

without formation of formylmethyl monuron (IX), an environment in which water is available and oxygen is essentially excluded appears to be a basic requirement. These criteria would appear to be fulfilled in the environment of the polyoxyethylene side chains adjacent to the lipophilic core of the micelle. (c) TMN-6 containing samples were photolyzed above cloud point, and sample turbidity disappeared after irradiation. If the lipophilic alkyl moiety of TMN-6 was being degraded to decrease turbidity, some interaction must take place between the surfactant and the solute which adsorbs the incident radiation. These observations therefore suggest that the aryl moiety of monuron is either dissolved into or is adsorbed onto the surface of the micellar lipophilic core.

In summary, the experimental results show nonparticipation of oxygen in the photoreactions of monuron when surface-active agents are present. Therefore, we are tentatively proposing that oxygen is being excluded from the surface and the inside of the surfactant micellar lipophilic core. Further studies must be conducted, however, to elucidate the exact cause for the nonparticipation of oxygen. In consideration of the evidence obtained, both mode 1 (adsorption onto the lipophilic core) and mode 2 (penetration into the lipophilic core) can be used to explain the observed effects. Perhaps both modes of micellar involvement are in operation or perhaps intermediate stages between these two extremes are in participation. The precise mode of micellar involvement is not critical with respect to the overall photochemical study being reported. However, employing nonionic surface-active agents in excess of CMC, the important observation revealed in this study is the fact that the photoreactions take place in the organic phase of the micelles rather than in the aqueous phase of the solvent.

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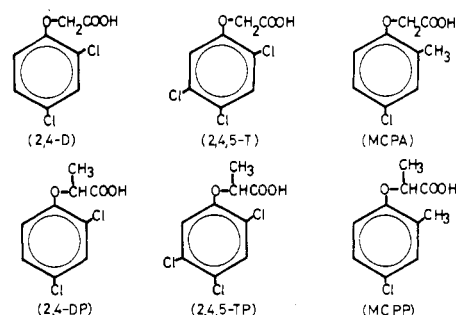
## Structural and Conformational Aspects of Phenoxyalkanoic Acids as Determined in the Solid State by Diffraction Methods

Graham Smith and Colin H. L. Kennard\*

A detailed X-ray structural investigation on active phenoxyalkanoic acid plant growth compounds [(2,4-dichlorophenoxy)acetic acid, (2,5-dichlorophenoxy)acetic acid, 2,4,5-trichlorophenoxyacetic acid, and ( $\pm$ )-2-(2,4,5-trichlorophenoxy)propionic acid] and inactive ones [(2,4,6-trichlorophenoxy)acetic acid and ( $\pm$ )-2-(3,5-dichlorophenoxy)propionic acid] has been carried out. Although there are structural differences occurring in members of this series, there appears to be no direct stereochemical relationship with herbicidal activity.

Since the discovery of the auxin and herbicidal property of (2,4-dichlorophenoxy)acetic acid (2,4-D) in 1942 (Zimmerman and Hitchcock), a number of plant growth regulators of the phenoxyalkanoic acid type have been synthesized. Their chemistry and postulated mode of action have been reviewed (Garraway and Wain, 1976).

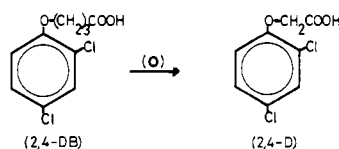
The members of the series that have been available for commercial use are 2,4-D, (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), (4-chloro-2-methylphenoxy)acetic acid (MCPA), and their propionic acid analogues; 2-(2,4-di-



chlorophenoxy)propionic acid (2,4-DP or dichloroprop), 2-(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP or fenoprop), 2-(4-chloro-2-methylphenoxy)propionic acid (MCPP or mecoprop).

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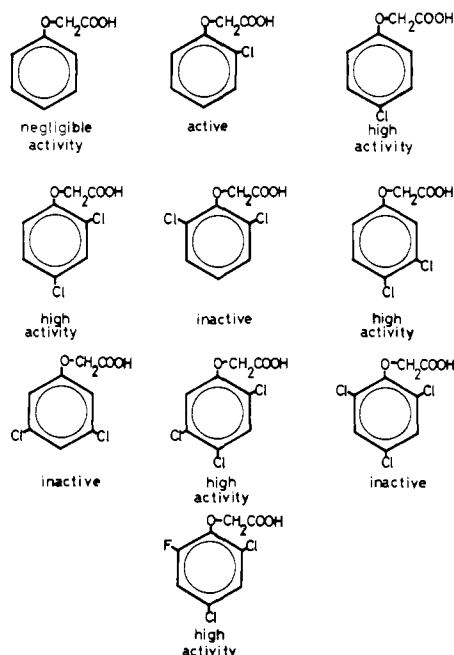
The  $\gamma$ -substituted butyric acid analogues, e.g., 4-(2,4-dichlorophenoxy)butyric acid (2,4-DB) and 4-(4-chloro-2-methylphenoxy)butyric acid (MCPB), also find use as



selective herbicides, but it has been demonstrated that these substances undergo  $\beta$  oxidation *in vivo* to yield the corresponding phenoxyacetic acid.

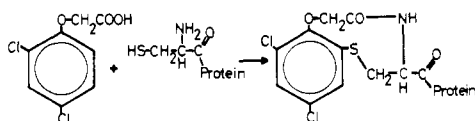
#### STRUCTURE-ACTIVITY RELATIONSHIPS

The parent compound phenoxyacetic acid is almost inactive as a plant growth regulator. Substitution of chlorine in the different positions in the ring system results in various effects on the auxin activity, reaching an optimum in the case of 2,4-D and 2,5-D (Veldstra, 1953).



Negligible activity is possessed by compounds having substituents in the symmetrical 2,6, 2,4,6, or 3,5 positions in the ring although an exception is found in the case of the active (6-fluoro-2,4-dichlorophenoxy)acetic acid. This, however, is considered acceptable on the basis of steric effects with the fluorine being virtually identical in size with a proton.

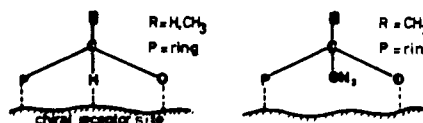
Theories put forward to account for the low activity associated with members having bulky substituents in the 2 and 6 positions included, logically, the possibility that a free ortho position was required for some interactive process, such as a molecular complex formation (Muir and Hansch, 1951). They proposed an interaction involving



the ortho position of the benzene ring of the herbicide and a cysteinyl group of a protein in a two-point mode of addition.

A three-point mode of attachment was also proposed (Smith and Wain, 1951), the three "essential" groups needed by the molecule being an unsaturated ring system (P), an  $\alpha$ -hydrogen (H) on the chiral center [C(2)], and a

carboxyl group (O). Absence of suitably spaced centers



resulted in a lack of herbicidal activity, as was observed with the compound (2,4-dichlorophenoxy)isobutyric acid.

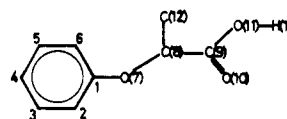
This would suggest that the receptor site should be stereospecific, with only one enantiomer being capable of association to give growth stimulation. Furthermore the activity of the active form could be suppressed by competition for the active receptor site (competitive antagonism) by the inactive form (Smith et al., 1952). (2,4-Dichlorophenoxy)isobutyric acid, with partial complexation, probably suppresses stimulus by a similar competitive process.

Thimann (1969) proposed that a molecule to possess auxin properties must have a discrete separation (550 pm) between two polar centers on the molecule. One center ( $\delta^-$ ) is on the carboxylic acid oxygen ( $O^-$ ), while the other center is a fractional positive charge ( $\delta^+$ ) induced on a particular ring position by substitution. The differences in activity between closely related compounds are considered to be largely due to the effects of substitution on the location and magnitude of the ( $\delta^+$ ) charge. Other secondary influences must also be considered, these being the angle of orientation of the side chain and the solubility of the auxin in lipids. On this basis, the activity or inactivity of the members of the phenoxy series and other plant growth regulators could be explained.

#### EXPERIMENTAL AIMS

This work was initiated in order to determine whether structural aspects for a number of phenoxy compounds, both herbicidally active and inactive, might be correlated with activity. X-ray crystallographic techniques were used to determine the solid-state structures and to obtain precise intramolecular information. The compounds studied are coded in the text as follows: (i) (2,4-dichlorophenoxy)acetic acid (2,4-D), Smith et al. (1976a), Figure 1, active; (ii) 2,5-dichlorophenoxyacetic acid (2,5-D), Smith et al. (1976c), Figure 2, active; (iii) 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), Smith et al. (1976b), Figure 3, active; (iv) 2,4,6-trichlorophenoxyacetic acid (2,4,6-T), Smith et al. (1977a), Figure 4, inactive; (v) ( $\pm$ )-2-(3,5-dichlorophenoxy)propionic acid (3,5-DP), Smith et al. (1978a), Figure 5, inactive; (vi) ( $\pm$ )-2-(2,4,5-trichlorophenoxy)propionic acid (2,4,5-TP), Smith et al. (1977b), Figure 6, active. It is the purpose of this paper to review in detail structural aspects of phenoxyalkanoic acids.

The general naming scheme used for atoms in the phenoxy series is



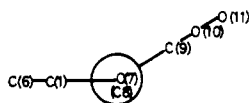
In discussing the conformational aspects of the acid group, the methods of classification are based on the following. (a) The acute dihedral angle ( $\alpha$ ) between the normals to the plane of the carboxylic acid group and the plane of the benzene ring.



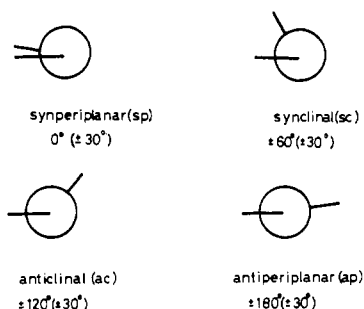
Table I. Comparative C-Cl Distances (pm) and *exo*-C(1) Angles (deg.) for Compounds I-IX (Mean Values for the Distances Are Shown in Square Brackets)

compd	C-Cl	O(7)-C(1)-C(6)	O(7)-C(1)-C(2)
I, 2,4-D	174.1, 174.1 [174.1 (4)]	124.7 (3)	116.2 (3)
II, 2,5-D	174.6, 175.3 [175.0 (5)]	125.1 (2)	117.8 (2)
III, 2,4,5-T	172.6, 173.1, 173.0 [173.0 (6)]	124.0 (4)	116.1 (3)
IV, 2,4,6-T	173.4, 173.0, 172.6 [173.0 (4)]	118.5 (4)	122.9 (4)
V, 3,5-DP	174.3, 175.0 [174.7 (6)]	113.4 (5)	124.3 (5)
VI, 2,4,5-TP	173.3, 173.1, 172.5 [173.0 (3)]	125.5 (5)	115.7 (3)
VII, 2-Cl (a)	174.4 [174.4 (14)]	122.1 (13)	116.8 (13)
(b)	168.1 [168.1 (18)]	115.8 (12)	116.8 (12)
VIII, 3-BR-P		121	114
IX, 3-MEO-P		117	117

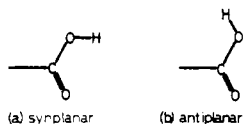
(b) The torsion angle of the plane of the benzene ring with respect to the plane of the carboxylic acid group, viewed down the bond, O(7)-C(8).



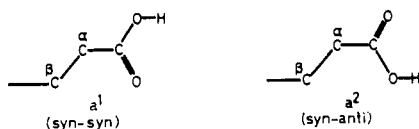
The classification of torsion angles according to the IUPAC rules (IUPAC, 1970) is shown.



(c) The carboxylic acid group which may adopt the synplanar (a) or the antiplanar (b) motifs.



The antiplanar motif, which is considered to be the less favored conformer energetically, to the extent of 2 kcal mol<sup>-1</sup> (Miyazawa and Pitzer, 1959) in a study of gaseous monomeric formic acid, is found only in those acids which participate in intramolecular hydrogen bonding, e.g., 2-ethoxybenzoic acid (Gopalakrishna and Cartz, 1972). In  $\alpha,\beta$ -saturated acids, the synplanar motif may be further classified as synplanar (a<sup>1</sup>) or antiplanar (a<sup>2</sup>).



## RESULTS AND DISCUSSION

A comparison of the important interatomic distances and angles is given in Table I.

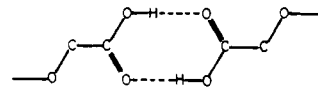
Included are the values for the reported phenoxyalkanoic acids. These are as follows: (a) 2-chlorophenoxyacetic acid (VII 2-CL), molecule a, molecule b (Chandrasekhar and Pattabhi, 1977); (b) (-)-2-(3-bromophenoxy)propionic acid (VIII 3-Br-P) (Karle and Karle, 1966); (c) (+)-2-(3-methoxyphenoxy)propionic acid (IX, 3-MEO-P) (Karle and Karle, 1966); (d) 3-indolylacetic acid (X, IAA) (Karle et al., 1964). Although IAA is not chemically related to this series, it is included because of its importance in a comparative study of auxins. (e) 3-(4-chlorophenyl)-

propionic acid (XI, 4-CL-PA) (Glusker et al., 1975). This compound is not a phenoxy but is very similar to the basic phenoxy structure, the ether oxygen being replaced here by a CH<sub>2</sub> group.

Interatomic distances and angles are normal for the series and generally do not warrant comment. The C-Cl bond distances [mean, 173.8(5) pm] agree well with the reported mean for 18 benzene ring carbon-chlorine distances (174.0 pm) (Domenicano et al., 1977).

Distortion of the *exo*-C(1) angles from the expected trigonal value occurs to a marked extent in the series. An exception is with 2,4,6-T where angles are not significantly abnormal. This effect is probably due to the carboxyl group assuming a preferred orientation away from the bulk of the chlorine substituent on the C(2) ring position, causing molecular overcrowding, an effect observed among a number of substituted benzoic acids. With 2,4,6-T, each of the ortho positions is equivalent and substituted so that repulsive effects can only be accommodated in a change in conformation of the carboxyl group to the anticlinal motif.

All members of the phenoxy series adopt the usual synplanar cyclic hydrogen-bonded dimer motif. Fur-



thermore, all except VIII have the a<sup>1</sup> conformation, which is found, without exception, in the analogous  $\alpha,\beta$ -saturated carboxylic acids (Leiserowitz, 1976) where the  $\beta$  carbon replaces the ether oxygen. With VII, the a<sup>2</sup> conformation is assumed.

The hydrogen bond length shows little variation through the series (Table II), the mean being 266.3 pm. This compares well with the values for compounds VIII, IX and X (262.8 pm mean) and with the values for the benzoic acid series (Table III) where the mean is 264.4 pm. The values of 247 and 245 pm for VII are abnormally short for carboxylic acids, and although short symmetric hydrogen bonds of this order seem to be the rule in acid salts of carboxylic acids [e.g., potassium hydrogen bis(4-chlorobenzoate) (245.7 pm) and potassium hydrogen bis(phenylacetate) (244.3 pm); Speakman, 1967], it is felt that the values for (2-chlorophenoxy)acetic acid are not reliable on the grounds that it is the only reported exception in more than 40 examples of aromatic carboxylic acids. A structure redetermination using diffractometer data is warranted to resolve the anomaly.

Distances and angles within the carboxylic acid dimer are normal (Table II) except for compounds IV and V where a clear-cut difference between the C-O (carbonyl) and C-O (hydroxyl) distance is not evident [123.5, 126.2 pm (IV) and 123.7, 127.6 pm (V)]. Acids I, II, III and VI [mean C-O (carbonyl) 121.3 pm and C-O (hydroxyl) 131.0 pm] compare with the average of 121 and 131 pm, respectively, for a series of nonorientationally disordered

Table II. Comparative Interatomic Distances (pm) and Angles (deg) about the Carboxylic Acid Group for Compounds I-X

compound	C-O- (carbonyl) distance	C-O- (hydroxyl) distance	C(8)-C(9)- O(10) angle	C(8)-C(9)- O(11) angle	O(10)-C(9)- O(11) angle	O(11)- H(11)...O(10') distance
I, 2,4-D	121.7 (6)	130.4 (5)	123.2 (2)	112.2 (2)	124.5 (3)	262.7 (4)
II, 2,5-D	120.8 (5)	132.5 (4)	124.1 (2)	112.0 (2)	123.8 (3)	266.8 (6)
III, 2,4,5-T	121.3 (7)	130.1 (8)	122.9 (4)	112.7 (3)	124.4 (4)	268.9 (7)
IV, 2,4,6-T	123.5 (5)	126.2 (5)	120.9 (4)	115.7 (4)	123.3 (4)	268.6 (5)
V, 3,5-DP	123.7 (7)	127.6 (7)	120.7 (6)	115.3 (5)	124.0 (6)	266.4 (6)
VI, 2,4,5-TP	121.3 (3)	131.1 (4)	123.9 (3)	111.9 (3)	124.1 (3)	264.5 (3)
VII, 2-CL (a)	125 (2)	132 (2)	121.4 (13)	113.2 (13)	125.3 (13)	247 (2)
(b)	125 (2)	135 (2)	120.7 (12)	110.6 (12)	128.7 (12)	245 (2)
VIII, 3-BR-P	127 (4)	131 (4)	127	113	119	260 (4)
IX, 3-MEO-P	120 (4)	134 (4)	124	116	120	262 (4)
X, IAA	122 (2)	130 (2)	124 (1)	113	123	267 (2)
lit. mean value <sup>a</sup>	121	131			123	

<sup>a</sup> Leiserowitz, 1976.

Table III. Hydrogen Bond Distances for Benzoic Acid and Substituted Benzoic Acids

acid	O-H...O distance, pm	ref.
4-chlorobenzoic	261.5	a
4-aminosalicylic	270	b
benzoic	264	c
salicylic	262.7	d
2-chlorobenzoic	263.2	e
2-chloro-5-nitrobenzoic	261	f
2-bromobenzoic	264	g
2-amino-3-methylbenzoic	264.6	h
acetylsalicylic	264.5	i
2-fluorobenzoic	264	j
4-nitrobenzoic	265	k
4-aminobenzoic	261.2, 264.1	l m
2,6-dimethylbenzoic	267.3	n
4-methoxybenzoic	264.3	o
3,5-dinitro-4-methylbenzoic	264.7	p
3,4,5-trimethylbenzoic	262	q
2,4,6-trimethylbenzoic	264.0	r
4-methylbenzoic	263	s
2,3-dimethylbenzoic	265.9	t
4-bromobenzoic	264.6	u
hexafluorobenzoic	266.8	v
2-nitrosobenzoic	261.9	w
3-chlorobenzoic	267	x
2,3-dimethoxybenzoic	268	y
2-iodobenzoic	263	z

<sup>a</sup> Toussaint, 1951; Miller et al., 1974. <sup>b</sup> Bertinotti et al., 1954. <sup>c</sup> Sim et al., 1955. <sup>d</sup> Cochran, 1953; Sundaralingam and Jensen, 1965. <sup>e</sup> Ferguson and Sim, 1961. <sup>f</sup> Ferguson and Sim, 1962a. <sup>g</sup> Ferguson and Sim, 1962b. <sup>h</sup> Brown and Marsh, 1963. <sup>i</sup> Wheatley, 1964. <sup>j</sup> Krausse and Dunken, 1966; Ferguson and Islam, 1975. <sup>k</sup> Sakore and Pant, 1966; Takwale and Pant, 1971. <sup>l</sup> Alleaume et al., 1966. <sup>m</sup> Lai and Marsh, 1967. <sup>n</sup> Anca et al., 1967. <sup>o</sup> Bryan, 1967. <sup>p</sup> Grant and Richards, 1969. <sup>q</sup> Cano et al., 1970. <sup>r</sup> Florencio and Smith, 1970; Benghiat and Leiserowitz, 1972. <sup>s</sup> Takwale and Pant, 1971. <sup>t</sup> Smith et al., 1971. <sup>u</sup> Ohkura et al., 1972. <sup>v</sup> Benghiat and Leiserowitz, 1972. <sup>w</sup> Dieterich et al., 1974. <sup>x</sup> Gougoutas and Lessinger, 1975. <sup>y</sup> Swaninathan et al., 1977. <sup>z</sup> Gougoutas, 1977.

carboxylic acids (Leiserowitz, 1976).

Oriental disorder is considered to occur as a result of the packing environment about the carboxyl dimer and the effect of environment on the carboxyl group. The phenomenon manifests itself in abnormal temperature factors in the carboxyl oxygen atoms and in a decrease in the difference between the C-O (carboxyl) and C-O (hydroxyl) bond lengths and the C-C-O bond angles.

When comparing C-O bond distances with disorder, Dieterich et al. (1974) have shown that there is a linear

relationship between the difference in the C-O lengths ( $\Delta r$ ) and the difference in C-C-O angles ( $\Delta\theta$ ) for the benzoic acid series. The range is from completely disordered dimers (small values of  $\Delta r$  and  $\Delta\theta$ ) to order dimers (large values of  $\Delta r$  and  $\Delta\theta$ ). The angle O(10)-C(9)-O(11) and the hydrogen bond distance O(10)-H(10)...O(11) is independent of the effects of orientational disorder.

For IV and V,  $|\Delta r|$  and  $|\Delta\theta|$  are 3.9 pm, 5.4° and 2.7 pm, 5.2°, respectively. The values found for I-X are plotted (Figure 7) to determine a possible relationship among  $|\Delta r|$  and  $|\Delta\theta|$  and disorder effects and to see if the phenoxy-alkanoic acids parallel the benzoic acid series.

For a direct comparison, the values are placed on the same graph as the benzoic acid series in which a number of other substituted benzoic acids not included by Dieterich are also included. In addition, 3-(4-chlorophenyl)propionic acid (Glusker et al., 1975) and four substituted cinnamic acids, 3-chloro-*trans*-, 3-chloro-*cis*-, and 3-methyl-*cis*- (Fillipakis et al., 1972), and 4-chloro-*trans*-cinnamic acid (Glusker et al., 1975) are included.

A. The phenoxy series is represented as circles: (1) (I, 2,4-D), (2) (II, 2,5-D), (3) (III, 2,4,5-T), (4) (IV, 2,4,6-T), (5) (V, 3,5-DP), (6) (VI, 2,4,5-TP), (7a) VIIa, 2-Cl, molecule a), (7b) (VIIb, 2-Cl, molecule b), (8) (VIII, 3-Br-P), (9) (IX, 3-MeO-P), (10) (X, IAA).

B. The cinnamic acid series, and others, are represented as crosses: (11)  $\beta$ -chloro-*trans*-, (12)  $\beta$ -chloro-*cis*-, (13)  $\beta$ -methyl-*cis*- [Fillipakis et al. (1972)], (14) *p*-chloro-*trans*- [Glusker et al. (1975)], (15) 3-(4-chlorophenyl)propionic acid [Glusker et al. (1975)].

C. The benzoic acid series (from Dieterich et al., 1974), is represented as triangles. Numbers 29-41 were not originally included. (16) 4-methyl-, (17) 4-chloro-, (18) 2-fluoro-, (19) 2,4,6-trimethyl-, (20) 3,4,5-trimethyl-, (21) benzoic acid, (22) 2,6-dimethyl-, (23) pentafluoro-, (24) 4-bromo-, (25) 2-nitroso-, (26) 2-chloro-, (27) 2,3-dimethyl-, (28) 2-bromo-, (29) 4-amino-(molecule a), (30) 4-amino-(molecule b), (31) 2-chloro-5-nitro-, (32) 2-amino-3-methyl-, (33) 4-methoxy-, (34) 3,5-dinitro-4-methyl-, (35) 2-hydroxy-4-amino-, (36) 3-chloro-, (37) 2-hydroxy-, (38) 4-amino-2-hydroxy-, (39) 2,3-dimethoxy-, (40) 2-iodo-, (41) acetylsalicylic acid.

With the exception of members VIII and IX, which were rejected, there appears to be an approximately linear relationship between disorder and the  $\Delta r$  and  $\Delta\theta$  values. The relationship, however, is not the same as for the benzoic acids but is parallel to it, the differences in  $\Delta\theta$  being much more pronounced with change in  $\Delta r$ . A similar parallel relationship exists for the cinnamic acid series.

The symmetrically substituted compounds are considered in relationship to disorder effects since the two phenoxy groups showing disorder are similarly substituted

Table IV. Comparative Conformational Angles (deg) for Compounds I-X

compound	torsion angle about O(7)-C(8)	torsion angle <sup>a</sup> classification	dihedral angle (ring to carboxyl)
I, 2,4-D	-75.2	synclinal	85.2
II, 2,5-D	-73.9	synclinal	81.2
III, 2,4,5-T	-174.6	antiperiplanar	4.2
IV, 2,4,6-T	-152.3	antiperiplanar	32.0
V, 3,5-DP	-73.1	synclinal	87.0
VI, 2,4,5-TP	-80.0	synclinal	77.8
VII, 2-Cl (a)	-173.6	antiperiplanar	7.0
(b)	173.3	antiperiplanar	6.6
VIII, 3-BR-P	76.5	synclinal	85.5
IX, 3-MEO-P	-76.5	synclinal	85.5
X, IAA	-85.6	synclinal	62.9

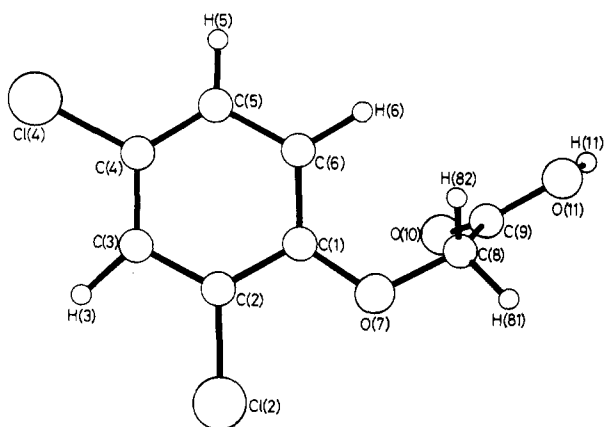
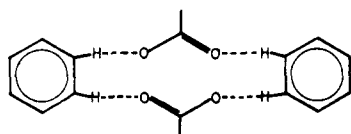
<sup>a</sup> IUPAC, 1970.

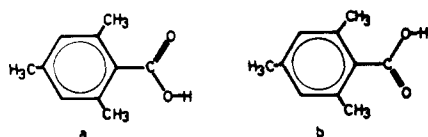
Figure 1. Molecular configuration and naming system for 2,4-D (I).

[(3,5-DP (V) and 2,4,6-T (IV)] to disordered benzoic acids. Symmetrical substitution in the benzoic acids precludes the possibility of lateral contacts between ortho- and meta-substituted ring hydrogens and the oxygens of the carboxyl dimer. This arrangement was found in 4-methylbenzoic acid (Takwale and Pant, 1971).



Of the *o*-halobenzoic acids, (F, Cl, Br), only *o*-fluorobenzoic acid (Krausse and Dunken, 1966) shows evidence of disorder, the F being sufficiently small to permit the existence of an approximate twofold rotational axis through the molecule.

2,4,6-Trimethylbenzoic acid is disordered, the effect thought to be due to the presence of *o*-methyl groups related by molecular twofold symmetry, providing similar contact geometry for the carboxyl dimer in its two orientations, a and b.



Also the O atoms are partially shielded from the intermolecular contacts by the *o*-methyl groups. Leiserowitz

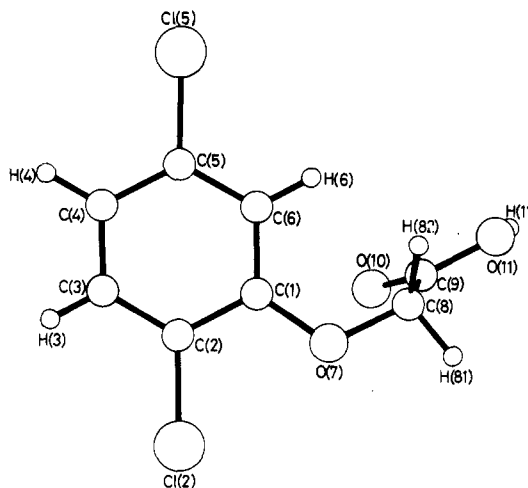


Figure 2. Molecular configuration and naming system for 2,5-D (II).

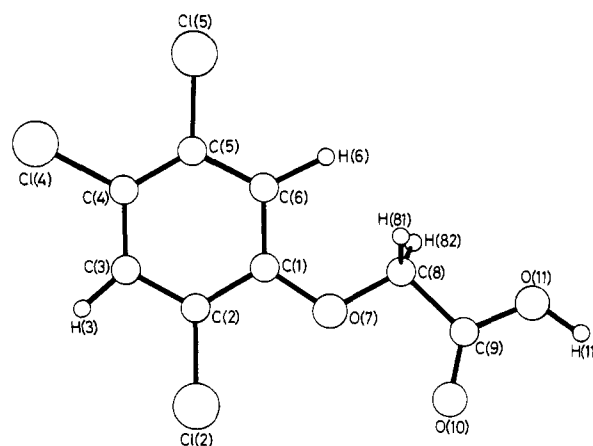


Figure 3. Molecular configuration and naming system for 2,4,5-T (III).

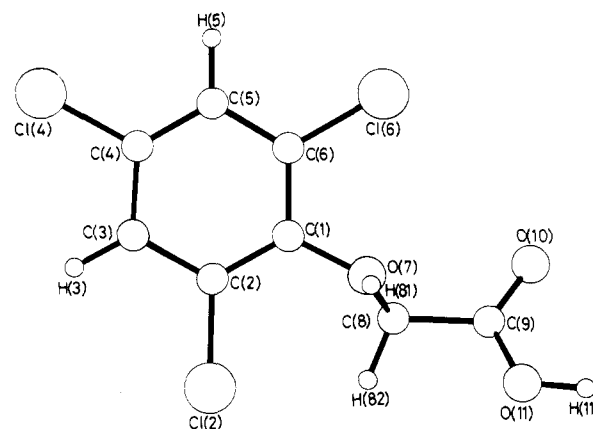


Figure 4. Molecular configuration and naming system for 2,4,6-T (IV).

considers that the extent of shielding is dependent on the degree of twisting of carboxyl dimer away from the plane of the benzene rings, the larger the angle of twist, the more exposed are the O atoms. 2,4,6-Trimethylbenzoic acid has an angle of twist of 48.5° compared with 53.5° for 2,6-dimethylbenzoic acid (Anca et al., 1967), which is less disordered on the basis of C-O bond lengths.

With the phenoxy series, the situation is further complicated, compared with the benzoic acids, by the presence of the extended chain with its additional conformational possibilities.

Table V. Comparison of Important Intramolecular Distances (pm) Involving the Carboxylic Acid Group for Compounds I-IX and XI<sup>a</sup>

compound	C(6)-O(10)	C(6)-O(11)	C(2)-O(10)	C(2)-O(11)	O(7)-O(10)	O(7)-O(11)
I, 2,4-D	343.3	419.9	416.6	551.5	271.7	357.8
II, 2,5-D	333.9	416.7	397.6	548.9	271.0	356.3
III, 2,4,5-T	492.6	508.4	471.1	585.8	260.5	352.5
IV, 2,4,6-T	427.5	549.7	504.7	542.0	268.3	347.3
V, 3,5-DP	424.8	528.5 <sup>c</sup>	364.4	367.8 <sup>c</sup>	274.5	350.9
VI, 2,4,5-TP	334.5	392.2	414.5	546.2	273.0	356.9
VII, 2-CL (a)	472.0	489.1	465.9	587.5	251.4	352.1
(b)	463.6	480.7	456.9	584.1	250.1	352.2
VIII, 3-BR-P	342.2	373.3	431.4	542.0	275.6	357.3
IX, 3-MEO-P	346.9	377.4	430.4	542.2	275.6	356.1
XI, 4-CL-PA <sup>a</sup>	514.3	512.7	523.3	612.3	282.4	365.9 <sup>b</sup>

<sup>a</sup> 3-(4-Chlorophenyl)propionic acid (Glusker et al., 1975). <sup>b</sup> In this example, O(7) is replaced by CH<sub>2</sub>. <sup>c</sup> Because positions 2 and 6 in the ring are equivalent in this example they should be reversed in the discussion.

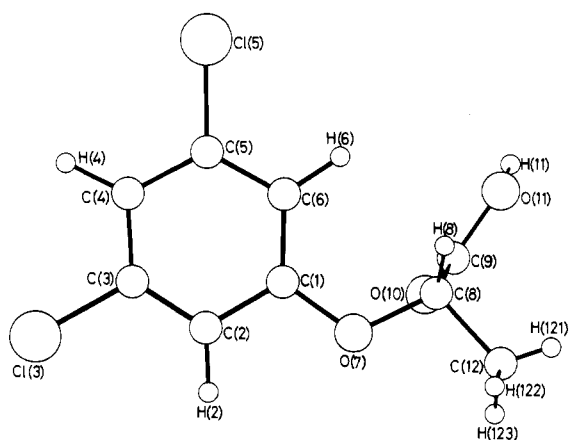


Figure 5. Molecular configuration and naming system for 3,5-DP (V).

The different conformations are considered in terms of the dihedral angle between the plane of the benzene ring and the plane of the carboxylic acid group [O(10)-C(9)-O(11)], as well as the torsion angle about the bond O(7)-C(8). A comparison is made in Table IV and Figure 8 for the series I-X. Most examples possess the synclinal conformation with the torsion angle varying from -73.1° (3,5-DP) to -80.0° (2,4,5-TP). The maximum synclinal angle observed over the entire series was -85.6° for IAA. All propionic acid analogues examined to date have similar angles (range -74.0 to -80.0°) and the values are probably due to the presence of the C(12) methyl group which forces the arrangement with the most energetically favored interactive distances.

A comparison of the important interactive distances between the carboxyl oxygens and other atomic positions [C(2), C(6), O(7)] is given in Table V. The distance between the carboxylic acid oxygen [O(11)] and the aromatic ring carbon [C(6)] is relatively constant throughout the series for the synclinal examples [range 367.8 (V) to 419.9 (I) pm]. Since there is no substituent group in either the C(2) or C(6) positions for IV, these positions should be interchanged in this discussion. The phenoxypropionic acids have consistently short distances, 367.8 (V), 373.3 (VIII), and 377.4 pm (IX), and this decrease is significant because each of these examples has no large substituent group in either of the ortho ring positions. Also, in these examples, the two oxygens are symmetrically oriented with respect to ring position C(6). The C(6)-O(10) and C(6)-O(11) distances are 364.4, 367.8 pm (V); 342.2, 373.3 pm (VIII); 346.9, 377.4 pm (IX), respectively. The most important factor in determining

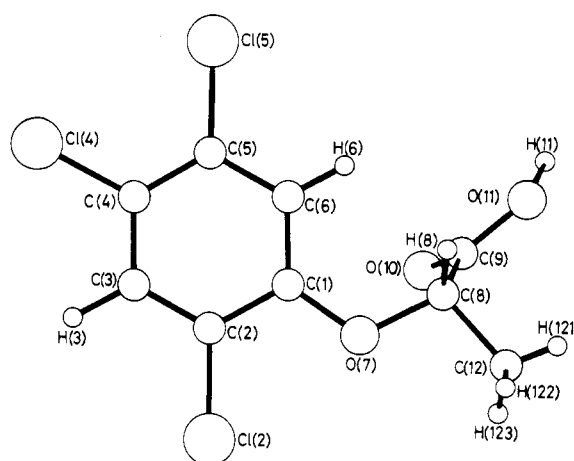
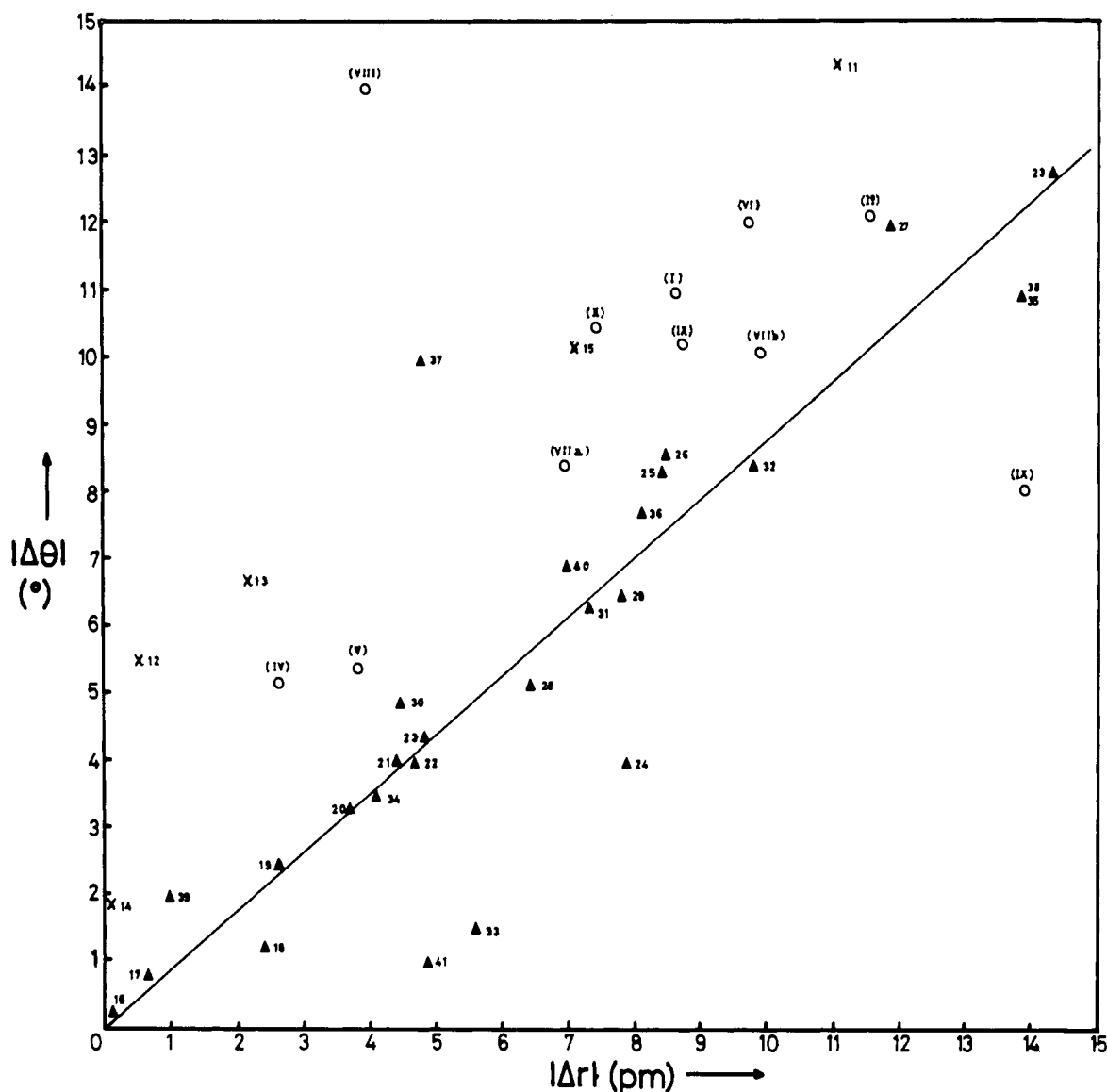


Figure 6. Molecular configuration and naming system for 2,4,5-TP (VI).

the packing mode in this series appears to be the interactive distances between the carboxylic acid oxygens and the ether oxygen.

Irrespective of the conformational orientations possessed by the acid, the distance between the hydroxyl [O(11)] and carbonyl [O(10)] oxygens and the ether oxygen [O(7)] is relatively constant. The range [O(10)-O(7)] is 250.1-275.6 pm (mean, 267.2 pm), while for O(11)-O(7), the range is 347.3-357.8 pm (mean 354.0 pm). This is comparable with the equivalent distances O(10)-C(7) (282.4 pm) and O(11)-C(7) (365.9 pm) found for the analogous  $\alpha,\beta$ -saturated acid, 3-(4-chlorophenyl)propionic acid (Glusker et al., 1975). In the  $\alpha,\beta$ -saturated acid, the  $\beta$  carbon replaces the oxygen. This means that for the phenoxy series, all atoms in the oxoacetic acid residue are essentially coplanar. The only variable factor within the series is the angle between this group and the plane of the benzene ring. It is considered (Leiserowitz, 1976) that in  $\alpha,\beta$ -saturated carboxylic acids the preferred orientation, resulting in the synplanar conformation, is determined by the nonbonded interactions between hydrogens on the  $\beta$  carbon and the carbonyl oxygen.

Furthermore, the planar conformation of the entire 3-(4-chlorophenyl)propionic acid is considered to be a consequence of the staggering of the hydrogen atoms in the CH<sub>2</sub>CH<sub>2</sub> group (Glusker et al., 1975). With the phenoxy series both arguments are untenable on the basis of an absence of  $\beta$  hydrogens. However, if the ether oxygen is considered to be a tetrahedral hybrid, it possesses two lone pairs of electrons in the tetrahedral positions occupied by the  $\beta$  hydrogens in the propionic residue. The lone pair



**Figure 7.** Graphical representation of the variation of differences in C-O bond lengths ( $\Delta r$ ) with the C-C-O bond angle ( $\Delta\theta$ ) for a series of aromatic carboxylic acids (after Dietrich et al., 1974).

lobes will tend to orient themselves symmetrically in staggered positions with respect to the  $\alpha$  hydrogens and the  $\pi$  cloud of the benzene ring. This will result in the planar conformation.

The solid-state structure of the parent compound phenoxyacetic acid has now been determined (Smith et al., 1978b) and has shown the molecule to be essentially planar.

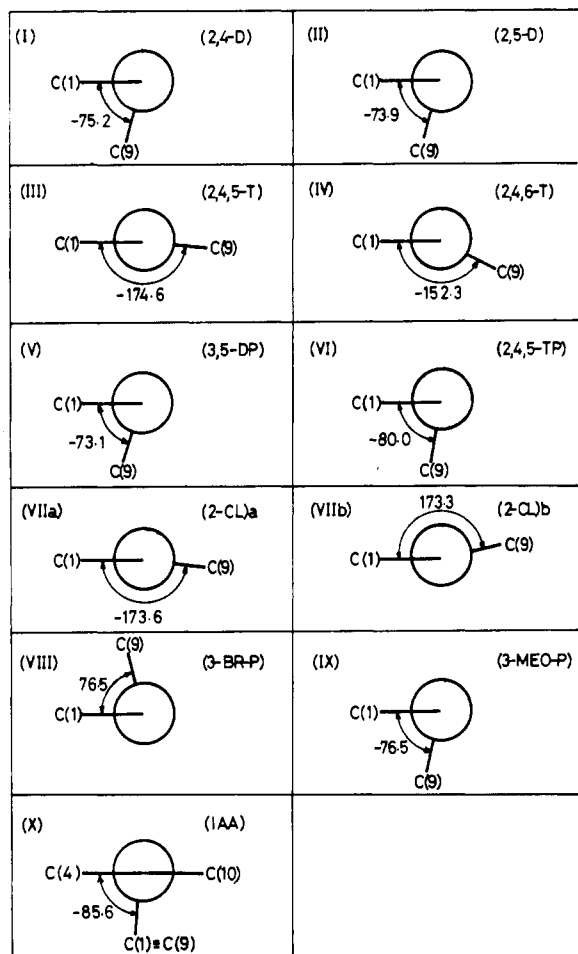
By the same reasoning, benzene ring-substituted ethoxy groups should also lie coplanar with the ring. This has generally been observed for such compounds, e.g., 1,1-bis(4-ethoxyphenyl)-2,2-dimethylpropane (DeLacy and Kennard, 1972), 2,2-bis(4-ethoxyphenyl)-3,3-dimethyl-oxetan (Holan et al., 1973), *N,N'*-bis(4-ethoxyphenyl)-acetamidiniumbis(*p*-nitrophenyl)phosphate monohydrate (Sax et al., 1971) and bis(2-ethoxyphenyl)butadiene (Taga et al., 1971). Furthermore, the  $-\text{OCH}_2\text{CH}_2-$  group in  $\beta$ -5-*n*-propoxy-*o*-benzoquinone-2-oxime (Romers, 1964) is coplanar with the quinone ring with only the terminal methyl group deviating from the plane by 122 pm.

The tendency therefore is for the phenoxyacetic acids to pack most efficiently with the planar molecular conformations, even though the O(7)-O(10) nonbonding interactions may be less than twice the van der Waals radii

for oxygen (280 pm). The conformations of the substituted phenoxyacetic acids appear to be a consequence of packing environment, which will be affected by steric factors introduced by the substituents in the ring or an additional chain group, such as the methyl group in the propionic acid analogues. Different packing modes may be artifacts of the crystallization technique employed, but no crystal morphology other than the triclinic forms studied have been obtained from any different solvents tried.

With two exceptions (II and V), the packing of the dimeric acid units in the cell does not result in superimposition of stacks of benzene rings along any preferred direction. With II, stacks of *para*-related chlorines in the benzene rings form down the *b* axis (754.8 pm) although the acid side chains are oppositely directed. The result of this effect is a pseudo B-face centering with a subsequent general weakness in the (*hkl*, *k* = odd) reflections. With 3,5-DP, a similar ring stacking effect down the *c* axis (750.5 pm) is observed, but the *meta*-related chlorines do not superimpose down the stack.

Stacking effects resulting in close inter-carboxyl oxygen contacts, related to disorder in some benzoic acids, do not exist in this series and cannot be considered important in the disorder observed in IV and V. In a general consid-



**Figure 8.** Torsion angles for the series I–X shown as projections down the bond O(7)–C(8). C(1)–O(7) represents the plane of the benzene ring, while C(8)–O(9) lies in the plane of the carboxylic acid group

eration of the conformational aspects of the phenoxyalkanoic acid series, there appear to be no unique factors, apart from the symmetrical ring-chlorine substitution, responsible for the disorder observed.

Furthermore, solid-state conformational differences in the molecules appear to have little, if any, bearing on their herbicidal activities. This is best illustrated in a review of the conformational features from Table IV. The highly active members 2,4-D and 2,5-D (synclinal) are very similar to the inactive 3,5-DP but are unrelated to the highly active 2,4,5-T (antiperiplanar) and the active 2-CL (antiperiplanar). The second inactive member (2,4,6-T) has the intermediate but antiperiplanar conformation.

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## Effect of Amino Acid(s) and Pulse Supplementation on Nutritional Quality of Normal and Modified *Opaque-2* Maize (*Zea mays* L.)

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Chemical analysis as well as rat feeding experiments indicate superior nutritive quality of modified *opaque-2* (*o2*) as compared with normal maize. Supplementation with lysine alone in modified *o2* and lysine + tryptophan in normal maize substantially improved the nutritive quality. Addition of Bengal gram (*Cicer arietinum*) to normal and modified *o2* maize in the ratio of 3:7 on protein basis improved their nutritional quality substantially and brought it at par to diet supplemented with amino acids. Diet protein quality affected growth, protein, and nucleic acids in rats.

Maize occupies an important place next to wheat and rice in the world food supply map. However, because of a deficiency of lysine and an excess of leucine, its nutritional quality is very low. The discovery of association of high lysine and tryptophan and low leucine with *o2* maize by Mertz et al. (1964) gave a major breakthrough and realization that maize proteins could be improved in quality by genetic manipulation. Although many new *o2* varieties have been developed, these have not found acceptability with the farmer and consumer mainly due to low yield, softness of the kernel, and susceptibility to insect attack during storage. Therefore, in the past few years breeders have developed modified *o2* maize with hard endosperm to overcome the agronomic and acceptability problems of original chalky *o2* maize. Chemical analysis of modified *o2* maize has shown improvement in nutritional quality as compared to normal maize.

However, the biological value of even modified *o2* is slightly lower than that of chalky *o2* (Gupta et al., 1979). Therefore, in the present study the effect of amino acid supplementation with lysine and tryptophan on nutritional quality has been studied. In addition the synergistic effects of addition of pulse to maize diet on nutritional quality has been studied because of the complementary nature of essential amino acid composition of pulses and cereals.

### EXPERIMENTAL PROCEDURES

**Sample Preparation.** The maize varieties SO/SN composite (a modified *o2* hard endosperm composite) and Vijay (normal) were tested. The BG-206 variety of Bengal gram (*Cicer arietinum*) was used for pulse. For endosperm separation, kernels were soaked in distilled water at 4 °C for 3 h, then the pericarp was removed, and the endosperm and embryo were separated with scalpel, and the endosperm was collected. Dried endosperm ground to 100 mesh flour was defatted by Soxhlet extraction method.

**Protein Fractionation.** Protein fractionation of the defatted endosperm samples was done according to the

Table I. Basal Diet Composition for Normal Maize, Modified *Opaque-2* Maize, and Pulse (on moisture-free basis)<sup>a, b</sup>

diet constituents	basal diet composition (g/kg of diet)		
	normal maize diet	modified <i>opaque-2</i> maize diet	pulse diet
normal maize	781.2		
modified <i>opaque-2</i> maize		823.7	
Bengal gram			491.8
mineral mixture <sup>c</sup>	40	40	40
vitamin mixture <sup>d</sup>	16	16	16
N-free mixture <sup>e</sup>	162.8	120.3	452.2
total diet weight	1000	1000	1000

<sup>a</sup> Each rat received 10 g of diet containing 150 mg of N daily. <sup>b</sup> Protein (percent of dry matter): normal maize, 12.0; modified *opaque-2* maize, 11.38; and pulse, 19.06. <sup>c</sup> Forty grams of mineral mixture added per kilogram of diet consisted of: CaCO<sub>3</sub>, 2.74 g; calcium citrate, 12.33 g; CaHPO<sub>4</sub>·2H<sub>2</sub>O, 4.5 g; K<sub>2</sub>HPO<sub>4</sub>, 8.75 g; KCl, 4.99 g; NaCl, 3.08 g; MgSO<sub>4</sub>, 1.53 g; MgCO<sub>3</sub>, 1.41 g; ammonium ferric citrate (brown, 20.5–22.5% Fe), 0.61 g; MnSO<sub>4</sub>·H<sub>2</sub>O, 8.0 mg; CuSO<sub>4</sub>·5H<sub>2</sub>O, 3.1 mg; KI, 1.6 mg; NaF, 20.3 mg; Al-NH<sub>4</sub>(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O, 3.6 mg. <sup>d</sup> Sixteen grams of vitamin mixture added to 1 kg of diet comprised of the following: vitamin A, 16 mg (~3200 IU); vitamin D<sub>3</sub>, 128 μg (~240 IU); thiamin, 640 μg; riboflavin, 1.6 mg; nicotinamide, 6.4 mg; pantothenic acid, 1.6 mg; α-tocopherol, 320 μg; pyridoxine, 160 μg; potato starch (autoclaved), 15.97 g. <sup>e</sup> The composition of the N-free mixture is given in Table II.

Table II. Composition of Nitrogen-Free Mixture

sucrose	9.0%
cellulose powder	5.2%
groundnut oil	5.2%
potato starch (autoclaved)	80.6%

method of Nagy et al. (1941). At each stage completeness of extraction was checked by measuring the absorbance of the last extract at 280 nm. Nitrogen was determined by micro-Kjeldahl method (AOAC, 1965).

**Preparation of Isonitrogenous Diets.** Normal, modified *o2*, and pulse isonitrogenous (1.5% N) diets were

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