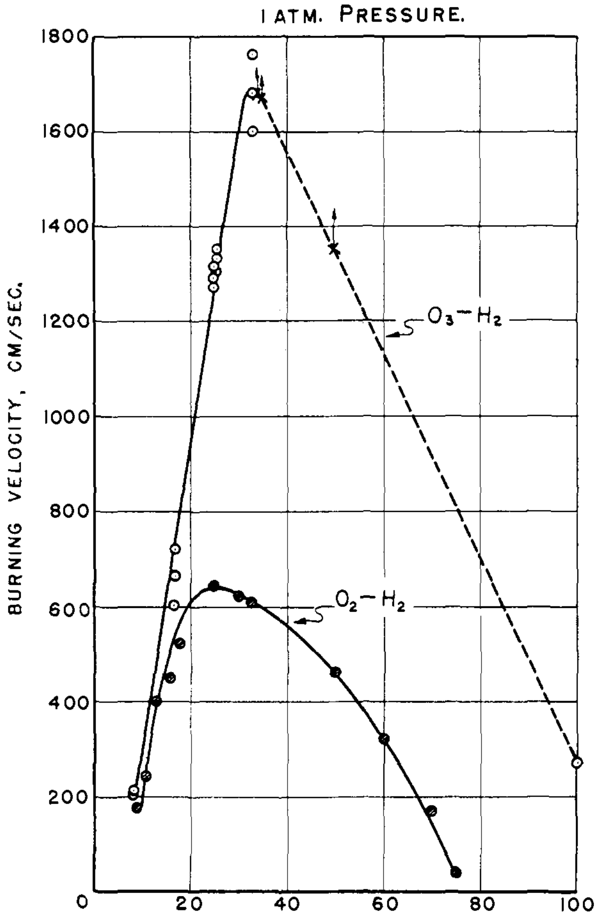

Fig. 1.—Burning velocities of $O_3 + H_2$ and $O_2 + H_2$ mixtures at 195°K. initial temperature and 1 atm. pressure.

tion front; it has not been possible as yet to burn such mixtures successfully.

The expected substantially faster burning velocity of the H_2–O_3 *vs.* the H_2–O_2 system has thus been proven experimentally. An intensive study of other O_3 flames is warranted.

THE RESEARCH INSTITUTE OF
TEMPLE UNIVERSITY
PHILADELPHIA 44, PA.
A. G. STRENG
A. V. GROSSE

RECEIVED MAY 2, 1957

THE CONFIGURATION OF BASE-DENATURED β-LACTOGLOBULIN[1]

Sir:

It has been shown by Cannan, Palmer and Kibrick[2] that titration curves of β-lactoglobulin, in acid and neutral solutions at 25°, obey the Linderstrøm-Lang equation,[3] with a value for the electrostatic interaction factor *w* which is reasonable for a molecule of molecular weight 40,000. Above *p*H 10, however, the titration curves were found to be steeper, indicative of a considerably smaller value of *w*. A change in the properties of this protein near *p*H 10 is in accord with the finding of Groves, Hipp and McMeekin[4] that β-lactoglobulin becomes denatured near this *p*H. The titration curve above *p*H 10 thus represents the behavior of the denatured protein.

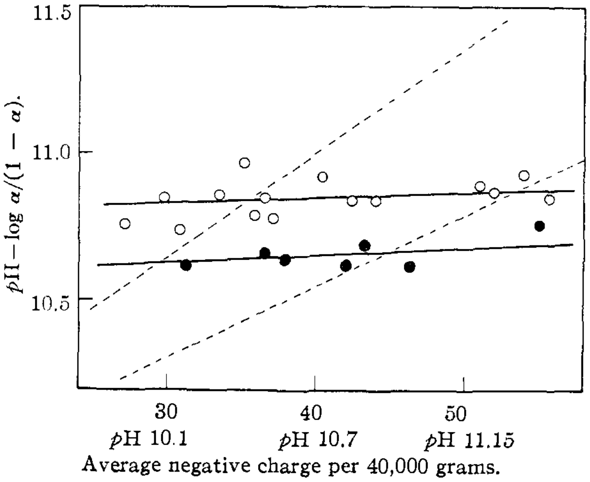

Fig. 1.—Titration of the phenolic groups of β-lactoglobulin at 25° and ionic strengths 0.08 (O) and 0.27 (●): the dotted lines show the predicted slopes for a compact sphere of molecular weight 35,000 to 40,000 at ionic strength 0.08 (upper line) and 0.27 (lower line). For a molecular weight of 17,500 the slopes of these curves would be reduced to about 0.6 of these values. The *p*H values are those at ionic strength 0.08; at ionic strength 0.27 the corresponding *p*H values are roughly 0.2 *p*H unit lower.

To investigate this behavior further, we have studied the dissociation of the phenolic groups of β-lactoglobulin, using the spectrophotometric method of Crammer and Neuberger.[5,6] The results are reported in the form of the logarithmic plot of Fig. 1.[7] The ordinate of such a plot represents the effective *pK* of the groups being titrated. According to any simple theory, such as the Linderstrøm-Lang theory, it should *increase* with increasing net negative charge because of the attractive force between this charge and the dissociating protons. In contrast to this prediction, Fig. 1 shows *p*H–log α/(1 − α) to be essentially independent of charge. This same phenomenon is served in serum albumin,[8] for the phenolic and amino groups above *p*H 11, and for the carboxyl

---

[1] This work was supported by research grant G-1805 from the National Science Foundation and by research grant RG-2350 from the National Institutes of Health, Public Health Service.

[2] R. K. Cannan, A. H. Palmer and A. C. Kibrick, *J. Biol. Chem.*, **142**, 803 (1942).

[3] K. Linderstrøm-Lang, *Compt. rend. trav. Lab. Carlsberg*, **15**, No. 7 (1924).

[4] M. L. Groves, N. J. Hipp and T. L. McMeekin, THIS JOURNAL, **73**, 2790 (1951).

[5] J. L. Crammer and A. Neuberger, *Biochem. J.*, **37**, 302 (1943).

[6] C. Tanford and G. L. Roberts, Jr., THIS JOURNAL, **74**, 2509 (1952); C. Tanford, J. D. Hauenstein and D. G. Rands, *ibid.*, **77**, 6409 (1955).

[7] The charge at a given *p*H is based on a molecular weight of 40,000 and was taken from the titration curves of Cannan, *et al.*[2] Above *p*H 10.8 the charges represent an extrapolation of their results. Neither the assumed molecular weight nor the accuracy of the extrapolation affects our conclusions, for *p*H–log α/(1 − α) is an experimental parameter independent of these variables, and we wish only to show that this parameter is virtually independent of charge.

[8] C. Tanford, J. G. Buzzell, D. G. Rands and S. A. Swanson, THIS JOURNAL, **77**, 6421 (1955).

groups below *p*H 4. It was interpreted as indicating that serum albumin exists below *p*H 4 and above *p*H 11 in an expandable configuration, resembling the configuration to be expected of a simple flexible polyelectrolyte with relatively few cross-links. In such a configuration an increase in charge is accompanied by an increase in charge separation, so that the force acting on the dissociating protons remains virtually unchanged.

Figure 1 thus indicates that above *p*H 10 β-lactoglobulin also exists in an expandable configuration. The work of Townend and Timasheff[9] suggests that, in addition, the molecular weight above *p*H 10 could well be much lower than 40,000. Dissociation by itself, however, will not account for the result observed. It would lead to a lower value of w (where the abscissa represents charge per *undissociated* molecule), but *p*H-log $\alpha/(1 - \alpha)$ would still increase markedly with increasing charge.

The titration curve of the phenolic groups was found to be reversible between *p*H 10 and 12. Experiments above *p*H 12, however, indicate that another change in configuration occurs there.

We wish to acknowledge the technical assistance of R. Berdo in these experiments, and to express our appreciation to Dr. T. L. McMeekin for providing us with the sample of β-lactoglobulin on which this work was carried out.

[9] R. Townend and S. N. Timasheff, THIS JOURNAL, **79**, July (1957).

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA
CHARLES TANFORD
SIGURD A. SWANSON

RECEIVED MAY 15, 1957

IBOGA ALKALOIDS. II.[1] THE STRUCTURES OF IBOGAINE, IBOGAMINE AND TABERNANTHINE

Sir:

The principal base of *Tabernanthe iboga Baillon*, the pentacyclic alkaloid ibogaine $C_{20}H_{26}N_2O$, has been shown to contain a 5-methoxyindole moiety,[1,2] but apart from the isolation of 3-methyl-5-ethylpyridine[3] no clue as to the nature of the hydroaromatic portion of the molecule is available. We have now found contrary to current belief that the C-alkyl[4] of ibogaine is a C-ethyl since propionic acid can be shown to be an important component of the volatile acids formed in the Kuhn-Roth determination.[5] This result eliminates from discussion the structure proposals for ibogaine[6] and voacangine[7] (a carbomethoxy ibogaine) both of which were considered to have a C-methyl. In contrast to the alkali fusion,[1,3] where ibogaine appears to be split in two, selenium dehydrogenation affords two heterocyclic bases containing all the carbons, both nitrogens and the methoxyl of the original alkaloid. One was a weakly basic compound, m.p. 208°; $\lambda_{\max}^{95\%\ \mathrm{alc}}$ (ϵ max) 226–8 mμ (34600), 308 mμ (16100), 340 mμ (20400); $\lambda_{\max}^{0.1N\,\mathrm{HCl}}$ (ϵ max) 317 mμ (25250). *Anal.* Calcd. for $C_{20}H_{22}N_2O$: C, 78.4; H, 7.2; N, 9.2; OMe, 10.1; 2CMe, 9.8. Found: C, 78.4; H, 7.5; N, 9.0; OMe, 10.1; NMe, 0.0; CMe, 6.7. Its chromophoric moiety was very similar to model $2,2^1$-aminophenylindoles, thus accounting for three of the four rings and all but five of the carbon atoms. The weakly basic nitrogen was found to be secondary since it gave a N-nitroso derivative, m.p. 196°, and it probably was hindered because its N-acetyl derivative, m.p. 246°, $\nu_{C=O}$ 1640 cm.$^{-1}$, $\lambda_{\max}^{95\%\ \mathrm{alc}}$ (ϵ max) 216 mμ (34580), 321-2 mμ (27,200) was resistant to hydrolysis by the usual methods (*cf.* the stability of N-acetyl-N-methyl-2,6-dimethylaniline[8]). The C-alkyl determination indicated two such groups one of which must have been a C-ethyl,[5] therefore at the most only two carbons were available to complete the fourth ring which must include the basic nitrogen since it is secondary and has no N-alkyl. The only structure which can be derived for this dehydrogenation product is II which contains a seven-membered ring C, the C-alkyls being placed so as to account not only for the observed properties (acetylation, infrared, oxidation) but also so that the formula Ia deduced from it for ibogaine should be consistent with other accumulated facts especially the products of the alkali fusion.[1,3]

The structure of the second selenium degradation product, the indoloquinoline III, m.p. 176°, follows from its analytical data, infrared and ultraviolet spectra, $\lambda_{\max}^{95\%\ \mathrm{alc}}$ (ϵ max) 237 mμ (39030), 276 mμ (43930), 298 mμ (22750), 333 mμ (5766), 349 mμ (2857); $\lambda_{\max}^{0.1N\,\mathrm{HCl}}$ (ϵ max) 219 mμ (27700), 230 mμ(28130), 269–71 mμ (43130), 296–7 mμ (27800), 310 mμ (19910), 327–35 mμ plateau (9450). *Anal.* Calcd., for $C_{20}H_{20}N_2O$: C, 78.9; H, 6.6; 3CMe, 13.8. Found: C, 78.5; H, 6.8; CMe, 8.8.

In view of the parallelism which has been demonstrated between the chemistry of ibogaine and its companion alkaloids,[4] tabernanthine can now be represented as Ib and ibogamine as Ic. In agreement with this deduction ibogamine on dehydrogenation with selenium affords products analogous to those obtained from ibogaine, *i.e.*, a weakly basic substance, II (MeO = H), m.p. 214° (*Anal.* Calcd. for $C_{19}H_{20}N_2$: C, 82.6; H, 7.3. Found: C, 82.4; H, 7.4), and a base III (MeO = H), m.p. 196–7°. *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.3; H, 6.6. Found: C, 83.2; H, 6.6. A confirmation of the proposed structures of the selenium degradation products has been provided by MacPhillamy, Lucas and Dziemian of these laboratories, who synthesized the indoloquinoline III (MeO = H) which

---

[1] E. Schlittler, C. A. Burkhardt and E. Gellért, *Helv. Chim. Acta*, **36**, 1337 (1953), this paper is regarded as part I of the series.

[2] M.-M. Janot, R. Goutarel and R. P.-A. Sneedon, *ibid.*, **34**, 1205 (1951).

[3] R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Compt. rend.*, **237**, 1718 (1953).

[4] The C-allyls recorded in the analytical data are presented as C-Me for convenience.

[5] The technique developed in these laboratories by Mr. L. Dorfman is a modification of that already used by H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955). By the same method we have shown a C-ethyl to be present in dihydrogelsemine, aspidospermine, ajmaline, tabernanthine and ibogamine.

[6] R. Goutarel, These Doct. ès Sciences, Paris, 1954.

[7] M.-M. Janot and R. Goutarel, *Compt. rend.*, **241**, 986 (1955). If the decarboxylation of voacangine to ibogaine does not involve a rearrangement then the most likely position for the carbomethoxy group is on the asterisked carbon in Ia.

[8] P. Friedländer and Brand, *Monatsh.*, **19**, 642 (1898).