ethers. A preferential rearrangement of the α-ether III has proved feasible, however. When held at 120° for 18 hours III undergoes rearrangement with the appearance of a deep blue ferric chloride test; a sample of pure IV, under the same conditions, develops only a very faint ferric chloride test. Claisen alkali extraction of the preferentially rearranged α-ether preparation permits the isolation of relatively pure rearranged α-ether, V, b.p. 95–96° at 0.18 mm; $n^{20}D$ 1.5266. Hydrolysis of V yields an acid, VI, m.p. 102.5–103°, *not identical* with the corresponding acid from the rearranged γ-ether, m.p. 115–116°[3], mixed m.p. 72–94°. *Anal.* of VI, calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.33; Found, C, 70.68; H, 7.58. Ozonolysis of V produces formaldehyde in amounts corresponding to 84 ± 8% rearrangement product with a terminal methylene group. Infrared spectra likewise confirm the terminal methylene group of V.

The generally accepted idea concerning the course of the *para*-Claisen rearrangement, *i.e.*, that the rearrangement proceeds in a way that allows equilibration of the migrating allylic system,[4,5,6] appears, therefore, erroneous; instead the rearrangement proceeds without inversion and must involve partial bonding of a sort which maintains, or restores, the original structure of the migrating fragment. Our findings accord with the results of Ryan and O'Connor[1] and with observations made by Marvell on a comparable pair of ethers.[7]

This work received support from the Research Corporation and the American Academy of Arts and Sciences.

(4) D. S. Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 3.

(5) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 548.

(6) P. D. Bartlett, "Organic Chemistry, an Advanced Treatise," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 72.

(7) Dr. E. N. Marvell, private communication.

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RECEIVED APRIL 18, 1953

ISOLATION AND CHARACTERIZATION OF GLYCOPROTEINS FROM HUMAN PLASMA

Sir:

Human plasma contains several glycoproteins which are distinguished by their acid isoelectric points and their low molecular weights. Recently, the major component of these glycoproteins (the "acid glycoprotein," an α_1-globulin) has been described.[1,2]

The purpose of this note is to report the isolation from human plasma of a further group of such glycoproteins and to describe some of their properties.

The starting material for these studies was the supernatant solution of Fraction V obtained after precipitation of over 98% of the proteins from pooled normal human plasma, according to the low temperature–low salt–ethanol fractionation method.[3] The proteins (Fraction VI) in this supernatant solution were concentrated with the aid of zinc hydroxide and fractionated by a method described earlier.[2] Following removal of the proteins identical with those of Fraction V and of the acid glycoprotein from Fraction VI, the remaining protein fraction appeared essentially homogeneous in the ultracentrifuge ($S_{20,w}$ approximately 3) and by electrophoresis at *p*H 8.6. The electrophoretic mobility, $u = -4.2 \times 10^{-5}$ cm.^{2}/volt × sec., corresponded to an α_2-globulin.

In acetate buffer solutions of ionic strength 0.1, this α_2-protein fraction separated into three components. Taking advantage of the specific interaction with cations, these α_2-glycoproteins were fractionated from each other. Two proteins were rendered insoluble, at low ionic strength, *p*H 5.7 and at −5°, in a solution containing 19% ethanol by addition of barium acetate to give a final concentration of 0.02 *M*. Further addition of an equal amount of zinc acetate to the supernatant solution precipitated the third glycoprotein[4] which was isoelectric between *p*H 4.1 and 4.3. The optical density in a 1-cm. cuvette of a 1% solution ($E^{1\%}_{1\ cm.}$) of the latter protein was approximately 15 at 278 mμ. The "barium-insoluble" proteins were separated from each other under similar conditions. After exchange of the protein-bound barium ions for zinc ions, one of these plasma constituents was removed as insoluble zinc-lead-complex upon the addition of lead acetate. This "lead-insoluble" glycoprotein, showing an extinction coefficient of approximately 5 at 278 mμ, was denatured in acid phosphate buffer solutions as judged by the insolubility in 0.15 *M* NaCl solution. Its isoelectric point was found to be between *p*H 3.5 and 3.8. The protein which remained in solution and represented the major component of these α_2-glycoproteins, absorbed at 278 mμ with a coefficient ($E^{1\%}_{1\ cm.}$) of about 5. Its isoelectric point was near *p*H 4.

Further details of these investigations will be reported later.

The author wishes to thank Dr. J. A. McComb, director of the Division of Biologic Laboratories, Massachusetts Department of Health, for providing the starting material.

(1) H. E. Weimer, J. W. Mehl and R. J. Winzler, *J. Biol. Chem.*, **185**, 561 (1950).

(2) K. Schmid, THIS JOURNAL, **75**, 60 (1953).

(3) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, *ibid.*, **68**, 459 (1946).

(4) This was the only glycoprotein which was colored.

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THE REARRANGEMENT OF THE NEOPHYL RADICAL

Sir:

Although several examples of the migration of a phenyl group to an adjacent radical center have been published,[1] no evidence concerning the process by which this rearrangement takes place has been reported. It has now been found that, in contrast to similar ionic migrations which pro-

(1) (a) W. H. Urry and M. S. Kharasch, THIS JOURNAL, **66**, 1438 (1944); (b) S. Winstein and F. H. Seubold, Jr., *ibid.*, **69**, 2916 (1947); (c) W. H. Urry and N. Nicolaides, *ibid.*, **74**, 5163 (1952); (d) D. Y. Curtin and M. J. Hurwitz, *ibid.*, **74**, 5381 (1952).

ceed through a cyclic "phenonium ion,"[2] the neophyl (β-phenylisobutyl) radical is produced as a discrete entity which may either interact with the solvent to yield unrearranged product, in the present case *t*-butylbenzene, or undergo isomerization to the β-phenyl-*t*-butyl radical by a 1,2-phenyl shift with an activation energy of approximately 8 kcal./mole to yield isobutylbenzene. As in previous investigations, no migration of the methyl group was observed.

The di-*t*-butyl peroxide-catalyzed decomposition of β-phenylisovaleraldehyde[1b] was carried out at 130° with the pure liquid aldehyde (initially 6.4 molar) and with a 1.0 molar solution of the aldehyde in chlorobenzene, a solvent known to be relatively inert to free radical attack.[3] The butylbenzene fractions, obtained in yields of 71 and 57% in the two reactions, respectively, were separated first by steam distillation and then analyzed by fractionation through a Piros–Glover spinning-band column at a 100:1 reflux ratio, by refractive index of the fractions, and by comparison of the infrared spectra with known standards.

If a cyclic intermediate which could react at either of two sites with the solvent to yield the observed products were important, the ratio isobutylbenzene (R_2H)/*t*-butylbenzene (R_1H) should be independent of the concentration of the hydrogen atom donor, in this case the aldehyde. The observed ratio, however, increased from 1.3 to 4.0 as the aldehyde concentration was decreased. This result is in accord with the reaction sequence

$$R_1\dot{C}O \xrightarrow{k_1} R_1\cdot + CO$$

$$R_1\cdot + R_1CHO \xrightarrow{k_2} R_1H + R_1\dot{C}O$$

$$R_1\cdot \xrightarrow{k_3} R_2\cdot$$

$$R_2\cdot + R_1CHO \xrightarrow{k_4} R_2H + R_1\dot{C}O$$

$$\frac{(R_2H)}{(R_1H)} \approx \frac{d(R_2H)}{d(R_1H)} = \frac{k_3}{k_2(R_1CHO)}.$$

This mechanism is strengthened by the observation that the peroxide-catalyzed chlorination of *t*-butylbenzene yields only the unrearranged derivative,[5] attack of the neophyl radical on such a highly reactive substrate as chlorine being so rapid as to preclude rearrangement.

The decomposition of the pure aldehyde was carried out at 150°, 57 ± 3% rearrangement, and at 170°, 63 ± 3% rearrangement, as well as at 130°, 57 ± 3% rearrangement. This small change over a 40° interval indicates that the activation energy for migration of a phenyl group to an adjacent primary radical center is about the same as that for abstraction of a hydrogen atom from the aldehyde by the neophyl radical. In similar cases, E_a for the latter process is 7–8 kcal./mole,[6] so that E_a (migration) can hardly exceed 8 kcal./mole.

(2) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949).

(3) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, and W. E. Vaughan, *Faraday Society Discussions*, No. 10, 242ff and 315 (1951).

(4) That exact proportionality to the initial aldehyde concentration was not observed may be due to an increased amount of rearranged dimer in the reaction in chlorobenzene.

(5) (a) M. S. Kharasch and H. C. Brown, THIS JOURNAL, **61**, 2142 (1939); (b) M. S. Kharasch and A. T. Read, *ibid.*, **61**, 3089 (1939).

(6) R. K. Brinton and D. H. Volman, *J. Chem. Phys.*, **20**, 1053 (1952).

An estimate of the heat of isomerization of the neophyl radical may be made by means of the following cycle.

	ΔH, kcal./mole
$H\cdot + C_6H_5C(CH_3)_2CH_2\cdot \longrightarrow C_6H_5C(CH_3)_2CH_3$	−95.5[7]
$C_6H_5CH_2CH(CH_3)_2 \longrightarrow C_6H_5CH_2\dot{C}(CH_3)_2 + H\cdot$	+86.5[8]
$C_6H_5C(CH_3)_2CH_3 \longrightarrow C_6H_5CH_2CH(CH_3)_2$	+ 0.3[9]
$C_6H_5C(CH_3)_2CH_2\cdot \longrightarrow C_6H_5CH_2\dot{C}(CH_3)_2$	− 8.7

Further studies of this and related free radical processes, including gas phase experiments, are now in progress.

(7) Assumed to be as in neopentane; E. I. Hormatz and E. R. VanArtsdalen, *J. Chem. Phys.*, **19**, 778 (1951).

(8) Assumed to be as in isobutane; J. S. Roberts and H. A. Skinner, *Trans. Faraday Soc.*, **45**, 339 (1949).

(9) E. J. Prosen, W. H. Johnson, and F. D. Rossini, *J. Research Natl. Bur. Standards*, **36**, 455 (1946).

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ELECTROPHORETIC CONTRIBUTIONS TO THE DIFFUSION OF ELECTROLYTES

Sir:

The effect of electrophoresis on the diffusion coefficient of an electrolyte may be represented by the equation

$$D = (1 + c\partial \ln y_\pm/\partial c)(D^0 + \Delta_1 + \Delta_2 + \cdots + \Delta_n + \cdots)$$

where Δ_n represents the electrophoretic contribution involving the n^{th} power of the potential due to the "central" ion, and D^0 is the Nernst limiting value. In the theory due to Onsager and Fuoss[1] terms beyond Δ_2 are ignored, and the resulting formula is satisfactory for 1:1 electrolytes,[2] but fails to account for the experimental data for calcium chloride[3] and lanthanum chloride[4] even at higher dilutions. I have now obtained a general expression for Δ_n and have evaluated terms up to $n = 5$.

The expression may be abbreviated to

$$\Delta_n = (-1)^n \frac{F_n(\kappa a)}{|z_1 z_2|} \cdot \frac{(z_1^n t_2^0 + z_2^n t_1^0)^2}{\mathring{a}^n}$$

where $F_n(\kappa a)$ is a function only of κa and solvent properties, κa being the familiar dimensionless quantity of the Debye–Huckel theory; z_1 and z_2 are the algebraic valencies of cation and anion, respectively; t_1^0 and t_2^0 are the respective limiting transport numbers; and $\mathring{a}$ is the distance of closest approach of the ions, *expressed in Ångströms*. It turns out that $F_n(\kappa a)$ for aqueous solutions at 25° remains of a fixed order of magnitude (for a given κa) for all values of n up to at least $n = 5$. Hence the convergence of the series $\Sigma\Delta_n$ for small n is dependent upon the behavior of the function $(z_1^n t_2^0 + z_2^n t_1^0)^2/\mathring{a}^n$. It is easily seen that for 1:1 electrolytes with $\mathring{a}$ in the typical range of 3–5, convergence will be rapid. For higher valence

(1) See H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943.

(2) H. S. Harned and R. L. Nuttall, THIS JOURNAL, **69**, 736 (1947).

(3) H. S. Harned and A. L. Levy, *ibid.*, **71**, 2781 (1949).

(4) H. S. Harned and C. A. Blake, *ibid.*, **73**, 4255 (1951).