

oxidative attack and hydrolysis of the phosphoric anhydride bonds, and the least water-soluble materials. An infrared absorption peak appeared between 11.00 and 11.10  $\mu$  with the  $\alpha$  fractions but not with the  $\beta$  and  $\gamma$  fractions. Starting with either the  $\alpha$  or  $\beta$  fraction from the carbethoxy analog, irradiation with ultraviolet light yielded a mixture of approximately 30-percent  $\alpha$  and 70-percent  $\beta$  material as shown by infrared analysis. If the  $\alpha$  and  $\beta$  fractions are isomeric, treatment of either isomer with ultraviolet light should produce a mixture of isomers with the more stable *trans* configuration predominating. All the experimental evidence is consistent with the hypothesis that the active  $\alpha$  fraction is the *cis* isomer for each of the substituted-vinyl phosphates.

The properties of the *cis* and *trans* carbethoxy analog are shown in Table 1. Comparison of the vinyl phosphates as anticholinesterase agents showed that the isomeric dimethyl phosphates were combining in a different manner with the enzyme than the diethyl phosphates (the comparison was based on the slopes of the inhibition curves). The difference in anticholinesterase activity of the isomers increased as the size of the group hindered in rotation by the rigidity of the double bond increased. A consideration of isomeric yields from different synthesis methods explained the difference in bio-

logical activity of various preparations.

The biological distribution and fate of the *cis* isomer of compound 2046 was studied by means of radiotagged material ( $P^{32}$ ). It was found that in contrast to other systemic insecticides currently available (5), compound 2046 does not require a preliminary "metabolic activation" within the plant (this finding is based on parallel radioactivity, bioassay, and anticholinesterase analyses) or within the insect or mammal (these findings are based on activation experiments with rat liver slices and cockroach intestines, 6) to produce the effective toxicant. Accordingly, the anticholinesterase method was standardized to give a residue analysis procedure sensitive to 0.05 ppm. Field residual studies on a technical sample of compound 2046 (67 percent *cis*, 33 percent *trans*, Shell Development Co.) on 13 vegetable crops showed less than 0.1 ppm of residue 4 days after treatment of the soil or foliage with  $\frac{1}{4}$  lb per acre of the insecticide. The substituted-vinyl phosphates had the shortest residual period of 20 organophosphates studied on carrots, potatoes, and cabbage. Immediately following treatment, the major loss of compound 2046 from plants was the result of volatilization, but about 12 hours later the decomposition within the plant became the significant factor. This enzymatic detoxification occurred throughout the plant and yielded a half-

life in young greenhouse pea plants of about 20 hours for *cis* 2046 and about 48 hours for the *trans* isomer.

The distribution, detoxification, and esterase specificity of *cis* 2046 was investigated for the white rat and American cockroach. Detoxification appeared to take place in the plasma of the rat and in the gastric caeca and nerve cord of the roach. Compound 2046 did not appear to be selectively localized in the rat but accumulated in the mid- and hindgut of the roach. Esterase specificity tests *in vivo* and *in vitro* showed this *cis* carbomethoxy phosphate to be one of the most selective inhibitors of acetylcholinesterase that we have found in our studies to date.

Biological specificity of geometric isomerides has been frequently observed. To my knowledge, this is the first demonstration of *cis-trans* specificity with organophosphate antiesterases. A description of the experimental details of this study on vinyl-substituted phosphates is in preparation.

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#### Atomic Charges in

#### Monosubstituted Benzenes

Newly available information on charge distribution in molecules (1, 2), even though it is somewhat speculative, should certainly be of interest in the field of aromatic substitution where no completely satisfactory interpretive theory has yet been developed (3). This paper presents such data for a number of monosubstituted benzenes.

Table 1 lists the substituents in order of decreasing electron release to, or increasing withdrawal from, the ring. The partial charge on the atom of the substituent group that is directly attached to

Table 1. Properties of *cis* and *trans* 0,0-diethyl 2-carbethoxy-1-methylvinyl phosphate

Item	<i>cis</i>	<i>trans</i>	Biological activity ratio <i>cis/trans</i> *
<b>Partition coefficients†</b>			
$\text{CCl}_4/\text{H}_2\text{O}$	58	14	
<i>n</i> -Hexane/ $\text{H}_2\text{O}$	5.5	1.1	
<b>Chemical reactivity</b>			
Hydrolytic half-life ( $-\text{P}=\text{O}-\text{C}=\text{C}$ ) (hr)‡	3.4	9.0	
Oxidative half-life ( $\text{MnO}_4^-$ ) (min)§	8.9	15.4	
<b>Biological activity</b>			
Blood cholinesterase, <i>in vitro</i> $\text{pI}_{50}$	7.75	5.93	66
Rat $\text{LD}_{50}$ , intraperitoneal (mg/kg) #	0.35	35	100
Fly $\text{LD}_{50}$ , topical (mg/kg) **	2.0	59	30
Aphid $\text{LD}_{50}$ , systemic (ppm) ††	10.5	770	73
<b>Method of synthesis</b>			
Schrader (1) (% yield)	5-9	91-95	
Stiles (7) (% yield)	67	33	

\* A ratio of the reciprocal of the amount of the *cis* isomer divided by the reciprocal of the amount of the *trans* isomer required to produce the same end-point.

† 2.0 mg organophosphate partitioned between 2.0 ml organic solvent and 2.0 ml distilled water at 28°C.

‡ Half-life in hours of vinyl phosphate bond at 28°C and pH 11.6 (0.1M  $\text{Na}_2\text{CO}_3$ ) based on loss of partitioning properties into chloroform as diethyl phosphoric acid is formed on hydrolysis.

§ Half-life in minutes of 0.0004M  $\text{KMnO}_4$  in acetone solution in the presence of 0.015M vinyl phosphate at 28°C, determined colorimetrically at 530 m $\mu$ .

|| Negative logarithm of molar concentration effecting 50-percent inhibition of esterase activity of whole human blood on acetylcholine with 1-hour preincubation of phosphate and enzyme prior to addition of substrate.

# Based on mortality of 250-g white rats 24 hours after intraperitoneal injection of organophosphate in isotonic saline.

\*\* Based on mortality 24 hours after application of organophosphate in 1.3  $\mu$ lit of acetone to the pronotum of 3-day-old adult male houseflies.

†† Insecticide needed for 50-percent mortality of pea aphids after 8 hours of feeding on pea plants pre-treated for 24 hours by immersing the roots in the indicated insecticide solution.

Table 1. Effect of substituents in benzene ring

Substituent	Charge* withdrawal (+) from ring	Charge* on atom next to ring	$\delta C^*$	$\delta H^*$	Conju- gation with ring	Orien- tation effect
O <sup>-</sup>	-0.627	-0.373	-0.084	-0.025	None	o,p
Si(CH <sub>3</sub> ) <sub>3</sub>	-0.241	0.289	-0.049	0.011	None	o,p(weak)
C(CH <sub>3</sub> ) <sub>3</sub>	-0.085	-0.035	-0.035	0.025	None	o,p
CH <sub>3</sub>	-0.052	-0.032	-0.032	0.028	None	o,p
H	-0.030	0.030	-0.030	0.030	None	
C <sub>6</sub> H <sub>5</sub>	0	-0.027	-0.027	0.033	Possible	o,p
NH <sub>2</sub>	0.092	-0.176	-0.019	0.042	None	o,p
CH <sub>2</sub> Cl	0.171	-0.012	-0.012	0.049	None	o,p
OCH <sub>3</sub>	0.174	-0.309	-0.012	0.049	None	o,p
CN	0.180	-0.011	-0.011	0.050	Possible	m
COCH <sub>3</sub>	0.181	-0.011	-0.011	0.050	Possible	m
OH	0.247	-0.303	-0.005	0.056	None	o,p
Cl	0.251	-0.251	-0.005	0.056	None	o,p
CHO	0.252	-0.005	-0.005	0.056	Possible	m
CHCl <sub>2</sub>	0.400	0.008	0.008	0.070	None	o,p
N(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup>	0.446	-0.148	0.012	0.074	None	m
COOH	0.480	0.015	0.015	0.077	Possible	m
CCl <sub>3</sub>	0.634	0.029	0.029	0.091	None	m
NO <sub>2</sub>	0.671	-0.129	0.033	0.095	Possible	m
SO <sub>3</sub> H	0.736	-0.039	0.038	0.101	Possible	m
NH <sub>3</sub> <sup>+</sup>	0.805	-0.120	0.043	0.105	None	m
CF <sub>3</sub>	0.975	0.060	0.060	0.123	None	m

\* All charge values were calculated by the methods described in references 1 and 2.

the ring, as well as the partial charges on carbon and hydrogen atoms, is given. Also indicated are the possibility of substituent conjugation with the ring and the usual orientation effect. It is extremely important in studying the charge data to keep in mind that they represent solely the partial charges that would be expected from bond polarities resulting from initial electronegativity differences. The mobility of certain electrons in these multiple-bonded systems also has an important influence on the over-all charge distribution in the molecule, but the quantitative effect of this influence cannot easily be reckoned.

If the general reactivity of a benzene ring may be taken as a reflection of the availability of pi electrons, the data of Table 1 are of especial interest. Electron availability will be determined chiefly by two factors: the charge on the carbon atom, and the capacity of the rest of the molecule to supply electrons without the result of excessive positive charge on any one atom. The first factor is evaluated in Table 1; the lower the positive charge or the higher the negative charge on carbon, the greater the electron availability. The second factor depends essentially on the number and kinds of atoms of the substituent group: if the electron release to the ring is equal for two different substituents, the substituent that is the better electron reservoir will contribute more to the availability of pi electrons.

The problem of orientation effects of substituents on the benzene ring seems

too complex to be susceptible to complete solution by any one simple rule or formula. In part, the complexity may arise from differences in polarizing effects exerted by attacking molecules. These differences require a different interpretation of each substitution. The following observations from Table 1 are of interest, however. Groups that are predominantly meta directors are generally either highly electronegative groups with strong electron-withdrawing power and with a positively charged atom attached directly to ring carbon, or groups of lesser withdrawing power that have a multiple bond capable of conjugation with the ring. Groups that are predominantly ortho, para directors are usually either electron-releasing groups, or electron-withdrawing groups in which the atom attached directly to ring carbon has an appreciable negative charge. The latter type may be regarded as an example of the electrostatic influence on pi electrons that is exerted by high charge on the substituent atom directly attached to ring carbon (4). This charge, if it is negative, may tend to compensate for the electron withdrawal by the group by repulsion of the pi electrons. Similarly, the weakness of the ortho, para directing powers of the (CH<sub>3</sub>)<sub>3</sub>Si-group (5), despite the group's strong electron-releasing action, may be associated with the electrostatic attraction of the positively charged silicon for the pi electrons.

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## References and Notes

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## Polygonization of a Plastically Bent Sapphire Crystal

If one thinks of edge-type dislocations as arising formally from the insertion of an extra partial plane of atoms, then a plastically bent crystal must have more of these wedges going in from the convex surface than from the concave one (1). From the extensive work on polygonization of plastically bent metal crystals it has been shown that thermal activation can induce these excess dislocations of like sign to segregate and form plane walls perpendicular to the slip planes (2). In fact, these walls are simply small-angle grain boundaries, which then separate blocks or polygons of unbent structure. Each recovered block thus differs slightly in orientation from its neighbors.

In recent years it has been demonstrated that many ionic crystals that are hard and brittle at room temperature can be deformed plastically at elevated temperatures (3). Of particular interest, from the point of polygonization, is the case of plane bending of crystals that deform on only one slip system. Figure 1 illustrates the geometry of a bent sapphire (Al<sub>2</sub>O<sub>3</sub>) (4). It shows in particular that the slip planes curve into in-

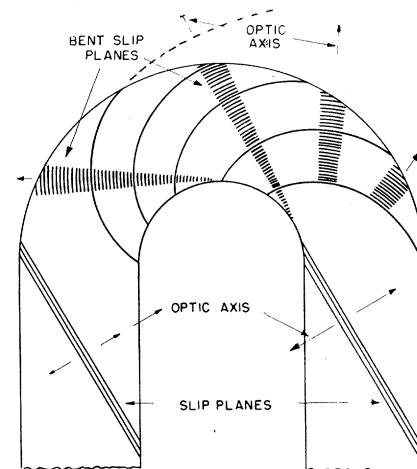


Fig. 1 Plane bending by slip on a single set of planes. The bent slip planes have the shape of an involute of a cylinder. Normals to the curved planes define the positions of the optic axis.