^{p(y)} v_i\,(\text{conc } y)\; dp + \mu_i[T, p(0), \text{conc } y] - \mu_i[T, p(0), \text{conc } 0] \tag{6}$$

With the usual definition of activity or fugacity coefficient, the last two terms are cast into the form

$$-M_i\,\psi\,(y) = \int_{p(0)}^{p(y)} v_i\,(\text{conc } y)\; dp + RT \ln \frac{\gamma_i[T, p(0), \text{conc } y]X_i(y)}{\gamma_i[T, p(0), \text{conc } 0]X_i(0)} \tag{7}$$

where $\psi(0)$ has been set equal to zero. Equation 7 is the exact relationship between concentration and gravitational potential. For gases the γ_i's represent the fugacity coefficients of substance i; for liquids they are the activity coefficients.

It is often possible to simplify Eq. 7. For single-component gases, for gas mixtures that are nearly ideal at $p(0)$, and for gas mixtures for which the fugacity coefficients at $p(0)$ change very little over the concentration range involved, the ratio of γ_i's is unity. Furthermore, if the gas mixture is ideal,

$$v_i = RT/p$$

the integration may be carried out, and, with use of Eq. 3, we obtain

$$M_i g y = M g y + RT \ln \frac{X_i(y)}{X_i(0)} \tag{8}$$

For liquid solutions, the ratio of γ_i's is unity if substance i obeys Henry's law up to the concentrations of interest (Raoult's law is, of course, a special case of Henry's law). For nearly incompressible solutions the integration may be carried out, and, with use of Eq. 4, we obtain

$$M_i g y = v_i \rho g y + RT \ln \frac{X_i(y)}{X_i(0)} \tag{9}$$

On the basis of the foregoing mathematical analysis, it is now possible to analyze the questions raised by Fenn, which seem to be the following: Suppose a column of gas and a column of gas-saturated liquid were in equilibrium at all depths through a membrane permeable only to the gas. The pressure in the gas-filled tube is given simply by the barometric formula, Eq. 3. In the liquid tube, on the other hand, pressure is given by Eq. 4 and concentrations are given by Eq. 9. How can gas solubility, buoyancy, and the hydrostatic head combine so as to yield Eq. 3 for equilibrium gas pressure? Is there a relationship, rigorously derived, that couples these quantities? If not, could perpetual motion occur? In particular, how does the linear hydrostatic head of Eq. 4 yield the exponential gas pressure, Eq. 3?

Fenn's questions are best answered by deriving the relationship between the gas pressures and the concentrations at 0 and at y. All of my results have arisen from the equilibrium criterion, Eq. 1; in this case since ψ has the same value on both sides of the membrane, so must μ_i. For the single-component gas visualized by Fenn, in the approximations used above, the right-hand side of Eq. 7 for gases and for liquids must be equal, with the result

$$\frac{p_{i,\,\mathrm{gas}}(y)}{X_{i,\,\mathrm{liq}}(y)} = \frac{p_{i,\,\mathrm{gas}}(0)}{X_{i,\mathrm{liq}}(0)} \exp \frac{v_{i,\,\mathrm{liq}}\rho_{\mathrm{liq}} g y}{RT} \tag{10}$$

The ratio of $p_{i,\,\mathrm{gas}}$ to $X_{i,\,\mathrm{liq}}$ is simply the Henry's law constant for substance i. In this light, Eq. 10 may be recognized as an adaptation of the Krichevsky-Kasarnovsky equation (*6*) for the pressure dependence of the Henry's law constant, where the pressure enhancement is caused by the hydrostatic head on the liquid. For O_2 dissolved in water, M_i happens to equal $v_i\rho$, and Eq. 9 shows that $X(O_2)$ is independent of depth. In this case, the X_i's drop out of Eq. 10, the $v_i\rho$ is replaced by M_i, and Eq. 10 generates Eq. 3. For other gases where $M_i \neq v_i\rho$, buoyancy concentrates the gas either at the top or at the bottom of the liquid, as described by Eq. 9. It is clear from the insertion of Eq. 9 into Eq. 10 that this concentration is precisely such as to preserve the validity of Eq. 3 for the equilibrium gas pressure.

It should not be surprising that the effect of pressure in enhancing p_i/X_i is exponential rather than linear; the well-known equation of Poynting (*5*, p. 221) shows that the partial vapor pressure of a constituent is enhanced exponentially with applied pressure. A crude, heuristic argument might be presented to justify this conclusion: The temperature dependence of the vapor pressure in an ideal solution is exponential in the enthalpy of vaporization (where T and T_0 are two different temperatures)

$$p_i(T) = X_i p_i^0(T) = X_i p_i^0(T_0) \exp \left[\frac{-\Delta h_{\mathrm{vap}}}{R} \left(\frac{1}{T} - \frac{1}{T_0} \right) \right] \tag{11}$$

according to Raoult's law and the Clausius-Clapeyron equation. This exponential dependence arises because the molecules are attracted by their neighbors at the liquid surface by a potential energy Δh_{vap}. Only fluctuations which give at least this much energy to a molecule can result in its freeing itself from the liquid to enter the vapor. The nature of the high-energy tail of the energy distribution leads to the exponential dependence. If the pressure on a solution is now increased by an amount $\rho g y$, the net effect is to increase the average force acting on the dissolved gas molecules that tends to push them out of solution. The effective cross-sectional area multiplied by the effective distance through which this enhancing force acts is of the order of v_i. Thus, the energy $v_i \rho g y$ is available to help overcome the enthalpy of vaporization. For fixed T, Eq. 11 shows that an effective reduction in the enthalpy of vaporization by $v_i \rho g y$ leads to something resembling Eq. 10, with its exponential dependence.

It is now clear that the complex correlation of properties noted by Fenn represents an equilibrium condition. The overriding generalization from experience is that the properties of isolated systems do stop changing, and equilibrium is eventually reached. The relationships among the properties in the final equilibrium states are often complicated because the decay to equilibrium left them that way, not because they combine in any complicated and marvelous way to achieve equilibrium.

On the basis of the mathematical

analysis presented here, it is also possible to analyze the suggestion of Turcotte and Oxburgh that the observed exponential depth dependence of radioactive heat sources in the earth's crust arose from their equilibrium distribution under some appropriately fluid conditions. If their idea were correct, my Eq. 7, or approximately Eq. 9, would describe the result. This result follows directly from equilibrium thermodynamics; there is no need to employ the Boltzmann factor from statistical mechanics. Furthermore, the quantity in parentheses in their equation 3, the result of their hypothesis, has the wrong sign and the wrong density in the denominator; according to my Eq. 9, their result should read

$$\frac{X_i(y)}{X_i(0)} = \frac{H}{H_s} = \exp\left[\frac{(M_i - v_i\rho)gy}{RT}\right] = \exp\left(\frac{\Delta\rho M_i gy}{\rho_i RT}\right) \qquad (12)$$

where H is the radioactive heat released in unit volume per unit time at the depth y; H_s is the value of H at the surface, where $y = 0$; $\Delta\rho = \rho_i - \rho$; ρ_i is the density of the molecular assembly under consideration; and ρ is the density of the solution. As Turcotte and Oxburgh observe, this distribution should hold for all chemical species frozen into an equilibrium distribution at a constant temperature and then not subsequently disturbed, provided they obey Henry's law and the solution is incompressible.

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References and Notes

1. W. O. Fenn, *Science* **176**, 1011 (1972). On the basis of my reading of Fenn's report, I believe the following changes should be made: line 4 after equation 1, change "g" to "mole"; equation 2, change "*Mx*" to "*Mgx*"; line 10 after equation 3, insert "any" after "at."
2. T. Enns, P. F. Scholander, E. D. Bradstreet, *J. Phys. Chem.* **69**, 389 (1965).
3. D. L. Turcotte and E. R. Oxburgh, *Science* **176**, 1021 (1972).
4. A. H. Lachenbruch, *J. Geophys. Res.* **75**, 3291 (1970).
5. F. C. Andrews, *Thermodynamics: Principles and Applications* (Wiley-Interscience, New York, 1971).
6. I. R. Krichevsky and J. S. Kasarnovsky, *J. Amer. Chem. Soc.* **57**, 2168 (1935); B. F. Dodge and R. H. Newton, *Ind. Eng. Chem.* **29**, 718 (1937); J. M. Prausnitz, *Molecular Thermodynamics of Fluid-Phase Equilibria* (Prentice-Hall, Englewood Cliffs, N.J., 1969), section 8.3.
7. I thank R. S. Coe for calling the report by Turcotte and Oxburgh (*3*) to my attention.

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Ragweed Hay Fever: Genetic Control and Linkage to HL-A Haplotypes

Abstract. *Clinical ragweed pollenosis (hay fever) and IgE antibody production specific for antigen E (the major purified protein antigen from ragweed pollen extract) correlated closely with HL-A haplotypes in successive generations of seven families. HL-A associated IgE antibody responsiveness was antigen specific and extended also to IgE antibody production. These data indicate an immune response (Ir) gene specific for antigen E necessary but not sufficient for the development of hay fever. This appears to be the first documentation of an Ir gene in man.*

Classical studies in clinical allergy (*1*) have shown a preponderence of atopic allergic diseases in successive generations of certain families. These statistical data have been interpreted as indicating a genetic predisposition to the later development of these diseases (*1*), although the nature of genetic factors involved has not been identified. The present study is on ragweed pollenosis (hay fever), an example of an allergic disease mediated by IgE antibodies (reagins) (*2*) to airborne allergens (pollen particles). Genetic studies on reagin (IgE) production in inbred strains of mice have demonstrated two kinds of genetic controls of reagin production (*3*). One genetic factor permits the production of high serum levels of reagin to many antigens (*3*). The other control system is by genes at a locus (or loci) closely linked to the H-2 major histocompatibility system, termed Ir (or immune response) genes (*4*). The Ir genes control immune responsiveness to synthetic polypeptide antigens and to minute doses of protein antigens (*4, 5*). This system shows antigen specificity. In most mouse strains, reagin production is a prominent part of the immune response (*6*). Ragweed hay fever in man shows many features similar to these immune response systems in the mouse (*6*). A small percentage of people exposed to minute doses of ragweed pollen particles develop an immune response in which IgE antibody is prominent. Antigenic specificity of ragweed hay fever is largely toward antigen E, a purified protein derived from ragweed pollen extract (*7*). Accordingly, we suggested that one kind of genetic control of ragweed hay fever might be by Ir genes specific for antigen E (*8*). We now report studies supporting this idea.

Seven families in which ragweed hay fever occurred in more than one member were studied for clinical ragweed hay fever, IgE response to antigen E, and HL-A haplotype (*9*). Figure 1 depicts one of the seven families. In this family, four of six (67 percent) family members having the HL-A1, HL-A8(1,8) haplotype had intense immediate wheal-and-flare skin reactivity to antigen E in dilute solutions, indicating IgE antibody (*9*), and severe ragweed hay fever. Neither of the two subjects having the other HL-A haplotype of the propositus (HL-A10,12) had immediate skin reactivity to antigen E or clinical ragweed hay fever. Of the blood relatives of the propositus who lacked the 1,8 haplotype, none of the seven had ragweed hay fever. Six of the seven did not have skin reactivity to antigen E. One of the seven (subject 11, a grandson of the propositus) had relatively weak skin reactivity to antigen E. In this exceptional case, another haplotype correlating with IgE antibody responsiveness to antigen E was inherited from the maternal side of the family. Table 1 and Fig. 1 show that the maternal grandfather, a maternal uncle, the mother, and subject 11 had the HL-A9,x haplotype, and that subject 11, his maternal grandfather, and his uncle had weak skin reactivity to antigen E without clinical hay fever.

The data for the seven families are totaled in Table 2. Of 26 family members having the hay fever–associated haplotypes, 20 members (77 percent) had ragweed hay fever and intense skin reactivity to antigen E (Table 2). By contrast, none of the 11 family members who had the other haplotypes of the propositi (and lacked the hay fever–associated haplotype) had clinical ragweed hay fever. Of these 11, 10 did not have skin reactivity to antigen E, and 1 had relatively weak skin reactivity to antigen E. This difference in the frequency of IgE antibody responsiveness to antigen E (and clinical ragweed hay fever) between the family members having the hay fever–associated haplotype and the family members having the other haplotype of