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PERSPECTIVE

In memoriam Professor Corwin Hansch: birth pangs of QSAR before 1961

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It was just half a century ago, June 14th 1961, that I joined Corwin Hansch at Pomona College as a postdoctoral fellow. My first impression of him was that he was intelligent and considerate. This was correct and our nice and friendly relationship had continued until his passing away. Except for the first several months in 1961, I was the only member of his group until September 1963. Through the face-to-face communication, I learned a lot from him explicitly as well as tacitly. It is really sad, especially when I realize that I cannot share with him academic interests as well as memories in good old postdoctoral days any more. Here, I would like to commemorate him by recalling what he had done before 1961 and "how and why" his previous research was evolved into the so-called QSAR. I would like to dedicate this article to Corwin anticipating his favorable (but never-realized) response, and to pray most sincerely for his repose.

Beginning of the structure–activity study of plant growth hormones at Pomona college: formulation of two-point attachment hypothesis for substituted phenoxyacetic acids

After indole-3-acetic acid (IAA) was identified to be the natural plant hormone to regulate the plant growth in 1934 [1], a number of analogous aromatic carboxylic acids were synthesized and tested. In 1941, 2-methyl-4-chlorophenoxyacetic acid (2-Me-4-Cl-POA: MCPA) and 2,4-Cl_2-POA (2,4-D), both being markedly active as the growth hormone, were found to be highly active as selective herbicides to eradicate broad leaf weeds while protecting grass crops by W. G. Templeman and W. A. Sexton at ICI in the UK (now a part of Syngenta) [2]. In the following years, not only substituted POAs but also substituted phenylacetic (PAA) and benzoic acids (BA) were explored extensively and the effect of ring-substituents on the potency variations was vigorously investigated by various groups of scientists. The reason was probably to discover compounds more potent and versatile than MCPA and 2,4-D as well as to elucidate structure–activity relationships for molecular mechanism of growth hormones in addition to simplicity in their structure and synthesis.

From 1949 to 1953, Corwin collaborated with Robert Muir, Professor of Botany at University of Iowa, and published five papers [3–7] in which they systematically investigated and analyzed the growth activity of synthetic hormones using a reliable bioassay procedure elaborated by them to measure the stem elongation of oat seedlings [3]. While the 3-Cl-, 4-Cl-, 3-Br- and 4-Br-POAs were about 100 times more potent than POA and about 1/10 less potent than 2,4-D, the 2,4,5-Cl_3-POA was as active as 2,4-D. The effect of 3-NO_2 and 4-NO_2 groups was to make the activity of POA about 4–7 times more potent. On the other hand, 3-Me, 4-Me, 3-OMe, and 4-OMe substituents did not improve the activity of POA. In addition, 2,4,6-Cl_3-, 2,4,6-Br_3-, 2,4,6-Me_3- and 2,4-Cl_2-6-Me- POAs were inactive as shown in Fig. 1 [7].

Because the simultaneous occupation of the 2- and 6-positions produced inactive compounds, and also because electron-withdrawing substituents such as halogen and NO_2 tended to promote activity and electron-donating substituents such as Me and OMe did not, the Pomona group assumed that the plant cell growth is a consequence

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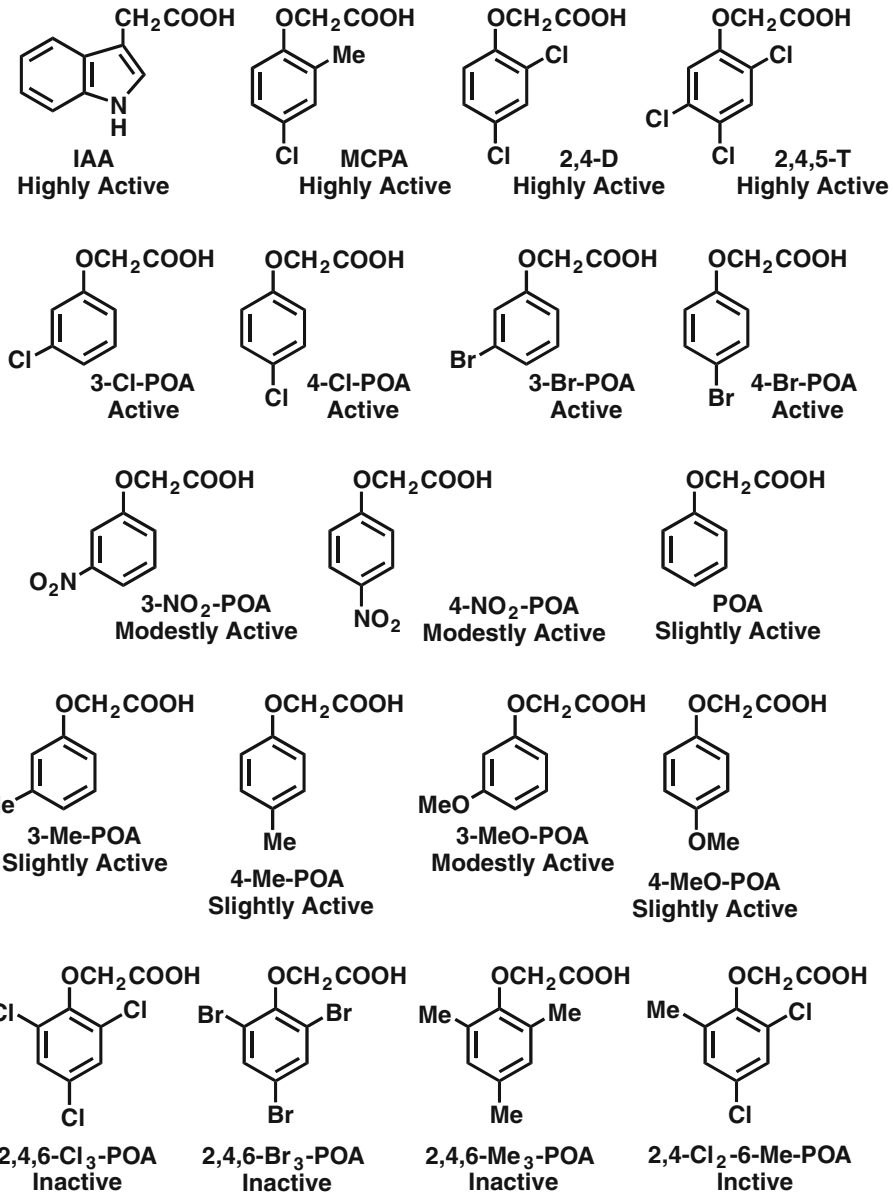


Fig. 1 Structure and activity of phenoxyacetic acids

of a true chemical reaction between growth hormone and plant substrate [3–5]. Their hypothesis was clearly formulated in the article published in 1951 [5] that one of the unoccupied ortho positions is attacked by (attaches to) an electron-rich site of a certain plant substrate leading to replacement with it releasing the ortho H. Because the side chain COOH is almost compulsory for the activity, it was supposed to attach to a basic group of substrate components. The Pomona group considered the cysteinyl side chain of a protein as the most likely substrate in the above two-point attachment hypothesis. The –SH and $-NH_3^+$ groups in the cysteinyl side chain of protein were assumed to be the nucleophilic and basic sites, respectively as depicted in Fig. 2.

Extension of the two-point attachment hypothesis to benzoic acid type plant growth hormones

The first growth hormone recorded in the substituted BA series was 2-Br-3-NO_2-BA, which was synthesized and tested at the Boyce Thompson Institute in the US in 1942 [8]. Because the activity of this compound was very low in a standard test, the effect of substituents in the BA series had not been studied so actively until 2,3,6-Cl_3-BA was discovered at Manchester University in the UK in 1950 [9] to be highly potent as the growth hormone and at ICI in 1951 [10] to be selectively toxic against dicot weeds but safe to wheat. The Pomona group observed that BAs that are unsubstituted and mono-substituted by electron-donating

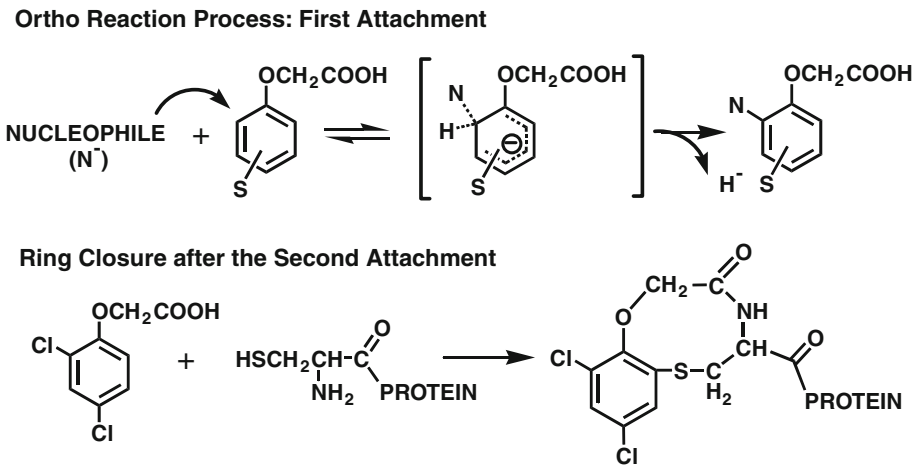


Fig. 2 Two-point attachment hypothesis for POAs

OH, OMe, and NH_2 groups at any positions were inactive, whereas electron-withdrawing Br, Cl, and NO_2 substituents at the 2-position induced the appreciable activity about 1/250–1/500 that of 2,4-D. More active were 2,5- and 2,6-Cl_2-BAs in a range of 1/10–1/100 that of 2,4-D, whereas 2,6-$(OMe)_2$-BA was inactive and 2,6-Me_2-BA was very slightly active as shown in Fig. 3. Other di- and tri-substituted BAs with substituents at the 4-position were inactive [7].

The substitution pattern favorable to the activity was apparently different from that in the POA series. The most conspicuous difference was the effect of 2,6-Cl_2-substitution, which is necessary for the high activity in BAs but unfavorable in POAs. To incorporate the active BAs in the two-point attachment hypothesis, they "logically" extended the concept of the nucleophilic substitution occurring at the ortho position. Because the COOH group is more electron-withdrawing than the OCH_2COOH substituent, the nucleophilic attack of the plant component, such as cysteinyl SH, to the ortho position was supposed to occur more easily in active BAs than in the POA counterparts [5]. For active BAs with a 2-Cl substituent, the growth reaction was anticipated to proceed with release of Cl^- ion as drawn in Fig. 4. To confirm this, the Pomona group analyzed the Cl^- ion concentration in the culture solution medium to measure elongation of oat segments using active 2,6- and inactive 2,4-Cl_2-BAs, and observed that the amount of Cl^- ion released from 2,6-Cl_2-BA was indeed higher than that from the inactive 2,4-isomer in 1951 [6].

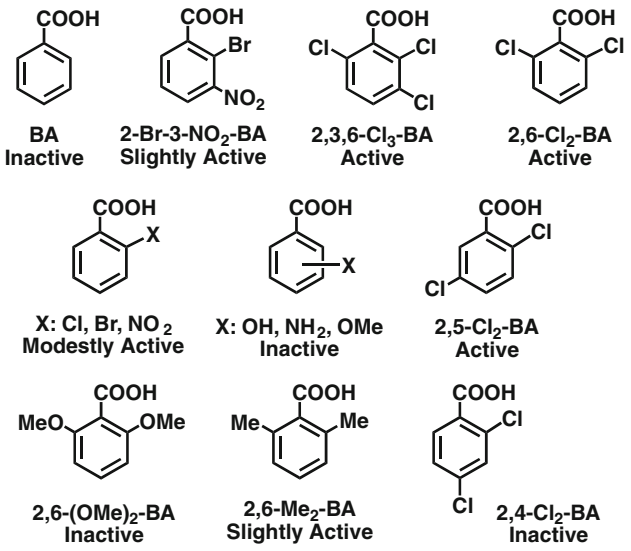


Fig. 3 Structure and activity of benzoic acids

Pros and cons of the two-point attachment hypothesis

The two-point attachment hypothesis for the mechanism of action of POA series was highly appreciated by James Bonner, Professor of Plant Physiology at California Institute of Technology in his review article of 1952 [11]. The Caltech group "supported" the hypothesis by showing that the growth reaction of oat segments with 2,4-D was analyzed and elucidated very well in terms of the Michaelis–Menten enzymatic kinetics. In this analysis, 2,4-D was regarded as an exogenous cofactor/substrate, and competitive antagonists against two types of attachment site were "identified", i.e., 2,4-Cl_2-anisole being only able to participate in the nucleophilic interaction at the unoccupied ortho position and 2,6-Cl_2-POA being only able to attach to the basic site of plant protein [12]. In addition, 2,4,6-Cl_3-anisole with neither site of attachment types was not an antagonist [13]. The situation is depicted in Fig. 5. The mechanism of action of BA series was also "supported" by K. Fukui, a Nobel Prize Professor of Theoretical Chemistry at Kyoto University in Japan. Fukui's group calculated a reactivity index, called superdelocalizability, for the ortho

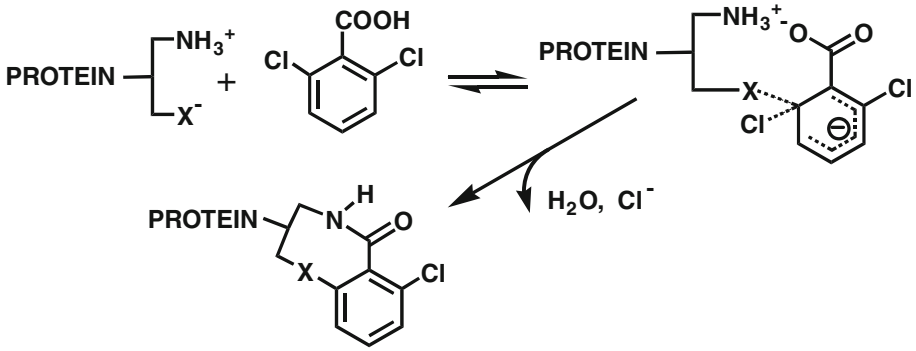


Fig. 4 Two-point attachment hypothesis for benzoic acids

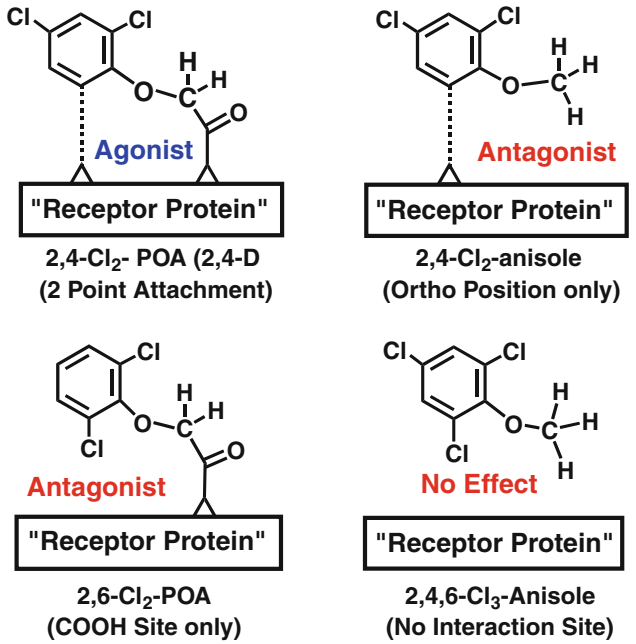


Fig. 5 Antagonism against growth reaction. Adapted from McRae and Bonner [13]

position of various substituted BAs to undergo "nucleophilic attack" quantum-chemically and showed a parallel with the growth hormone potency in their article of 1958 [14]. It should be admitted that the parallel was not complete and the higher reactivity indexes belonged to not only highly active BAs but also a few inactive BAs.

In spite of efforts to elucidate the structure–activity patterns as rationally as possible and "supports" from physiological and theoretical points of view, the two-point attachment hypothesis was not sufficient and a number of newer experimental results that did not fit the hypothesis came out from various groups. To cite a couple of examples, in 1953–1956 R. L. Wain, Professor of Agricultural Chemistry at Wye College in Kent, UK, and his group reported that 2,4-Cl_2-6-F- and 2,4-Br_2-6-F-POAs were highly active to the growth of oat tissues [15, 16]. In addition, whereas the high activity of 2,4-Cl_2-, 2,4-Br_2-, and 2,4,5-Cl_3-POAs is maintained in their side chain α-Me homologs (or α-phenoxypropionic, POP, analogs retaining the POA scaffold), 2,4-Cl_2-6-F- and 2,4-Br_2-6-F-POPs were inactive. To the contrary, the inactive 2,6-Cl_2- and 2,6-Me_2-POAs "recovered" the activity in their corresponding POPs [17]. Thus, for POAs to exhibit high activity, one of the ortho positions may not necessarily be unoccupied contrary to the two-point attachment hypothesis. Besides, potency variations are highly affected not only by ring-substitution pattern but also by side-chain branching not additively/independently but interdependently. The "complex" structure-activity patterns are summarized in Fig. 6.

Haaye Veldstra at the Combined Quinine Works in Amsterdam (moved later in 1959 to be Professor of Biochemistry at Leiden University in Netherlands) reported in 1952 that 2,6-Me_2-3-X-BAs, in which X is NO_2, Cl, Br, and I, were moderately to highly active, whereas 2,6-Br_2-BA was inactive (Fig. 7) [18, 19]. The activity of these BAs was measured using pea seedling sections originally, but reproduced and confirmed later by the Pomona group using oat segments [20]. The sequence of the activity was reverse of that of the anticipated susceptibility to nucleophilic attack according to the two-point attachment hypothesis. The Br^- ion from 2,6-Br_2-BA would be released much easier than Me^- ion from 2,6-Me_2-3-X-BAs.

The two-point attachment or two-point ortho-reaction hypothesis somehow inherits the concept from that proposed by F. W. Went, Professor of Plant Physiology at Caltech in 1941 [21], that the plant growth hormone might be a kind of coenzyme (cofactor) required for some processes essential in growth, the initial steps of which proceed with covalent bond formation [3, 22]. Unfortunately, however, the hypothesis formulated by the Pomona group was obviously inconsistent with newer experimental results as described above. Corwin wanted to rationalize the experimental results observed by Wain's group. He proposed that the activity of 2,4-Cl_2-6-F-POA could be associated with the release of F^- instead of H^- anion [20]. According to a review of van Overbeek at Shell Development Co. in California (now a part of DuPont) [23], J.

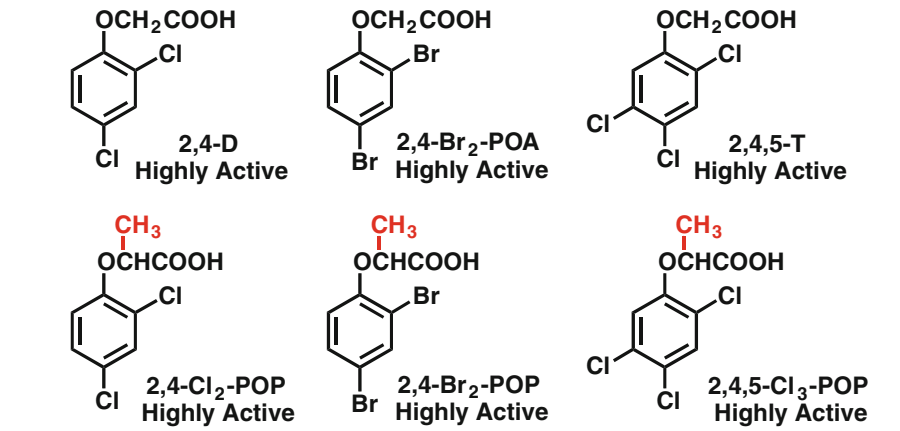


Fig. 6 Effect of α-Me group on the activity of POAs

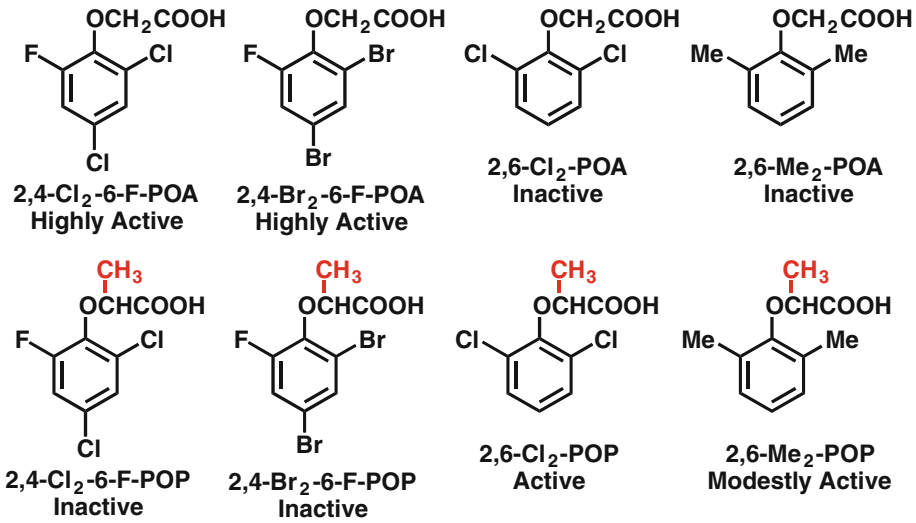
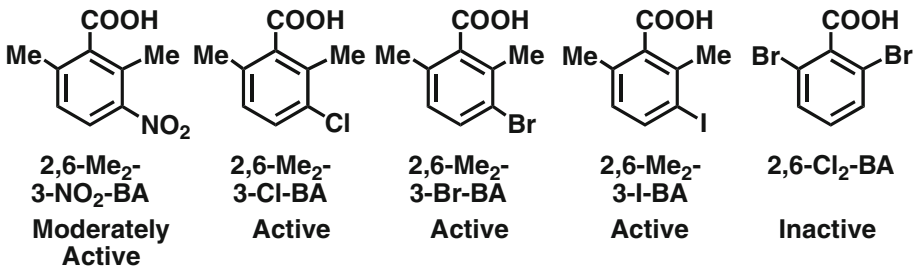


Fig. 7 Structure and activity of some 2,6-disubstituted BAs



Bonner of Caltech had failed to obtain any evidence of the F^- ion release in the culture medium for the growth test of 2,4-Cl_2-6-F-POA.

Physicochemical-mechanism-based hypothesis for structure–activity patterns of plant growth hormones of H. Veldstra

H. Veldstra at the Quinine Works was perhaps the scientist who most severely criticized the two-point attachment hypothesis [19]. The molecule of plant growth hormones generally consists of a lipophilic aromatic ring system and a hydrophilic functional group attached to a particular position of the lipophilic moiety. Based on examinations of structure–activity patterns in other series of bioactive compounds such as androgens and estrogens, he considered that the plant hormone molecules do not work chemically as coenzyme or cofactor, but purely physicochemically [24]. The most important conditions, under which the molecule would work as plant hormone, are a certain balance of the hydrophilic versus lipophilic character and

the COOH group (actually, its dipole moment) projecting from the plane of the lipophilic moiety as perpendicularly as possible. The aromatic moiety was proposed to be located at or adsorbed to a boundary between lipophilic and hydrophilic phases inside the cells such as cellular membrane, and the projecting COOH group (dipole) was assumed to influence the transport to supply cells with water including "nutrients" across the boundary. He published two papers arguing over his hypothesis in detail as early as 1944 (submitted in 1942) [25, 26]. According to Veldstra's hypothesis, a few definite bonds such as those caused by two-point reactions are not able to confer the specificity as the plant growth reaction, but many weak bonds such as hydrogen-bonds and London-van der Waals attractions are necessary for interactions occurring at the cellular boundary. In this hypothesis, such ring substituents as OH and NH_2 would be accounted to work as hydrophilic groups and Cl, Br, I, and Me could be as lipophilic substituents, both participating in the HL-character of the aromatic moiety rather than those of electron-donating and -withdrawing properties, respectively.

Structure–activity observations of Veldstra described above [18, 19] that, while the 2,6-Me_2-3-NO_2-BA was moderately active, the 2,6-Me_2-3-X-BAs (X = Cl, Br, and I) were highly active, could be elucidated by the twisting of the COOH group out of the aromatic ring plane forced by two ortho substituents together with variations in the lipophilicity of substituents at the 3-position. The NO_2 group, being a hydrogen-bond acceptor, is more hydrophilic than Cl, Br, and I. The fact that 2,6-Br_2-BA was inactive could be due to two Br substituents, the total lipophilicity of which is too high beyond optimum and/or the bulkiness of which is so high that the effect of COOH is masked intermolecularly [19].

Two sides of the coin: individually insufficient but complementary two hypotheses

Placing particular emphasis on the physicochemical mechanism but not on the reactivity concept at all, Veldstra did not mention any contribution of an electronic mechanism governing variations in the growth activity [19]. To the contrary, Corwin did not pay much attention to the importance of HL-balance or lipophilicity included in total mechanism in those days perhaps before 1955. In the paper published in 1952 [7], he stated, "from a general consideration of great difference in activity of very similar compounds such as mentioned above, it would seem that knowledge of the HL-ratio would be of little help in predicting or explaining the relative activity except in extreme cases", referring to highly active 2,4,5-Cl_3-POA and inactive 2,4,6-Cl_3-POA.

As a matter of fact, the antagonism in Michaelis–Menten kinetics elaborated by Bonner and his group was not necessarily associated with the covalent formation. Calculations were based on the assumption that the binding of antagonists such as 2,4-Cl_2-anisole and 2,6-Cl_2-POA are absolutely reversible without any bond formation, and possible validity of this kinetics had nothing to do with "definite two sites" in the molecule. It would merely imply that two factors are operating without information about detail of their properties [27]. According to the Fukui's group, the superdelocalizability of a certain position for a series of aromatic compounds to encounter "nucleophilic attack" is not necessarily for the ease of replacement reaction, but could also be an index for the total stabilization energy of charge-transfer complex formation (of charge accepting type) [28].

With such situations that were not necessarily favorable to sticking to the original two-point ortho reaction hypothesis, Corwin gradually shifted his mind toward accepting the significance of hydrophilic/lipophilic character in the growth hormone activity. In his paper published in 1961 for the structure–activity pattern of newly discovered non-aromatic hormones, *S*-(*N*,*N*-dialkylthiocarbamoyl)-thioglycolic acids and their esters [29], he stated citing the review article of Veldstra [19], "since a great amount of evidence has been accumulated in favor of hydrophilic/lipophilic character of a compound as a factor in activity, attention was directed toward compounds with an increased lipophilic character". In this series of compounds, only the *N*,*N*-Me_2- and *N*,*N*-Et_2-thiocarbamoyl acids were significantly active (Fig. 8). Because free acids as the active principle were highly polar, the polarity was reduced by esterification to cause increases in the activity. More lipophilic esters could reach the target more easily. On the other hand, introducing higher alkyl or lipophilic groups to the nitrogen atom nullified the activity. Higher homologs or bulkier analogs at other than the esterifiable site would be intrinsically inactive. These observations could probably motivate Corwin to recognize the significance of the lipophilicity especially at least for processes to reach the target and to seek for the way to analyze individual contributions from various physicochemical factors

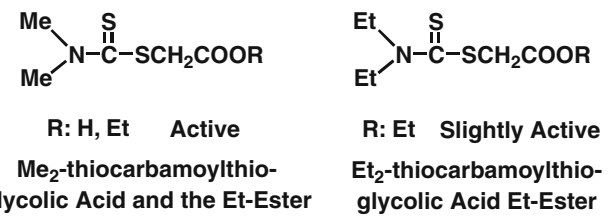


Fig. 8 Structure and activity of dithiocarbamates

including electronic effect of substituents on variations in the activity.

Struggles at Kyoto university before 1961

In the laboratory of Department of Agricultural Chemistry (now Division of Applied Life Sciences) at Kyoto University where I spent my career, the plant growth hormone was taken as one of research subjects in 1939 [30]. In 1943 my mentor, Professor Tetsuo Mitsui, discovered that 1-naphthoic acid (1-NA) and partially hydrogenated analogs such as 1,4-H_2-, 3,4-H_2-, and 1,2,3,4-H_4-1-NAs were active growth hormones, the potency being about equivalent to that of naphthalene-1-acetic acid in the promotion of rooting using petunia cuttings [31]. He confirmed their activity subsequently using the epinasty test of tomato petiole. In this test, the activity of the 1,4-H_2-analog was highest followed by the 1,2,3,4-H_4 acid, and that of 1-NA and 3,4-H_2 acid was lowest and only weakly active. He also resolved racemic 1,4-H_2- and 1,2,3,4-H_4-1-NAs, and showed that the (+)- and (−)-isomers, respectively, were more active than the corresponding antipodes (Fig. 9). Because of the wartime mess, these results were not published until 1951 [32, 33].

When I started my research career in 1951, I decided to explore structure–activity relationships of 1-NA and its analogs. My special concern was how to rationalize the fact that only small structural modifications in these compounds were turned out to have rather large variations in the potency. In those postwar days, it was very difficult to access updated international journals in Japan. The paper that I first perused as my guiding reference was that of Veldstra published in 1944 [25]. Thus, I measured/estimated the HL-balance by a polarographic method as well as from additive-constitutive fragmental indexes empirically defined [34, 35]. No good parallel of the activity was found with the HL-balance when used singularly. I also measured dipole moments and UV and IR spectra to establish the 3-dimensional structure of related compounds [36–38]. Although a possibility of ring conversion equilibrium in the first two compounds would make the situation a bit inconclusive, the extent of projection of the COOH group from the benzene ring in the order of 1,4-H_2- > 1,2,3,4-H_4- > 3,4-H_2-1-NA ≥ 1-NA coincides with the order of the growth activity. Because HL-balance does not vary much among them, Veldstra's physico-chemical hypothesis was thought to match at least for the structure–activity pattern of this small set of compounds.

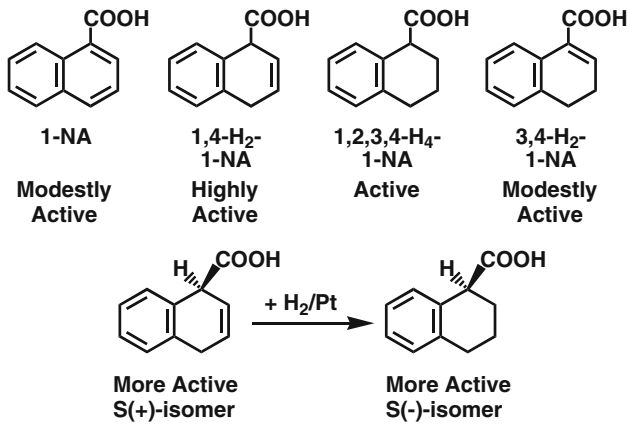


Fig. 9 Structure and activity of 1-naphthoic acid and analogs

After learning about the two-point attachment hypothesis from Pomona and Fukui's support to it, my group also calculated the superdelocalizability for the nucleophilic attack to various positions of 1-NA substituted variously by halogen, alkyl, and NO_2 substituents. There was a certain correspondence between activity and superdelocalizability at the 8-position within each set of compounds with the same substituent, but not for the set of entire series of 1-NAs [39, 40]. This result would also suggest that the correspondence of activity with a certain physico chemical factor could be observed only under conditions other factors including the HL-balance being nearly equal. To separate total contributions from various factors (parameters) into individual importance of each parameter, a multiparameter approach was also needed to elucidate structure–activity patterns of 1-NA analogs. However, I did not know how to do so. I arranged and organized my articles written over about 10 years as a volume and filed it as my doctoral thesis to Mitsui just before I left for Pomona in 1961.

The birth of QSAR of the phenoxyacetic acid type plant hormones

In Pomona, my first job was to synthesize substituted POAs. In addition, I started to measure their partition coefficient, P, in late June. Corwin had apparently accepted the importance of lipophilicity and decided to model it with the 1-octanol–water partition coefficient measured experimentally. He also had realized that, to separate such a composite as the sum of contributions into individual components, a quantitative treatment is indispensable. For the electronic effect of substituents, he decided to use Hammett σ constant. He was striving, however, how to work out the quantitative formulation. In mid-July 1961, Corwin and I discussed how to do so. We agreed that the formulation should follow the form of the Taft equation, that is, a linear combination of free-energy related parameters such as electronic σ^* and steric E_s for aliphatic compounds [41]. I suggested to use π value for the

lipophilicity of substituent X, defined as π (X) = log P (X-substituted compound) – log P (unsubstituted compound) [42]. With this definition, the π value has the same status as Hammett σ, Taft σ*, and E_s.

Subsequently, Corwin elaborated the idea and introduced the π^2 term for accounting the optimum lipophilicity during processes to reach the site of action. The first QSAR for the mono-substituted POAs was published in 1962 in Nature [43]. It was improved as Eq. 1 and published in 1963 in JACS [44].

$$\log 1/C = -1.97\pi^2 + 3.24\pi + 1.86\sigma + 4.16 \quad (1)$$

where $s = 0.484, r = 0.881, n = 21$ including 16 with meta substituents, 3 with para substituents, unsubstituted, and the 2-naphthoxy compounds, and C is the molar concentration to produce a defined growth promotion of oat seedling segments. The compounds included in Eq. 1 were selected under conditions mostly restricted by steric dimensions: (1) para-substituted derivatives with substituents larger than Cl are inactive perhaps due to discontinuously occurring steric effect [45], (2) meta-substituted derivatives with substituents larger than Pr are inactive, (3) there is a limit for 3,5-disubstitution in "lateral" width, (4) the proximity effects of ortho substituents were not estimable at that time as Hammett-Taft type parameters. This set of meta—plus a few para—substituted derivatives was only a set of compounds of which activity was accurately measurable and included in the analysis. In Eq. 1, the σ_{para} value was used for meta-substituted and σ_{meta} value for para-substituted POAs. This combination of σ values assumed the electronic effect of substituents on the ortho position, and worked better than that directing to the side chain.

The sign of the σ term is positive meaning that electron-withdrawing property of substituents is favorable. That is, a sort of "nucleophilic" reaction with the plant substrate was still assumed to occur at the ortho position. Eq. 1 inherits the two-point attachment hypothesis with separation of lipophilic effects in the transport processes. Although it was still too far from the complete solution of structure–activity pattern, Eq. 1 was able to rationalize a number of potency variation patterns that had not been elucidated well. Furthermore, we soon found that the methodology separating composite outcome into component factors quantitatively has a general applicability to diverse series of drugs and agrochemicals with sound physicochemical backgrounds [46]. Since then and as is well known, Corwin had been devoting his life to the generalization, computerization, and application of the QSAR methodology with extraordinary enthusiasm [47, 48]. With constant encouragements and supports of Corwin, I have been able to keep exploring QSAR mainly of agrochemicals in Kyoto [49, 50].

Post script

The Pomona group also published the QSAR analysis of monosubstituted PAAs in 1967 when the methodology was gradually being favorably recognized [51]. The effect of substitution patterns on the activity was somewhat different from that found in the POA series. The correlation for PAAs was formulated as Eq. 2.

$$\log 1/C = -0.56\pi^2 + 1.30\pi + 1.16\sigma + 5.30 \quad (2)$$

where $s = 0.488$, $r = 0.858$, $n = 16$ including 14 with meta substituents, 2 with small para substituents. The σ value used here was taken so that it expresses the electronic effect toward one of the meta positions. The meta position was assumed to be involved in the two-point attachment growth reaction in this PAA series. Although the same σ value can also apply to the electronic effect directed toward the functional side chain, Corwin did not want to abandon the two-point attachment hypothesis at this time in 1967.

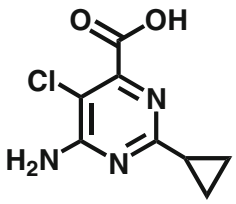
In 1995, Eq. 1 was revised and updated by Corwin as Eq. 3 [47].

$$\log 1/C = 1.25\pi + 0.97\sigma_{meta} + 0.95L - 5.54 \log(\beta \cdot 10^L + 1) + 1.39 \quad (3)$$

where $n = 19$ (including only meta-substituted POAs), $s = 0.242$, $r = 0.975$. For this set consisting of only meta-substituted POAs, the σ_{meta} value worked much better than σ_{para}. This means that, in contrast to the original results expressed as Eq. 1, the electronic effect is exerted directly on the functional side chain. The steric effect along with its optimum was revealed to exist, and expressed in terms of L, the Verloop STERIMOL length parameter of meta substituents [52]. The optimum is expressed by the Kubinyi bilinear model [53]; L(opt) = 3.74, which corresponds with OMe, beyond which activity falls off sharply. The activity maximum was found to exist due to the steric effect, perhaps at the receptor site, but not in the hydrophobic effect of substituents. The positive π term may include favorable hydrophobic contributions to the transport processes plus the receptor interactions. Corwin was finally liberated from the spell of the two-point attachment hypothesis involving "reactivity" of the ortho position. Although hydrophobic, electronic, and steric effects of meta substituents are nicely separated in this revised equation, its physicochemical validity should be elaborated further in terms of interactions with receptor protein.

The receptor protein of natural growth hormone, IAA, was identified recently in 2005 almost three fourths of a century after the first native ligand discovery [54]. Certain members of F-box proteins of the ubiquitin protein ligase family were found to function as receptors of IAA and

Fig. 10 Aminocyclopyrachlor



analogs including 2,4-D. Discovery researches of the synthetic growth hormone for agricultural use as selective herbicides have been still going on, the most recently launched herbicide-active compound being a tri-substituted pyrimidine carboxylic acid named aminocyclopyrachlor (Fig. 10) from DuPont in 2010 [55].

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