for a sufficient length of time. The *p*H-gradient method is particularly useful for the analysis of very dilute solutions and appears to offer advantages over Macheboeuf's electrorheophoresis (*5*) because of its flexibility in directing the displacements of the bands and because of its avoiding excessive concentration of buffer salt on the paper.

H. HOCH
G. H. BARR
Department of Biophysics, Medical College of Virginia, Richmond

References and Notes

1. A. Kolin, *J. Chem. Phys.* 22, 1628 (1954).
2. This work was made possible by an A. D. Williams fellowship and research grant, Medical College of Virginia, and by funds provided under contract DA 49-007-MD-99 between the Office of the Surgeon General, Department of the Army, and the Medical College of Virginia, Richmond.
3. E. L. Durrum, *J. Colloid Sci.* 6, 274 (1951).
4. B. Swahn, *Scand. J. Clin. Lab. Invest.* 4, 98 (1952).
5. M. Macheboeuf, *Chem. Weekblad* 49, 237 (1953); M. Macheboeuf *et al., Bull. Soc. Chim. biol.* 35, 334 (1953).

8 April 1955

Direction of Ionic Addition to Olefinic Double Bonds

When the addition of an unsymmetrical molecule to an olefinic double bond begins with addition of a cation to the pi electrons (*1*), the direction of the addition can be simply explained, without the concept of hyperconjugation (*2*) or the assumption of polarity in the double bond (*3*). The cation tends to become finally joined to that one of the two unsaturated atoms from which an electron is less readily removed, except where this effect is overcome by electrostatic forces. As a general principle, two factors appear to control the ease of withdrawing an electron from an atom. One is the partial charge on the atom: the less positive and more negative the charge, the greater the ease of electron withdrawal. The other is the nature of attached atoms and groups: the more readily these atoms can supply charge to compensate for the withdrawal, the greater is the ease of withdrawal.

The fundamental basis for the proposed explanation is information on charge distribution obtained by methods recently described (*4*). It is possible to estimate what the partial charge on each atom of a molecule would be, if the only factor were the initial electronegativity differences and the process of equalization during combination (*5*). Similarly, the effect of adding a cation to a double bond may be estimated, assuming that the principle of electronegativity equalization is valid here. The detailed application of such partial charge information can best be illustrated by examples.

Consider an olefinic bond in an alkene. According to the theory, such a bond must always be electrically symmetrical (nonpolar), because an alkyl group contributes exactly the same partial charge to an unsaturated carbon as does hydrogen. However, alkyl groups are potentially more capable of contributing negative charge (are better reservoirs). When a cation—for example, a proton from CHl—adds to the pi electrons of an unsymmetrical olefin like propene, the charge may be considered as becoming distributed throughout the resultant carbonium ion by an adjustment of bond polarities, causing in effect an electron flow toward the adding proton. The partial charges on carbon and hydrogen in propene are -0.040 and 0.020 electron. In the carbonium ion they would be 0.055 and 0.119. The charge of 0.881 contributed to the proton would come 0.293 from the CH_2 side of the double bond and 0.586 from the CH_3CH side.

In order that a cation become finally attached by a covalent bond to one of the originally unsaturated carbon atoms, one of the electrons for the bond must be removed entirely from the other carbon. This removal quite logically can occur more readily from the carbon that has the greater reservoir of charge. As is indicated by the afore-mentioned relative charge contributions, this carbon is the center one of propene. The proton, accordingly, becomes permanently attached to the more hydrogenated carbon of the double bond. This leaves the central carbon with an unoccupied orbital, a ready acceptor of an electron pair of the chloride ion. Markownikoff addition to other unsymmetrical olefins may be explained similarly.

The opposite mode of addition may occur when a strongly electron-withdrawing group is attached to the side of the double bond that otherwise would be expected to serve better as an electron reservoir. The inductive effect of this group makes the removal of an electron from the unsaturated carbon nearer it more difficult. Hence, the cation becomes attached to this carbon, and the anion adds farther from the electronegative group. For example, in the α,β-unsaturated acid, CH_2=CHCOOH, each hydrogen bears a charge of 0.102 and each carbon, 0.042. Addition of a proton to the pi electrons would result in a carbonium ion in which a contribution of 0.803 electron would be made to the adding proton. The electron-withholding action of the oxygen prevents the central carbon from contributing more than 0.278, leaving 0.524 to be contributed by the CH_2 group. Accordingly, the proton here becomes attached to the less hydrogenated center carbon, and the adding anion joins the unsaturated carbon farther from the carboxyl group.

On the other hand, an electron-releasing atom such as silicon has the effect in an olefin that the adding cation becomes attached to the carbon farther from this atom. This occurs, for example, in hydrogen halide addition to $(CH_3)_3Si$—CH_2—CH=CH_2 (*6*).

Major exceptions to addition as explained in the foregoing paragraphs result when an atom attached directly to an olefinic carbon bears a relatively high partial charge. Then the electrostatic effect on the pi electrons appears dominant. One illustrative example is addition to vinyl chloride, CH_2=CHCl. Electrons should be more available from the CH_2 than from the CHCl. Explained on this basis, an adding cation should become attached to the chlorinated carbon. However, the partial charge of -0.238 on the chlorine appears sufficient to repel the pi electrons, making them actually more available at the opposite carbon. The double bond is thus permanently polarized, and it is the anion that becomes attached to the chlorinated carbon. An opposite illustration is the example of HCl addition to $(CH_3)_3Si$—CH=CH_2. Despite the electron-releasing action of the silicon, the addition is non-Markownikoff (*7*) and the proton becomes attached to carbon next to silicon. Evidently the dominant effect is the attraction of the pi electrons by the silicon, with its partial charge of 0.273.

None of the afore-mentioned factors is likely to be completely dominant except in extreme instances. The explanations offered are therefore intended to account for principal trends only.

R. T. SANDERSON
Department of Chemistry, State University of Iowa, Iowa City

References

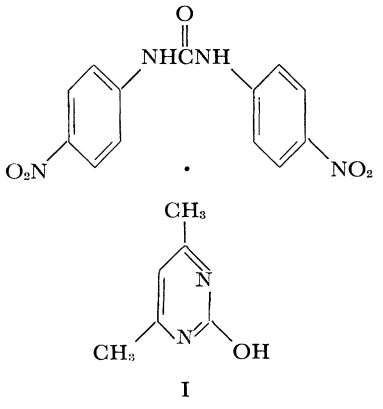
1. E. R. Alexander, *Principles of Ionic Organic Reactions* (Wiley, New York, 1950).
2. J. W. Baker, *Hyperconjugation* (Oxford Univ. Press, London, 1952).
3. A. R. Day, *Electronic Mechanisms of Organic Reactions* (American Book, New York, 1950).
4. R. T. Sanderson, *J. Chem. Educ.* 31, 2, 238 (1954); 32, 140 (1955); *Science* 121, 207 (1955).
5. ——— *J. Chem. Educ.* 29, 539 (1952).
6. L. H. Sommer, L. J. Tyler, F. C. Whitmore, *J. Am. Chem. Soc.* 70, 2872 (1948).
7. L. H. Sommer et al. *J. Am. Chem. Soc.* 76, 1613 (1954).

16 May 1955

Antiparasitic Activity of Substituted Carbanilide Complexes

As part of an investigation of the therapeutic potentialities of aryl ureas, we have observed that molecular complexes of certain substituted carbanilides possess antiparasitic activity. In particular, several of these complexes have shown significant activity in avian coccidiosis. The complex (I) of 4,4′-dinitro-

carbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP) was found to be among the most effective.

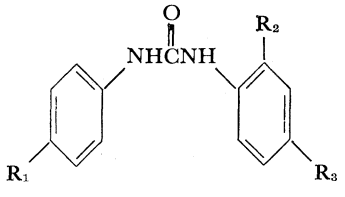


I

Some of the substituted carbanilides examined for anticoccidial activity are listed in Table 1. The compounds were mixed in the ration in concentrations of 0.01 percent or 0.1 percent and fed to young chicks at varying intervals before or after inoculation with oocysts of *Eimeria tenella*. Standardized procedures (*1*) were used throughout, and the criteria of anticoccidial effectiveness included survival rate, severity of lesions, inhibition of oocyst production, and relative weight gain. Based on all these criteria, the responses were classified as negative (0) to maximal (++++).

Under these conditions, the substituted carbanilide complexes varied from effective to ineffective. None of the complexing agents was active. Although DNC had definite anticoccidial activity when it was used alone, the potency was increased at least tenfold when it was complexed with HDP. No increase in anticoccidial activity was observed, however, on administration of a simple mixture of DNC and HDP. Similar studies with *E. acervulina* and *E. necatrix* in chicks and *E. meleagrimitis* and *E. gallopavonis* in poults have shown that the DNC · HDP complex effectively inhibited these species. Comparatively, the DNC · HDP complex is approximately fivefold more potent than nitrophenide (m,m′-dinitrophenyl-disulfide) in cecal coccidiosis.

Table 1. Anticoccidial response of substituted carbanilides.



R_1	R_2	R_3	Complexing agent	Dosage (% in feed)	Relative anticoccidial response
NO_2	H	NO_2	None	0.1	+
NO_2	H	NO_2	HDP	0.01	++++
NO_2	H	NO_2	AT	0.01	++++
NO_2	H	NO_2	PYR	0.01	+++
NO_2	CH_3	NO_2	HDP	0.1	+
NO_2	CH_3	NO_2*	None	0.1	0
NO_2	H	CN	HDP	0.01	+
NO_2	H	CN*	None	0.1	0
Cl	H	Cl	None	0.1	0
H	H	H	None	0.1	0
Reference standard— Nitrophenide				0.05	++++

* A description of the preparation of this previously unreported carbanilide is in preparation.

This complex has been examined also for antiparasitic activity in other protozoan infections. These have included *Plasmodium gallinaceum* in chicks, *Trichomonas foetus* in mice, and *Histomonas maleagridis* in turkeys. The DNC · HDP addition compound has about one-tenth of the antimalarial potency of quinine, but there was no evidence of antitrichomonas or antihistomonas activity.

Chemical studies have indicated that in addition to HDP and the 2-hydroxypyrimidine, a variety of other polar compounds yield 1-to-1 molecular complexes with DNC. These include 3-amino-*as*-triazine (AT), 2-hydroxypyridine (PYR), 2-mercapto-4,6-dimethylpyrimidine, formamide, dimethylacetamide, dimethylformamide, tetramethylurea, and acetylpiperidine. Certain hydrochlorides, for example, pyridine hydrochloride and trimethylamine hydrochloride, complexed with DNC in an equimolar ratio, whereas the free bases did not react. The numerous DNC complexes showed varying anticoccidial activity. None was more active than the DNC · HDP adduct.

It was of ancillary interest to examine the behavior of structural analogs of DNC (Table 1) toward HDP under uniform complexing conditions. It is interesting that those carbanilides that gave equimolar complexes with HDP contained at least one electron-withdrawing parasubstituent. Others, for example, 4,4′-dichlorocarbanilide and carbanilide, failed to react. The same effect was observed also in the phenylurea series. Although p-nitrophenylurea and p-cyanophenylurea afforded equimolar complexes, p-chlorophenylurea, and phenylurea did not under the same reaction conditions.

The preparation of the DNC · HDP complex illustrates the general method used in this work (*2*). At room temperature the sparingly soluble DNC extracted exactly one molar equivalent of HDP within 30 min from a stirred methanolic solution. On filtration, a nearly quantitative yield of the equimolar DNC · HDP complex, mp 265° to 275° dec., was obtained. (Analysis calculated for $C_{19}H_{18}N_6O_6$: C, 53.51; H, 4.25; N, 19.71; found C, 53.63; H, 4.30; N, 19.75.) Ultraviolet light absorption in concentrated sulfuric acid: $\lambda_{max}^{m\mu}$ 298, $A_{1\,cm}^{\%}$ 670. The infrared spectrum (Nujol mull) was characterized by disappearance of the N—H stretching frequency (3.03 μ) present in the DNC spectrum, retention of the 5.75 μ C=O band, and shifting or splitting of several maxima in the 6 to 16 μ region. The x-ray powder diagram of the DNC · HDP complex is different from that of either component. Other complexes were similarly identified.

Although it has not been definitely established, hydrogen bonding between the complexing agent and the urea portion of the substituted carbanilide appears likely. In this connection it is noteworthy that Birtwell (*3*) recently postulated a resonance stabilized, eight-membered, hydrogen-bonded, cyclic structure for the urea · HDP equimolar complex. We have assigned the generic name, nicarbazin, to the DNC · HDP complex.

A. C. Cuckler
C. M. Malanga
A. J. Basso
R. C. O'Neill
Merck Institute for Therapeutic Research and *Research Laboratories, Chemical Division, Merck and Company, Rahway, New Jersey*

References and Notes

1. A. C. Cuckler and C. M. Malanga, *J. Parasitol.* 41, 302 (1955).
2. We are greatly obliged to our colleagues, R. W. Walker, J. Wood, and R. N. Boos for analytic data presented in this paper.
3. S. Birtwell, *J. Chem. Soc.*, 1725 (1953).

3 May 1955

Chronic Uncontrolled Cross-Circulation in Unanesthetized Dogs

A technique for performing cross-circulation in anesthetized dogs was described in a previous report from this laboratory (*1*). In that study, the animals were cross-circulated for periods up to 24 hr by means of polyethylene tubing connections between the carotid artery of each animal and external jugular vein of the other. Regulation of blood flow between the partners was not necessary. The present report (*2*) describes a method for cross-circulation in unanesthetized dogs. Eight pairs of dogs were cross-circulated for periods from 47 to 100 hr in the nonanesthetized state.

Under sodium pentobarbital anesthesia, an external jugular vein and carotid artery of two dogs are cannulated with polyethylene tubing (No. 350, Clay-Adams, animal-tested). The necks of the