REVIEW ARTICLE

Plant growth regulators—their structure and interactions

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The normal development of a plant is controlled by a delicately balanced complex of growth coordinating, stimulating and inhibiting substances. Several classes of these substances, collectively known as plant growth substances, have been identified, and among these, auxins and cytokinins have attracted the attention of biologists, chemists and crystallographers. Here I review various theories proposed for auxin activity in the context of results obtained from single-crystal studies. From the analysis it appears that conformational, electronic and stereochemical features play a major role in determining the activity of these substances. Results obtained from crystallographic studies on cytokinins and carbamates have also been presented.

PLANT growth regulators, also known as phytohormones, are chemical substances known to be involved in the control of normal development in plants by delicately balancing growth-coordinating factors. The use of the word 'hormones' has been questioned recently[1], as in plants, growth-regulating compounds are not necessarily synthesized at points removed from their sites of action. In some instances the word hormone is used for naturally occurring compounds rather than for the synthetic analogues. Nevertheless, plants do contain low-molecular-weight substances active at very low concentration in regulating growth and development. Several of these substances, like auxins, cytokinins, gibberellins, ethene, abscisic acid, unsaturated lactones, coconut milk factors, etc., have been identified and their roles defined. Indole-3-acetic acid (IAA) and abscisic acid are well-known naturally occurring growth regulators while 2,4-dichlorophenoxyacetic acid is the best known synthetic auxin. While the traditional concept of growth regulation invokes changes in concentration of growth substances, it has been proposed by Trewavas[1] and others that tissue sensitivity to growth substances is the key factor in plant development. The tissue sensitivity idea leads, logically, to the existence of hormone receptors, as change in sensitivity, i.e. the ability of a tissue to respond to a given concentration of a hormone, can be equated to some change in receptor properties like hormone binding affinity, number, etc. The existence of the hormone receptor is further substantiated by the stringent structural and stereochemical constraints on plant growth substances for activity.

The study of plant growth substances alone cannot provide all the answers to the problem. This article presents a summary of the work carried out on auxins and other plant growth regulators in my laboratory and elsewhere. Structure–activity concepts have been developed in the case of auxins but other classes of plant growth regulators have not attracted the same attention. Figure 1 gives examples in each class of compound.

Theoretical models

Several theories for the action of auxins based on their chemical structures have been proposed. Most important of these are the conformational change theory of Kaethner[2] and the charge separation theory of Porter and Thimann[3] which was later modified by Ferrimond *et al.*[4]

The relevance of charged regions of auxins to receptor binding led to the formulation of the charge separation theory. The theory suggests that active auxins have a fractional positive charge (on the indole nitrogen in the case of IAA) located at a distance of 5.5 Å from the negatively charged carboxyl group. However, Ferrimond *et al.*[4] calculated a net negative charge rather than a positive charge for the indole-ring nitrogen. Likewise, 2,4-dichlorophenoxyacetic acid was calculated to carry a negative charge in that ring position which the Porter and Thimann proposal required to be positive. More anomalies were reported when a comparison of active and inactive analogues in the phenoxy- and naphthoxyacetic acid series of auxins[4] was made. Further, there was no correlation between the magnitude of a fractional positive charge and auxin activity, and the theory was unable to explain the contrasting auxin activities of enantiomeric pairs like the active $R(+)$ and inactive $S(-)$ phenoxy propionates. Hence it was concluded that, at best, the charge separation theory could represent a minimal structural requirement for activity.

In the conformational change theory, hormonal activity of auxins was attributed to the ability of the bound auxin to undergo conformational change simultaneously with the receptor. According to this theory competence as auxin requires adoption of the planar recognition conformation (i.e. the carboxyl group is coplanar with the ring system) and an ability to move in concert with the receptor to the modulation

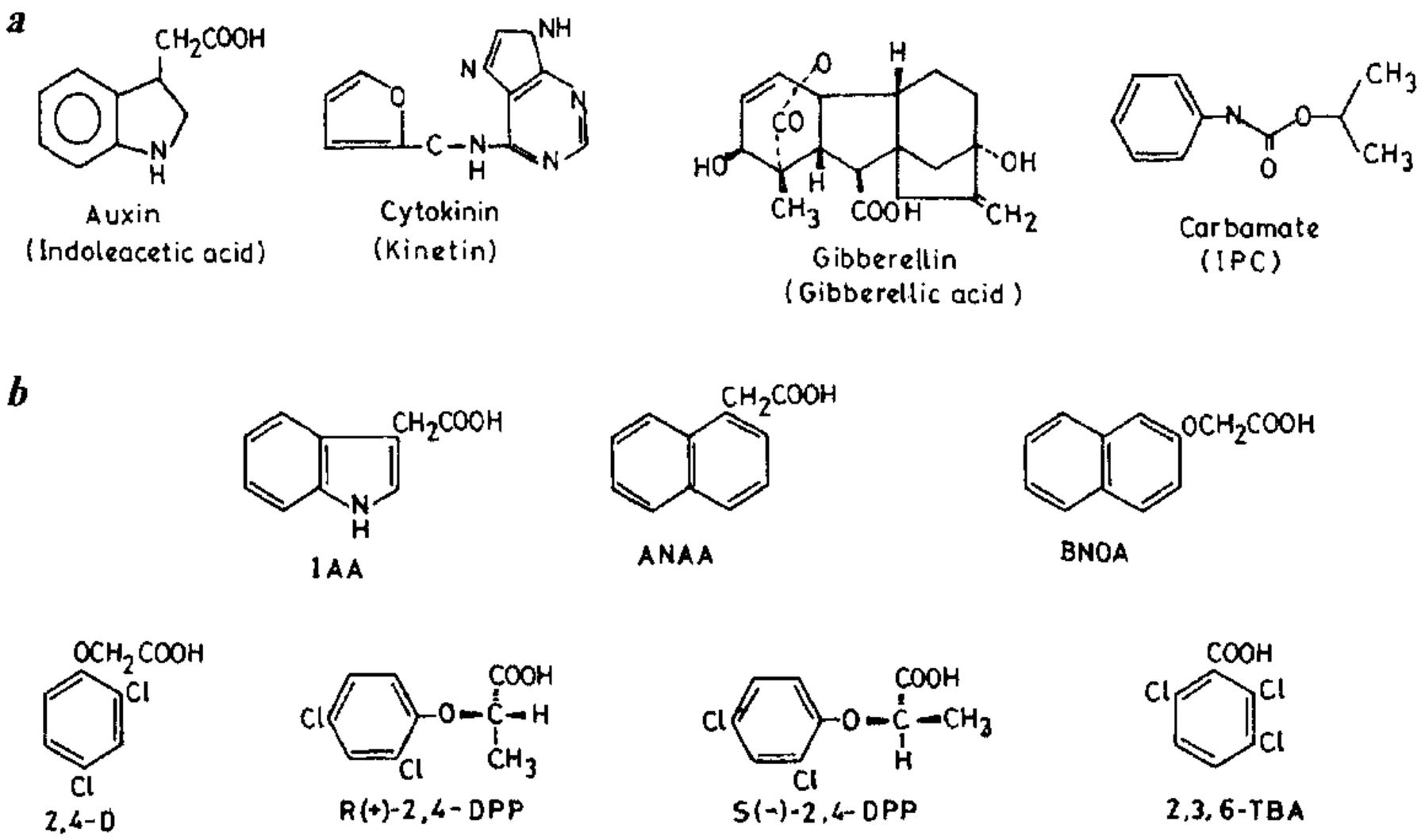


Figure 1. *a*, Examples in each class of plant growth regulators. *b*, Structural formulae. IAA, Indoleacetic acid; ANAA, α-naphthaleneacetic acid; BNOA, β-naphthoxyacetic acid; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DPP, 2,4-dichlorophenoxy-propionic acid; 2,3,6-TBA, 2,3,6-trichlorobenzoic acid; Trans CA, *trans*-cinnamic acid; Cis CA, *cis*-cinnamic acid.

or perpendicular conformation (the carboxyl group is perpendicular to the plane of the ring). Veldstra[5] noted that the requirement with regard to substituents implies the absence of hindrances to the fitting of the molecule on the receptor, rather than specific binding spots.

Several more recent theories subscribe to these general principles by making explicit proposals for receptor configuration that would be needed to accommodate the diverse range of active auxin structures[6]. None of these proposals was without difficulties, but by proposing a model for the receptor there is a shift in emphasis. Figure 2,*a* shows Kaethner's receptor model, which contains five regions of auxin interaction, viz. i, ii and iii, which are electrophilic, iv, which is nucleophilic, and v, which is a hydrophobic cleft (this must be electrophilic according to Ferrimond *et al.*'s proposal[4]).

Figure 2,*b* shows the receptor site proposed by Katekar[6]. This was conceived as complementary to the IAA molecule and had IAA binding the receptor in an extended planar conformation. The hatched areas represent regions of steric obstruction. In addition to a carboxyl-acceptor region, the receptor is considered as an electrophilic area that accepts the indole ring (Ar_1 and Ar_2), and extends beyond the boundaries of the indole ring (areas a–f). The suggestion of an electrophilic rather than a nucleophilic ring-binding region is consistent with the findings of Ferrimond *et al.*[4] Conformational change after hormone–receptor binding does not feature in Katekar's proposal. All the receptor topography theories are based on model building. However, with modern computer graphics it should be possible to come out with more satisfactory proposals.

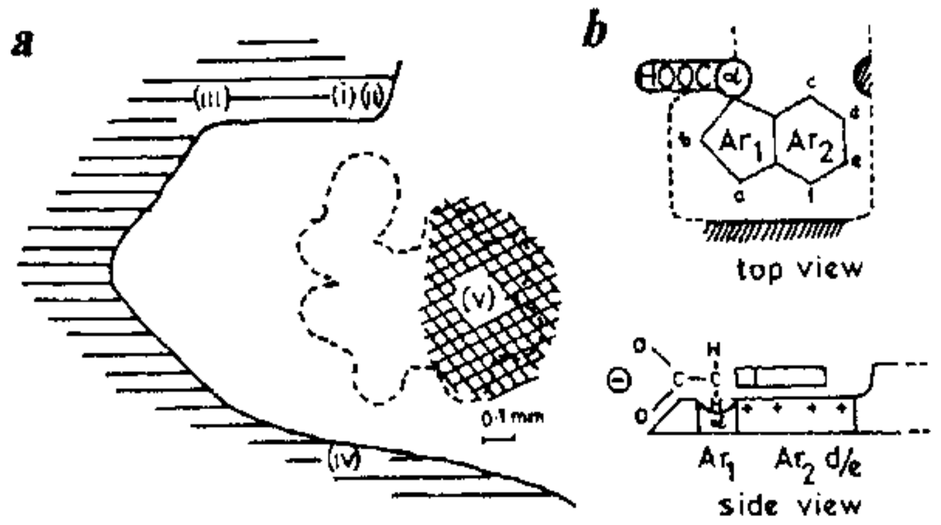


Figure 2. Models of auxin receptor proposed by (*a*) Kaethner (1977) and (*b*) Katekar (1979).

Crystal-structure studies of auxins

The approach of my laboratory to the problem was multifaceted. We have determined the crystal structures of several plant hormones and have attempted to identify the similarities and differences in these structures.

Figure 3,*a* gives the stereo view of an auxin molecule. Table 1a gives the important torsion angles as observed in crystal structures of some representative molecules, and Table 1b gives the angle between the ring and the carboxyl-group planes. It can be seen that, though the observed torsion angles do not explain the degree of activity of these molecules, the dihedral angle, which describes the orientation of carboxyl group with respect to the ring, does show a relationship with activity. All the active auxins, except 2-chlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and β-naphthoxyacetic acid, have assumed perpendicular conformation in the solid state (Table 1b).

Secondly we have calculated the charge densities for various auxin molecules, using the Del Re method[7] for calculation of σ charges and the Huckel LCAO MO method[8] for π charges (Figure 4). The details of these calculations have been published elsewhere[9]. We have used crystallographic coordinates for calculating the charge separations between the negatively charged carboxyl-group oxygen and an atom with positive charge in the ring nucleus (Table 2). Table 2 shows that the charge separation is of the order of 5.5 ± 0.4 Å in the case of perpendicular conformation and varies between 3.6 and 6.8 Å in the case of planar conformation.

Finally, semi-empirical potential energy calculations were done for some auxins to verify Kaethner's conformational change theory. Non-bonded energies were calculated using the Buckingham model potential function[10] at 10° intervals for rotation about the O7–C8 bond (Figure 4, *a*). Table 3 gives the results of the energy calculations. It can be seen that the torsion angle about O7–C8 is quite flexible for 2-chlorophenoxyacetic acid (varies between +93 and −86°). Similar observations were made for β-naphthoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid, which explains the anomaly observed in the dihedral angles of these active molecules in Table 1b. At the same time, it is obvious from Table 3 that the energy needed to change from one conformation to the other in some cases is very high. Further, it is known that *cis* cinnamic acids are active auxins while their *trans* isomers are not. From Table 1b one can notice that the *cis* isomers adopt perpendicular conformation while planar conformation is preferred by the *trans* isomers. If Kaethner's theory is valid then *trans* isomers can bind the receptor but they are inactive as they cannot undergo conformational change. But this theory cannot explain the activity of *cis* isomers as they cannot assume planar conformation, which is stated to be necessary for binding. Benzoic acid is another interesting example. The molecule generally exists in planar conformation, but when both 2 and 6 positions are substituted the carboxyl group takes up a perpendicular conformation, making 2.3,6-

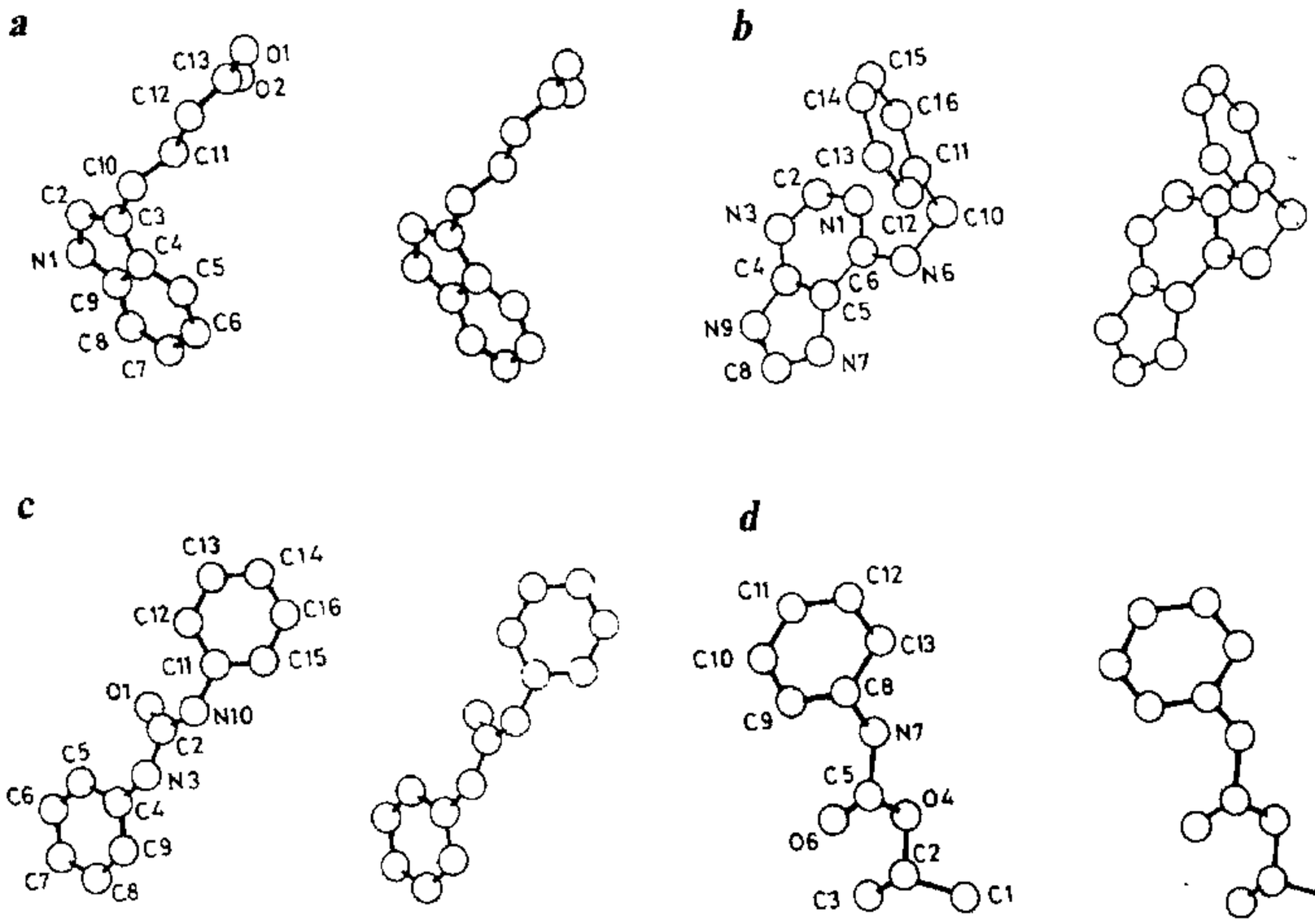


Figure 3. Stereo views of (*a*) indolebutyric acid; (*b*) N^6-benzyladenine, (*c*) diphenylurea, (*d*) isopropyl *N*-phenyl-carbamate.

Table 1. Conformational parameters for auxins and analogues.

a, Torsion angles*.

Compound	C2–C1–O7–C8	C1–O7–C8–C9	C7–C8–C9–O11	Activity†	Ref.
Phenoxyacetic acid	176.1	−175.1	179.2	I	21
2-Chlorophenoxyacetic acid	178.9	−173.2	−177.5	A	22
2,4-Dichlorophenoxyacetic acid	179.1	80.4	−173.1	HA	23
2,4,5-Trichlorophenoxyacetic acid	174.2	−171.6	−179.6	HA	24
±2-(2-Chlorophenoxy) propionic acid	181.0	66.3	−161.0	A	25
±2-(3,5-Dichlorophenoxy) propionic acid	181.8	73.1	−148.9	I	26

*Numbering as in Figure 4,*a*.
†A, Active; HA, highly active; I, inactive.

b, Dihedral angle between the carboxyl group and the rigid nucleus.

Compound	Dihedral angle	Activity	Ref.
Phenoxyacetic acid			
2-Chlorophenoxyacetic acid	(a) 7 (b) 6.6	A	22
2,4-Dichlorophenoxyacetic acid	85.2	HA	23
2,5-Dichlorophenoxyacetic acid	81.2	HA	27
2,4,5-Trichlorophenoxyacetic acid	4.2	HA	24
2,4,6-Trichlorophenoxyacetic acid	32.0	I	28
Phenoxypropionic acid			
3,5-Dichlorophenoxypropionic acid	87.0	I	26
2,4,5-Trichlorophenoxypropionic acid	77.8	A	29
3-Bromophenoxypropionic acid	85.5	I	30
3-Methoxyphenoxypropionic acid	85.5	I	30
2,4-Chlorophenoxypropionic acid	73.6	A	21,31
Benzoic acid			
Benzoic acid	2		32
4-Chlorobenzoic acid	5.7		33
2-Chlorobenzoic acid	13.7		34
4-Nitrobenzoic acid	3.3		35
4-Bromobenzoic acid	5.8		36
2,6-Dimethylbenzoic acid	53.5	A	37
3,4,5-Trimethylbenzoic acid	5.1		38
2,4,6-Trimethylbenzoic acid	48.5		39
2,3-Dimethylbenzoic acid	10		40
Cinnamic acid			
cis-Cinnamic acid		A	
β-Chlorocinnamic acid	35.4		41
β-Methylcinnamic acid	83		41
2-Ethyoxycinnamic acid	61.4		42
trans-Cinnamic acid		I	
2-Coumaric acid	4.8		43
3-Coumaric acid	6.5		44
4-Coumaric acid	5.0		45
β-Chloro-*trans*-cinnamic acid	11.7		41
3,4-Methylene-dioxy-*trans*-cinnamic acid	5.4		46
3-Methoxy-4-hydroxy-*trans*-cinnamic acid	4.0		47
Others			
α-Naphthaleneacetic acid	98.7	A	48
β-Naphthoxyacetic acid	4.2	A	49
Indoleacetic acid	89.9	HA	50, 51
Indolebutyric acid (Form I)	93.6	A	52
Indolebutyric acid (Form II)	3.9		53
4-(3-Indolyl)butyric acid (picric acid complex)	82.9 (Mol. I) 86.9 (Mol. II)	A	54

tribromobenzoic acid active. The inactive nature of 3,5-dichloro derivatives cannot be explained on the basis of the charge separation theory, but the size of the molecule, i.e. stereochemical criteria, may be the restricting factor in this case[9].

We infer from the above that the active auxins bind the receptor in perpendicular conformation rather than in the planar conformation.

Lastly, it has been reported that, in general, D–isomers are more strongly auxinic than the L–isomers[11]. For example, D-phenoxypropionic acid shows stronger auxin activity than its antipode. However, both positive and negative isomers possess the essential groupings, charge separation, etc., but, presumably, only in the former do they occur in appropriate positions for presentation to the receptor groups; in the negative isomer these are unsuitably placed for receptor binding, so this isomer has only negligible growth-regulating activity.

Thus it is apparent that the stereochemical criterion is the deciding factor in receptor binding while electronic configuration plays a secondary role. Factors like lipophilicity of the molecule may also contribute to variation in activity. Hence the size of the molecule, in conjunction with appropriate orientation of active groups, is necessary for activity of auxin molecules. Further, change in conformation after receptor binding appears to be unnecessary. Thus the receptor model proposed by Katekar seems to be in agreement with several factors observed crystallographically.

Cytokinins

The first cytokinin to be described was kinetin (6-

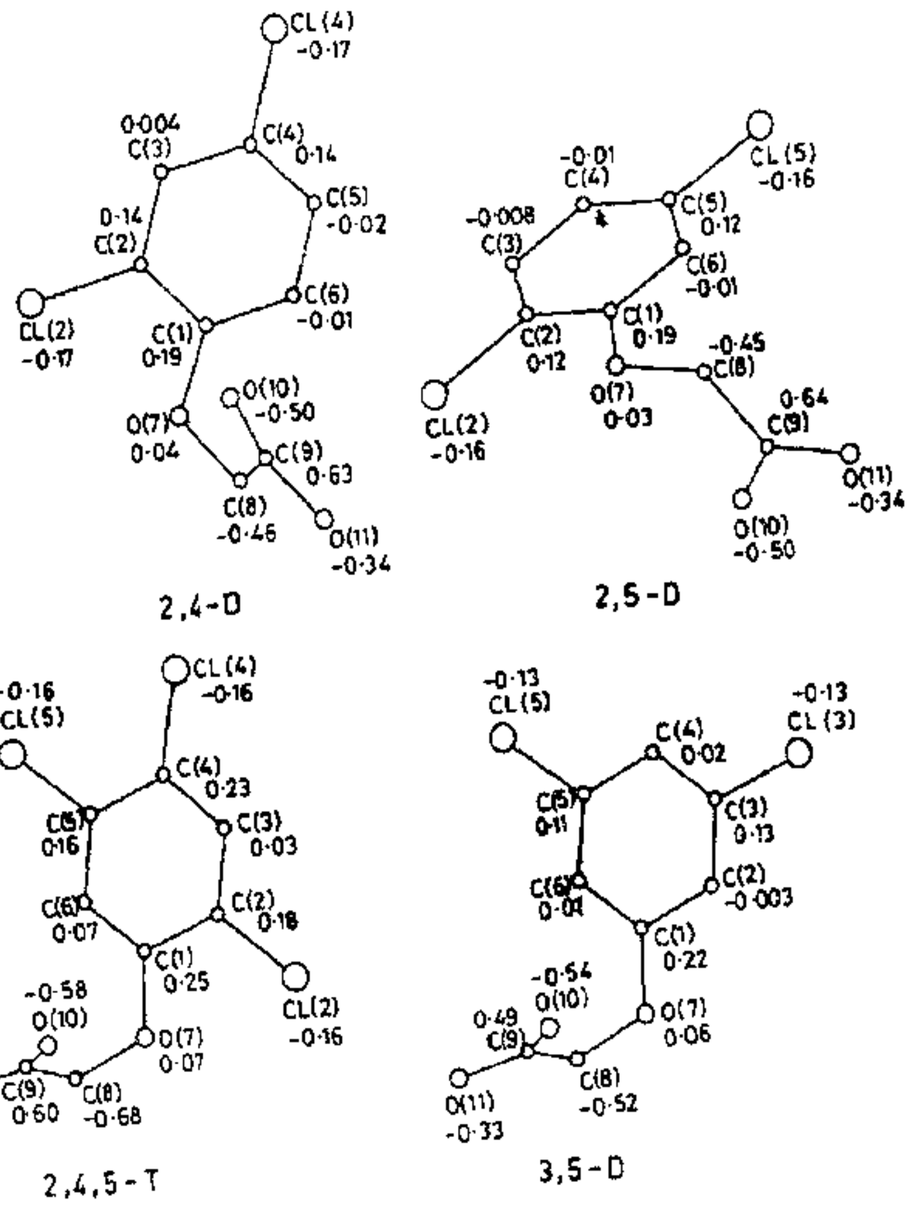


Figure 4. Calculated charge densities for various auxins.

furfurylaminopurine), which is actually a breakdown product of an animal nucleic acid preparation discovered during plant tissue culture studies[12]. Subsequently naturally occurring cytokinins were detected in a

Table 2. Charge separation (in Å) in various auxins.

Compound	Perpendicular conformation	Parallel conformation
Active auxins		
Indoleacetic acid O(1) . . . C(9)*	5.71	5.94
Indolebutyric acid O(2) . . . C(2)	5.97	4.76
α-Naphthaleneacetic acid O(1) . . . C(7)	5.35	6.47
β-Naphthoxyacetic acid O(3) . . . C(6)	5.30	6.80
2,4-Dichlorophenoxyacetic acid O(10). . . C(3)	5.12	4.11
2,4,5-Trichlorophenoxyacetic acid O(11) . . . C(3)	5.98	6.74
Inactive auxins		
3,5-Dichlorophenoxyacetic acid O(10) . . . C(4)	5.25	3.63

*Numbering as in Figure 4.

number of plants. In tissue cultures, cytokinins, unlike auxins and gibberellins, appear to influence elongation as well as cell division. Figure 5 shows the chemical structures of typical members of the cytokinin family. A stereo view of N^6-benzyladenine molecule is shown in Figure 3,*b*. Table 4 lists conformational parameters for cytokinins in the solid state. It is apparent from the table that in all the active cytokinins the N^6 substituent is distal to the imidazole ring of the adenine moiety. The angle between the mean planes of the adenine base and the N^6 substituent is 65 to 90°. Base stacking is very minimal or nil. Thus, a free N1 position, a distal N^6 substituent, and absence of base stacking seem to be the necessary requirements for cytokinin activity[13].

Coconut milk factors

Inositol, diphenylurea (Figure 3,*c*) and sorbitol are components of an active fraction in coconut milk. These plant growth regulators are reported to have kinin-like activity. However, diphenylurea is structurally unlike other cytokinins as it does not have an adenine nucleus with the purine ring intact and with N^6 substituents. Diphenylurea is a derivative of urea which is reported to be an effective fertilizer that can be applied as a foliar spray. Through enzyme action urea is hydrolysed within the plant into various amino acids and may finally be converted into ammonia[14]. Conformational features observed in crystal structure of diphenylurea are as follows[15,16]: the torsion angle C4–N3–C2–N10 is −175.34°, which is different from the value observed in cytokinins for the corresponding torsion angle, viz. C6–N6–C10–C11; the angle between the two aromatic groups is 27.2°, whereas in active cytokinins this dihedral angle is about 90°. From these observations one may expect diphenylurea to exhibit only mild cytokinin activity.

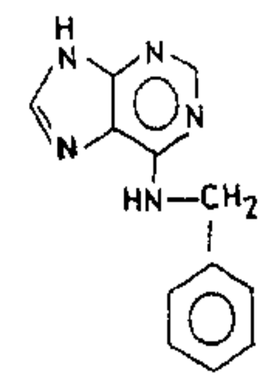
Table 3. Calculated energies for various values of torsion angles in auxins.
T_1, Observed torsion angle C–O–C–C*.
T_2, Various values of torsion angle for energy calculations.

Torsion angle T_2	Energy (kJ mol^{-1})
Indoleacetic acid, $T_1 = 108.09°$	
36	12.13
96	8.56
156	8.84
186	9.86
216	8.85
306	9.57
336	11.40
Indolebutyric acid, $T_1 = -179.55°$	
50	10.72
90	8.33
170	8.59
250	8.50
330	18.46
2-Chlorophenoxyacetic acid, $T_1 = -173.2°$	
23	881.0
63	30.2
83	19.3
103	17.4
143	17.1
184	17.2
234	17.1
284	21.5
324	255.4
β-Naphthoxyacetic acid, $T_1 = 176.5°$	
7	1827.0
97	19.6
187	19.7
277	20.3
2,4,5-Trichlorophenoxyacetic acid, $T_1 = -174.7°$	
11	2026.0
100	10.8
190	10.9
280	12.0
2,4,6-Trichlorophenoxyacetic acid, $T_1 = -152.3°$	
15	151.0
95	15.3
135	6.4
175	6.6
215	6.3
295	17.5
335	44.7
2,4-Dichlorophenoxyacetic acid, $T_1 = -80.42°$	
19	421.0
49	29.4
79	10.3
169	9.7
199	9.7
289	11.3
319	47.3
349	610.0

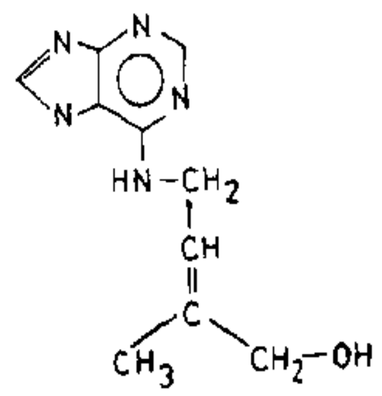
*For IAA, ANAA and IBA, T_1 is C–C–C–C connecting the carboxyl group and the rigid nucleus.

Carbamates

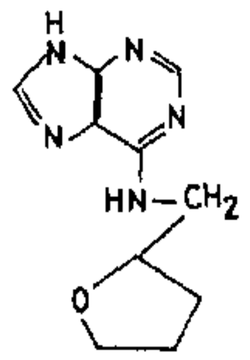
Carbamates like isopropyl *N*-phenylcarbamate, its chlorine derivative, and dithiocarbamate are selective growth inhibitors. Activity of thiocarbamates in fact suggests that the requirement of an unsaturated ring does not seem to be always valid. Figure 3,*d* shows the crystal structure of isopropyl *N*-phenylcarbamate[17]. Table 5 lists some of the conformational features of carbamates. It can be inferred from this table that though T_1 takes all values from 0 to 180°, T_2 has a preference for *gauche* conformation. Charge-density



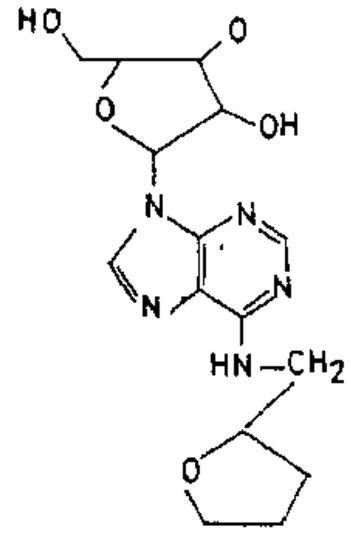
N^6–benzyladenine



Zeatin



Kinetin



Kinetin riboside

Figure 5. Chemical structures of some active cytokinins.

Table 4. Conformational parameters for cytokinins.
a, Torsion angles*.

Angle	N^6-Benzyl-adenine	N^6-(Δ^2-iso-pentenyl) adenine	Kinetin riboside	Kinetin	Zeatin
C5–C6–N6–C10	−174.4(3)	−177.0(1)	−168.0(11)	174.2(7)	−177.1(6)
C6–N6–C10–C11	80.9(3)	92.2(2)	73.6(17)	−78.7(3)	−116.4(7)
C16–C11–C10–N6	−110.0(4)	−117.1(1)	−120.6(20)	107.8(3)	−109.9(8)

b, Dihedral angle between adenine plane and mean plane through N^6 substituent.

Compound	Dihedral angle	Ref.
N^6-Benzyladenine	78.5	55
Kinetin	79.0	56
Kinetin ribonucleoside	97.7	57
N^6-(Δ^2-isopentenyl)adenine	72.0	58
2-Methylthio analogue of N^6-(Δ^2-isopentenyl)adenine	91.0	59
N^6-Benzoyladenine†	7.4	60
Zeatin Mol. I	65.6	61
Mol. II	63.3	61

*Numbering as in Figure 3,*b*.
†Shows only mild cytokinin activity.

Table 5. Conformational parameters (angles in degrees) for carbamates.

Compound	C O–C–C*	N–C–O C	C–N C–O	T_1	T_2	Ref.
bis(4-Hydroxybutyl)4,4′-methylene*bis*(phenylcarbamate)	170.9	176.9	179.3	13.7	84.6	62
Ethyl carbamate	−179.1	−179.2	0.96	1.5	—	63
2-Propylpentyl carbamate (at −100°C)	−160.3	−179.1	2.0	35.1	72.5	64
4-Propylheptyl *N*-phenylcarbamate (at 20°C)	−159.2	179.8	—	—	59.9	64
Isopropyl *N*-(methylfuroxan)carbamate, isomer A	154.2	179.5	92.5	159.0	88.0	65
Isopropyl *N*-(methylfuroxan)carbamate, isomer B	−124.0	171.1	3.9	54.0	50.0	65
Isopropyl *N*-phenylcarbamate	−143.0	−175.0	−170.0	31.0	32.0	17

*See Figure 3.*d*.

T_1, Angle between the rigid nucleus and the carbamate group plane; T_2, angle between the rigid nucleus and the tail-group plane.

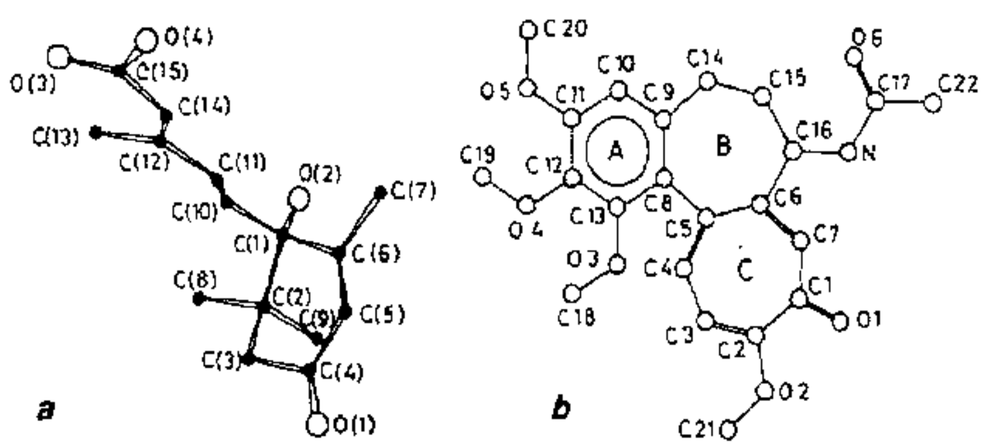


Figure 6. Numbering scheme used in (*a*) abscisic acid and (*b*) colchicine.

calculations for IPC gave 5.53(5) Å and 5.82(5) Å for the distance of separation between the negatively charged methyl carbons (C3 and C1 respectively) and the positively charged C8 atom of the ring (Figure 3,*d*), which are comparable with the suggested value of 5.5 Å for auxins. From the above it appears that carbamates, like auxins, require a particular spatial orientation of the tail-group with respect to the rigid nucleus in addition to the charge separation of 5.5 Å for their activity. However, further studies are necessary for a conclusive argument.

Others

It may be appropriate to mention crystal structures of abscisic acid and colchicine[18, 19] here (Figure 6). Abscisic acid causes abscission of leaves and induces lormancy in buds and seeds while colchicine arrests nitosis in plants[20]. Conformational features of interest .re as follows:

Dihedral angle between the carboxyl group and the aromatic group in abscisic and is 102.9°, while the torsion angle C11–C12–C14–C15 is 176.8° (Figure 6). In colchicine the dihedral angles between various planes are:

Plane		Molecule A	Molecule B
Ring A	Ring C	53	51
Ring A	Group D	67	66
Ring C	Group D	87	90

Ring A and group D, i.e. the *N*-acetyl side-chain (C16, N, C17, O6 and C22), are nearly coplanar.

It is interesting to note that the dihedral angle between various planes in both these molecules is in the range of 50 to 100°, as in the case of other active plant growth regulators.

Conclusion

Data on several plant growth substances are being accumulated. Each class of compounds has special structural characteristics and has effects on different parts of plants. I have attempted to fit crystallographic data with results obtained from other studies. From the results discussed one may conclude that these substances have specific active groups, the relative orientations of which provide an idea of the shape of the binding site of the receptor molecule. In addition, the presence of electrophilic regions and the difference in activity of enantiomers suggest specific binding of these groups with the receptors.

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