added. The mixture was heated at reflux for one hour, and the reaction mixture concentrated to dryness. The residue was taken up in 50 ml. of 1.2 M hydrochloric acid and heated on a water-bath at 40–50° for 15 minutes. The mixture was concentrated to dryness under reduced pressure in a water-bath at 50°. The residue was dispersed in 30 ml. of water, and the insoluble phthalylhydrazide removed by filtration. The aqueous solution, on dilution with 75 ml. of 95% ethyl alcohol, precipitated 2.9 g. of carnosine hydrochloride as an amorphous, hygroscopic solid. It was converted to carnosine by passing an aqueous solution of the hydrochloride through an ion exchange column containing Deacidite. The aqueous eluate was concentrated to dryness and the residue was recrystallized from aqueous alcohol to give 0.6 g. of carnosine.

Anal. Calcd. for $C_9H_{14}O_3N_4$: N, 24.7. Found: N, 24.5.

(**Method B**).—The procedure was a modification of that described by Shuman and Boissonnas.[4d] To 1.78 g. of phthalylcarnosine (0.005 mole), there was added 25 ml. of 95% ethyl alcohol, 0.5 g. of triethylamine and 1.55 g. of phenylhydrazine. The mixture was refluxed for three hours on a water-bath. At the completion of the heating period, the clear yellow solution was cooled, and acidified with 1 g. of glacial acetic acid, and the mixture poured into 80 ml. of methyl ethyl ketone. An amorphous precipitate was obtained which was dissolved in 5 ml. of water and reprecipitated by the addition of 75 ml. of 95% ethyl alcohol. The dried product weighed 0.63 g., and after recrystallization from aqueous ethyl alcohol, 0.41 g. of carnosine was obtained.

DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
YALE UNIVERSITY SCHOOL OF MEDICINE
NEW HAVEN, CONNECTICUT

Stereochemistry of 1,4-Addition. II. The Bromination of Butadiene

BY KURT MISLOW

RECEIVED NOVEMBER 28, 1952

A recent paper[1] reports the 1,4-adduct of bromine and butadiene, 1,4-dibromo-2-butene (m.p. 53°), to have the *cis* configuration. This claim rests on the observed Raman frequency of 1655 cm.$^{-1}$, associated with *cis*-ethylenic double bonds,[2] and is the basis for the assumption that butadiene enters into reaction with bromine in the "bent" or s-*cis* form.

It has been shown that a frontal transition state cannot be of any appreciable importance in the 1,4-addition of chlorine to butadiene[3]; the implied claim that this argument does not apply in the case of bromine addition would therefore be of considerable interest. The following observations may however be marshaled as convincing evidence in favor of the identity of 1,4-dibromo-2-butene (m.p. 53°), I, with *trans*-1,4-dibromo-2-butene. (a) The infrared spectrum of I exhibits a pronounced and characteristic[4] *trans* peak near 10.3 μ, absent in the saturated analog.[5]

(b) Lithium aluminum hydride reduction of I affords *trans*-2-butene, as evidenced by conversion to *meso*-2,3-dibromobutane.[6] The present author has repeated this experiment and obtained *meso*-2,3-dibromobutane, b.p. 46° (14 mm.), $n^{25}\text{D}$ 1.5088 (repd.[7] $n^{25}\text{D}$ 1.5091).

(c) The dipole moment of I, 1.63 D, is similar to that of *trans*-1,4-dibromo-2,3-dimethyl-2-butene, 1.72 D, but smaller than that of the *cis*-isomer 2.49 D.[8]

(d) A *cis*-1,4-dibromo-2-butene (II), prepared from authentic *cis*-2-butene-1,4-diol,[9] differs from I in a manner characteristic[4a] of the relative properties of *cis* and *trans* isomers. Thus, the melting point of I is higher than that of II, II is thermally unstable with respect to I, and I and II give different 1,2,3,4-tetrabromobutanes, m.p. 116 and 39°, respectively.

The evidence here adduced compels us to maintain that as yet no satisfactory experimental basis exists for the view of frontal attack in the 1,4-addition of halogen to butadienes.[10] Equally, the tetrabromides, m.p. 116 and 39°, must be assigned the *meso* and racemic configurations, respectively, the claim[1] to the contrary notwithstanding.

---

(1) Ya. M. Slobodin and S. A. Zaboev, *Zhur. Obshchei Khim.* (*J. Gen. Chem., U. S. S. R.*), **22**, 603 (1952).

(2) *E. g.*, N. Sheppard and D. M. Simpson, *Quart. Revs.*, **6**, 1 (1952).

(3) K. Mislow and H. M. Hellman, THIS JOURNAL, **73**, 244 (1951).

(4) *E.g.* (a) L. Crombie, *Quart. Revs.*, **6**, 101 (1952); (b) L. Crombie, *J. Chem. Soc.*, 2997 (1952); (c) F. Sondheimer, THIS JOURNAL, **74**, 4040 (1952); (d) K. Mislow, *ibid.*, **74**, 5155 (1952).

(5) A Baird Model B instrument with 0.1-mm. cells was employed. In this connection, the assistance afforded by correspondence with Dr. Ralph Nusbaum and his staff, Spectroscopy Section, Atomic Energy Project, U. C. L. A., Los Angeles, Calif., is gratefully acknowledged.

(6) L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

(7) R. T. Dillon, W. G. Young and H. J. Lucas, *ibid.*, **52**, 1953 (1930).

(8) O. J. Sweeting and J. R. Johnson, *ibid.*, **68**, 1057 (1946).

(9) A. Valette, *Ann. chim.*, [12] **3**, 644 (1948).

(10) Some recent developments pertaining to this concept as originally expressed (ref. 3): the 1,4-addition of sulfur dioxide to terminally substituted butadienes involves the s-*cis* form of butadiene (O. Grummitt and J. Splitter, THIS JOURNAL, **74**, 3924 (1952)); halonium ions can be incorporated in a stable symmetrical 5-membered ring as part of a diphenyl system (R. B. Sandin and A. S. Hay, *ibid.*, **74**, 274 (1952)); the argentation constants of monoargentated *cis*-1,2-diiodoethylene and *o*-diiodobenzene are indicative of the existence of symmetrical 5-membered onium rings (L. J. Andrews and R. M. Keefer, *ibid.*, **73**, 5733 (1951)).

DEPARTMENT OF CHEMISTRY
NEW YORK UNIVERSITY
NEW YORK, N. Y.

D-Glucuronolactone Isonicotinyl Hydrazone

BY PETER P. T. SAH

RECEIVED OCTOBER 1, 1952

D-Glucuronolactone isonicotinyl hydrazone, a new compound with comparatively low toxicity and very high antitubercular activity *in vitro* as well as *in vivo*,[1] may be prepared easily by the following procedure.

D-Glucuronolactone (Eastman Kodak Co., 88 g.) was placed in a 3-l. round-bottomed flask and covered with 1.5 liters of methyl alcohol (acetone-free). The mixture was boiled gently on the steam-bath for 10 minutes when a clear solution was obtained. To the hot solution, isonicotinic acid hydrazide (Pfizer, 70 g.) was added all at once. The mixture was boiled vigorously for 10 minutes and the clear solution filtered without suction through a piece of lens paper into a 2-l. erlenmeyer flask. After standing for 24 hours at room temperature, the beautiful crystals (white rods and narrow plates) were filtered off with suction, washed with a small amount of methyl alcohol, and sucked completely to dryness. The product was dried in a vacuum desiccator for 3 days; yield 148 g. The product thus ob-

---

(1) Biological tests were performed by W. B. Sutton of the Lilly Research Laboratories, Indianapolis, Indiana, and the results later confirmed by Dr. E. G. Roberts of Stanford University School of Medicine. The new drug is now undergoing clinical trial. Results will be reported elsewhere.

tained is already very pure. It may be recrystallized from a large amount of methyl or ethyl alcohol (absolute). The recrystallized product showed the same physical properties as the unrecrystallized.

D-Glucuronolactone isonicotinyl hydrazone thus prepared is in the form of white plates and rods from methyl alcohol or needles from absolute ethyl alcohol. On heating, it charred and decomposed with foaming between 150 and 160° without any sharp melting point. The decomposition point depends on the rate of heating and the type of apparatus used. The new compound is very soluble in water from which it cannot be recrystallized. It is practically insoluble in cold methyl or ethyl alcohol but slightly soluble in these boiling solvents (100 cc. of methyl alcohol dissolves about 1.2 g. of the product at 66°).

Anal. Calcd. for $C_{12}H_{13}O_6N_3$: C, 48.79; H, 4.45; N, 14.24. Found: C, 48.58, 48.63; H, 4.33, 4.29; N, 14.51, 14.48.

UNIVERSITY OF CALIFORNIA
COLLEGE OF PHARMACY
SAN FRANCISCO, CALIFORNIA

On Salt Effects and the Temperature Coefficients of Solubility of Benzoic and Phenylacetic Acids in Aqueous Solutions

BY MARTIN A. PAUL

RECEIVED NOVEMBER 14, 1952

Recent publications call attention to the anomalous effect of temperature on the solubility of benzoic acid in water and in aqueous salt solutions.[1,2] The anomalies may be briefly summarized as follows.

(1) The solubility s_0 in water fails to satisfy a linear relationship between log s_0 and $1/T$, such as would be expected of an ideal dilute solution if the heat of solution were not exceptionally temperature sensitive; it increases instead at a much more accelerated rate with increasing temperature.[3]

(2) The solubility s in aqueous salt solutions for a particular salt fails to satisfy the Setschenow equation

$$\log (s_0/s) = K'm_s \qquad (1)$$

Instead, the parameter K' called for by this equation, which is quite generally satisfied by slightly soluble non-electrolytes, shows a tendency to decrease in magnitude with increasing concentration m_s of the electrolyte, this tendency being more marked at higher than at lower temperatures.

(3) The total effect of a given salt on the solubility, whether it salts-out or salts-in the benzoic acid, appears to increase markedly with increasing temperature, in contrast with the rather slight decrease in the salt effect normally observed for other slightly soluble non-electrolytes.

Similar anomalies are shown by phenylacetic acid,[1] with the further anomaly that if one assumes both phenylacetic and benzoic acids to be ideal solutes, then the effects of salts on their respective solubilities appear to differ in magnitude rather more than one would expect in view of their close similarity in molecular size and structure.

These anomalies receive a consistent explanation, as pointed out by Long and McDevit,[4] if one supposes that the solute is not an ideal solute, but deviates from Henry's law in the sense that its activity coefficient with respect to the infinitely dilute solution decreases with increasing concentration. It then "salts-in" itself, so to speak, at the increased concentrations normally accompanying the higher temperatures; the apparent effects of electrolytes on the solubility are thereby enhanced, because any appreciable change in the solute's concentration normally associated with the presence of the electrolyte is accompanied by a further change in the same direction as a result of the changing self interaction. It should be noted that deviation from Henry's law is a natural consequence of failure of the solute to follow Raoult's law, that is, failure of its activity to decrease in exact proportion to its mole fraction over the entire composition range.[5] The only special point at issue is whether such deviations can indeed become significant at the solute concentrations attained in the cases here under consideration.

By making certain simplifying assumptions, we may in fact use the deviation of the temperature coefficient of solubility from ideal-dilute-solution behavior in the pure solvent (as would be embodied by a linear relationship between log s_0 and $1/T$) to calculate a self-interaction parameter for the solute. Such a parameter, k_i', is defined by the first term in a series expansion of log γ' as a function of the molality, m_i

$$\log \gamma' = k_i'm_i \qquad (2)$$

where γ' represents the molal activity coefficient referred to infinite dilution in the pure solvent, water.[6] Let us assume that such an expression can be made to fit the data over the concentration ranges of interest (up to about 0.3 m in the case of benzoic acid and 0.7 m in the case of phenylacetic acid), and that furthermore we may neglect the variation of ΔH, the enthalpy of solution at infinite dilution, with temperature. Then from the thermodynamic equation

$$\frac{\mathrm{d} \ln (s_0\gamma')}{\mathrm{d}T} = \frac{\Delta H}{RT^2} \qquad (3)$$

it follows that

$$\log s_0 + k_i's_0 = -\frac{\Delta H}{2.303RT} + C \qquad (4)$$

where s_0 represents the molal solubility at absolute temperature T and C is an integration constant.

---

(1) T. J. Morrison, *Trans. Faraday Soc.*, **40**, 43 (1944).

(2) J. O'M. Bockris, J. Bowler-Reed and J. A. Kitchener, *ibid.*, **47**, 184 (1951).

(3) See ref. 2, where the empirical equation, ln $s_0 = A + 0.0357\ T$, is given for the molal solubility between 25 and 85° in water containing 0.01 m sodium benzoate to repress ionization. If benzoic acid were an ideal solute, the implied enthalpy of solution would have the form 0.0357 RT^2, corresponding to a heat capacity difference between solute in infinitely dilute solution and in the pure crystalline state of magnitude 0.142 T cal./mole deg. While the heat capacity of crystalline benzoic acid is 42.5 and that of the pure liquid, 63.2 cal./mole deg. (at the melting point, from data quoted in the "International Critical Tables"), it seems likely that the partial molal heat capacity in dilute aqueous solution is much closer to that of the crystalline solid, since the comparatively high value for the pure liquid no doubt corresponds with extensive dimerization undergoing decrease with rising temperature.

(4) F. A. Long and W. F. McDevit, *Chem. Revs.*, **51**, 119 (1952).

(5) This is made clear in the discussion and diagram given by J. H. Hildebrand and R. L. Scott, "The Solubility of Nonelectrolytes," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1950, p. 12.

(6) See ref. 4; primes will be used to distinguish symbols based on moles per kilogram of water as concentration measure from corresponding symbols used by Long and McDevit based on moles per liter of solution. The "solvent" in the present instance is actually a 0.01 m aqueous solution of sodium benzoate or sodium phenylacetate, respectively.