[CONTRIBUTION FROM THE DOW CHEMICAL COMPANY, WESTERN DIVISION]

Intramolecular Hydrogen Bonding to Halogens. II.[1] Interorbital Repulsive Interaction in *o*-Halophenols.

BY A. W. BAKER AND W. W. KAEDING

RECEIVED FEBRUARY 28, 1959

The infrared spectra of *o*-halophenols show a $\Delta\nu_{OH}$ shift of the bonded OH group in the order $F < Cl < Br < I$. This has been interpreted previously as a measure of the strength of the hydrogen bond. However, on evidence obtained from the OH spectra of unsymmetrical 2,6-di-halophenols, the order of the hydrogen bond strength is shown to be $Cl > Br > F > I$. The anomalous order is attributed to both the varying size of the halogens and to an orbital–orbital repulsive interaction which increases in the order $Cl < Br < I$. This interaction occurs between the O–H bonding orbital and the donated lone-pair orbital of the halogens, and is due to the small amount of directional character in the lone-pair orbitals, and to interaction with lower-lying completed electronic shells.

The doubling of the O–H bands in *o*-halophenols[2–6] was originally attributed[5] to resonance interaction between the O–H group and the aromatic ring. It was postulated that this leads to two coplanar positions of minimum potential energy which orient the O–H group either toward (*cis*) or away from (*trans*) the halogen. The energy of the hydrogen bond was found to favor the *cis* configuration by 2–3 kcal./mole, resulting in a *cis/trans* ratio of about 10. The $\Delta\nu_{OH}$ shifts were shown to increase with the size of the halogen and, since Badger's rule[6] was believed to apply, the energy of the hydrogen bond was considered to follow the same order.

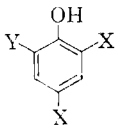
Although the resonance interaction is well substantiated, the theory that this produces the doubling is inadequate because it does not explain the lack of similar doubling in N or O compounds even though $\Delta\nu_{OH}$ shifts comparable to those in the halophenols are observed in some compounds.[7] Neither does it explain the anomalous increase in the relative intensity of the "*trans*" band as the size of the halogen increases nor the parallel behavior of both $\Delta\nu_{OH}$ shifts and relative intensities in β-halo alcohols (to be published).

More recently, a tentative explanation for the anomalous[8] intensities was presented which was based on a concept of competitive resonance interaction with the aromatic ring. It was reasoned that, since the resonance ability of the halogens increases markedly from iodine through fluorine,[9] the resonance interaction of the hydroxyl group with the ring should decrease in the same order. This would tend to destabilize the "*trans*" O–H adjacent to the smaller halogens and to decrease the relative amount of the unbonded O–H. However, although this is supported in part by recent work showing (1)[10] that a *p*-fluoro group is effectively electron donating to an O–H group (decreasing O–H resonance) and (2)[11] that the effects of *ortho* and *para* halogens are nearly equal, evidence obtained here from the spectra of unsymmetrical (mixed) 2,6-dihalophenols indicates that this accounts for only a minor portion of the observed effects. Instead, it appears that the anomalous behavior of the halogens is due primarily to a lone-pair orbital geometry which leads to relatively large orbital–orbital overlap with the O–H bonding orbital when a hydrogen bond is formed. This may be particularly important for these intramolecular hydrogen bonds because the O–H—X bond is bent in excess of 85° from the optimum co-linear position. Since these orbitals are mutually exclusive, the overlap produces a considerable amount of repulsive energy which tends to destabilize the intramolecular hydrogen bond. This is not, however, manifest in the $\Delta\nu_{OH}$ shifts, probably because the O–H group is held within interacting distance by molecular geometry and resonance. Consequently, although the $\Delta\nu_{OH}$ shift is a measure of the interaction between the OH and the halogens, it is not a measure of the net energy of the resultant bonds. We must conclude, therefore, that Badger's rule is not applicable in these cases where the interacting groups are not free to take up their preferred orientation or interacting distances. This paper will consider these points in detail.

Experimental

The data presented in this paper were obtained from the O–H spectra of 2,4,6-trisubstituted phenols by means of a Beckman DK-2 spectrophotometer. The frequencies were calibrated by the vapor bands of water and ammonia[12] and are probably accurate to within ±2 cm.$^{-1}$. The reproducibility of the bands and their relative values are, however, good to within ±1 cm.$^{-1}$. The samples were run at approximate concentrations of 0.01 *M* in CCl_4 in a 1 cm. cell. Interfering water was removed by the direct addition of P_2O_5 to the sample cells.

The phenols prepared for this work are indicated in structure I in which X and Y are different halogen substituents.



I

The halogen *para* to the OH group does not contribute to the discussion and can be ignored because it produces no steric effect on the other two halogens and no changes in the elec-

---

[1] For paper I, see A. W. Baker, THIS JOURNAL, **80**, 3598 (1958). This paper will be referred to as "Intramolecular Hydrogen Bonding to Halogens. I. On the *cis–trans* Equilibria in *o*-Halophenols."

[2] O. R. Wulf, U. Liddel and S. B. Hendricks, *ibid.*, **58**, 2287 (1936).

[3] L. R. Zumwalt and R. M. Badger, *ibid.*, **62**, 305 (1940).

[4] M. M. Davies, *Trans. Faraday Soc.*, **36**, 333 (1940).

[5] L. Pauling, THIS JOURNAL, **58**, 94 (1936).

[6] R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

[7] A. W. Baker and A. T. Shulgin, THIS JOURNAL, **80**, 5358 (1958).

[8] Both the $\Delta\nu_{OH}$ shifts and the relative intensity of the "*trans*" bands increase in the order $F < Cl < Br < I$. The relative intensity of the "*trans*" band should decrease as the energy of bonding increases if no additional interactions occur.

[9] John W. Baker, *J. Chem. Soc.*, 1448 (1936).

[10] A. W. Baker, *J. Phys. Chem.*, **62**, 744 (1958).

[11] A. W. Baker and A. T. Shulgin, THIS JOURNAL, **81**, 1523 (1959).

[12] A. R. Downie, M. C. Magoon, T. Purcell and B. Crawford, Jr. *J. Opt. Soc. Am.*, **43**, 941 (1943).

tron environment of the vicinal X, Y or OH groups important enough to influence the conclusions.

2-Fluoro-4,6-diiodophenol was prepared by dissolving 5.6 g. (0.05 mole) of *o*-fluorophenol and 4 g. of potassium hydroxide in 100 ml. of water. In a second beaker, 27 g. of pulverized iodine (0.106 mole) was dissolved rapidly in a cold solution of 13 g. of potassium hydroxide in 200 ml. of water and immediately added to the phenol solution. Cold, 25% sulfuric acid was added dropwise until a *p*H of 7 was reached. A small amount of excess iodine was removed by the addition of solid sodium thiosulfate. The oil which formed solidified on cooling with ice and was recrystallized from pentane to give soft white needles, m.p. 56–57°. All melting points are uncorrected.

Anal. Calcd. for $C_6H_3FI_2O$: C, 19.80; H, 0.83; I, 69.75. Found: C, 19.79; H, 0.86; I, 69.86.

2-Fluoro-4,6-dibromophenol, m.p. 34–35°, was prepared by the bromination of *o*-fluorophenol in acetic acid by the method of Raiford and LeRosen.[13]

2-Fluoro-4,6-dichlorophenol.—Eight grams (0.11 mole) of gaseous chlorine was bubbled into a solution of 5 g. (0.042 mole) of *o*-fluorophenol in 50 ml. of carbon tetrachloride over a one hour period of time. The solution then was greatly refluxed for 15 min. and the solvent evaporated at 20 mm. from a water-bath. A solid melting at room temperature was obtained from the remaining yellow oil (8.2 g.) by crystallizing from a pentane–methylene chloride solution at Dry Ice temperature. When the solid, at Dry Ice temperature, was placed on a cold porous plate, one gram of granular white crystals, m.p. 59–61°, was obtained. However, analysis showed that this compound was only mono-chlorinated.

Anal. Calcd. for C_6H_4ClFO: C, 49.17; H, 2.75; Cl, 24.20. Found: C, 48.88; H, 2.87; Cl, 24.18.

The infrared spectrum contains a double hydroxyl band characteristic of intramolecular bonds to both chlorine and fluorine. Therefore, the compound is 2-chloro-6-fluorophenol, the only isomer capable of giving this result.

In order to obtain the dichloro compound, the reaction was repeated with 15 ml. of CCl_4 and a large excess of chlorine (50 g.). The resultant solid was recrystallized from pentane to give white needles, m.p. 41–42°.

Anal. Calcd. for $C_6H_3Cl_2FO$: C, 39.81; H, 1.67; Cl, 39.18. Found: C, 39.86; H, 2.10; Cl, 38.78.

Alternate Synthesis to Verify Structure.—Since there is reason to suppose that the second chlorine might substitute at the 3-position adjacent to the fluoro group rather than *para* to the O–H group, the following additional preparation route was followed. 2,4-Dichlorophenetole (85 g.) and 175 ml. of acetic anhydride were mixed with 75 ml. of 21 *N* HNO_3 at 110–115°. After refluxing for two hours, the solution was poured on ice until hydrolysis was complete. A yellow solid was isolated, m.p. 27–28° (lit.[14] value, 28°).

This nitro compound was reduced to the amine with zinc and HCl in ethanol, m.p. of product, 51–52°. Sixteen grams of the latter was diazotized in aqueous solution and treated with 14 g. of a saturated solution of $NaBF_4$. The diazonium fluoborate salt precipitated immediately and was filtered and dried over P_2O_5, m.p. 132–140° dec. This salt was decomposed by heating to give 2.5 g. of 2,4-dichloro-6-fluorophenetole. The entire sample was refluxed with constant boiling HBr for 6 hours. Approximately 1 g. of 2,4-dichloro-6-fluorophenol was obtained, m.p. 34–38°. The infrared spectrum was nearly identical to that of the dichloro compound prepared by the first method (above). The impurity was identified as 2,4-dichlorophenol.

2,4-Dichloro-6-iodophenol was prepared by the iodination of 2,4-dichlorophenol in a manner similar to that described above. White needles were obtained from pentane, having a melting point (62°) similar to that reported by Kohn and Sussmann.[15]

2-Bromo-4,6-dichlorophenol was prepared by the bromination of 2,4-dichlorophenol in carbon tetrachloride solution. White needles were obtained which melted at 64°. A melting point of 68° was reported by Garzino.[16]

Anal. Calcd. for $C_6H_3BrCl_2O$: C, 29.79; H, 1.25; Cl, 29.3; Br, 33.0. Found: C, 29.62; H, 1.35; Cl, 29.0; Br, 32.8.

2,4-Dibromo-6-iodophenol was prepared by the iodination of 2,4-dibromophenol in a manner similar to that described above. Recrystallization from hexane yielded white needles melting at 104°, identical to the m.p. found by Kohn and Sussmann.[14]

Spectra.—Evidence for orbital–orbital repulsive interaction is exhibited by the O–H spectra of the phenols described above. The spectra, Fig. 1, contain two bands corresponding to intramolecular hydrogen bonds formed to each of the adjacent halogens. These bands are similar to the bands of the respective monosubstituted phenols but are displaced to slightly lower frequencies. With both *ortho* positions occupied, resonance effects tending to make the OH group coplanar with the ring will influence structures II and III about equally and, therefore, should have slight influence on multiple band structure.

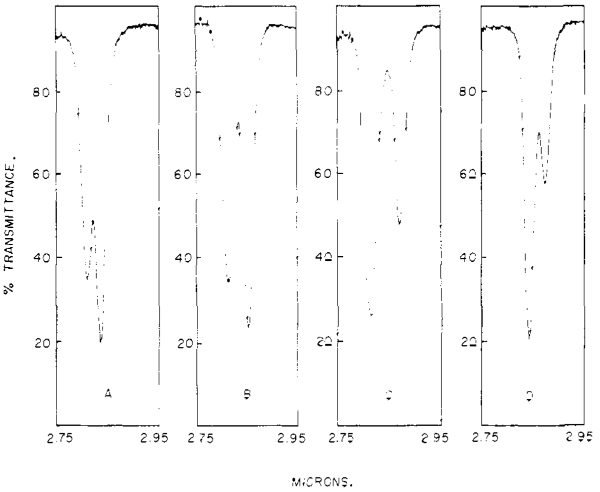
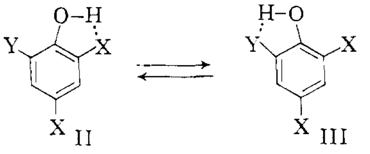


Fig. 1.—The O–H spectra in carbon tetrachloride of A, 2,4-dichloro-6-fluorophenol; B, 2,4-dibromo-6-fluorophenol; C, 2,4-di-iodo-6-fluorophenol; D, 2,4-dichloro-6-iodophenol. Details are given in Table I and under Experimental.

Although the $\Delta\nu_{OH}$ shifts do not reflect the energy of the hydrogen bond, the relative intensities of the two bands in each compound should be a reliable index of the energy for several reasons: The entropy difference ΔS, for the change II $\rightleftarrows$ III is essentially zero, and, therefore, $\Delta F = \Delta H$.



Since ΔF can be obtained from the equilibrium constant, ΔH can be evaluated from the relative absorbances of the two bands if the absorptivities are equal. To check this point, the relative absorptivities of the *o*-fluoro- and *o*-iodophenol bands (the extremes) were measured. Allowing for the fact that 7.5% of the O–H groups in *o*-iodophenol are "*trans*" to the iodine,[1] the absorptivities were found to be within about 96% of each other. Therefore, by assuming that these measurements can be extended to the 2,6-disubstituted compounds, the relative amounts of structures II and III and the relative bond energies can be obtained.

In Table I, the frequencies (ν_{OH}) and the ratio of the relative absorbances of the two O–H bands in 2,4,6-trisubstituted phenols are listed. Columns 1, 2 and 3 indicate the substituents in the 2, 4 and 6-positions; columns 4 and 5, the OH band frequencies, respectively, of the OH groups bonded to the 2 and 6-position halogens; and column 6, the ratio of the absorbances of the two bands. For combinations 1–4, both the frequencies and the absorbances of each band can be measured with good accuracy; for combinations 5

---

[13] L. C. Raiford and A. L. LeRosen, THIS JOURNAL, **66**, 2080 (1944).

[14] F. Fischer, *Z. Chem.*, 387 (1868).

[15] M. Kohn and S. Sussmann, *Monatsh. Chem.*, **46**, 594 (1926).

[16] L. Garzino, *Gazz. chim. ital.*, **17**, 495 (1887).

TABLE I

	Ring substituent			Frequencies		Relative absorbance
	2	4	6	2	6	A_2/A_6
(1)	F	I	I	3568	3504	1.96
(2)	F	Br	Br	3574	3522	0.72
(3)	F	Cl	Cl	3580	3541	0.66
(4)	Cl	Cl	I	3535	3502	3.25
(5)	Cl	Cl	Br	3535	sh3515	1.6
(6)	Br	Br	I	3515	sh3496	2.2

and 6, however, only the values of $(\nu_{OH})_2$ can be measured accurately. The values of $(\nu_{OH})_6$ and the absorbance ratios for combinations 5 and 6 can only be estimated because these bands occur as unresolved shoulders on the sides of the stronger, higher frequency bands.

Results

The frequencies in Table I are not constant for a given halogen but vary slightly with the halogen in the opposite *ortho* position. This is due to both the polar and the steric effects of the additional halogen. The polar effect is such as to make the other halogen less basic and the OH group more acidic, but since the Hammett σ-value is greater for a *meta* than for an *ortho* halogen, the reduction in basicity will probably predominate and the strength of the hydrogen bond will decrease. Oppositely, the steric effect will increase the $\Delta\nu_{OH}$ shift by decreasing the interacting distance. However, these effects are secondary to the principal effects discussed here and will be investigated in detail in a forthcoming paper.

The values of the relative absorbances are quite consistent in showing that the increasing strength of the hydrogen bond is I < F < Br < Cl. Fluorine, in competition with iodine, gives an absorbance ratio of nearly 2 to 1. Therefore, despite the larger $\Delta\nu_{OH}$ shift of iodine, the hydrogen bond is stronger when the bond is formed to fluorine. On the other hand, fluorine is a weaker competitor for the OH group than is either chlorine or bromine. This is indicated by the absorbance ratios for F/Cl and F/Br of 0.66 and 0.72, respectively. In the remaining compounds, the ratios are Cl/Br, 1.6; Cl/I, 3.25; and Br/I, 2.2. These are consistent with the F/Cl and F/Br ratios in showing that chlorine forms stronger intramolecular hydrogen bonds than does bromine.

The trend in the strengths of the hydrogen bonds indicates that the O–H—F bond is weaker than either O–H—Cl or O–H—Br, primarily because the small size of the fluorine prevents the OH group from getting close enough for strong bonding. The balance between optimum interacting distance and minimum repulsive interaction is reached in chlorine—it thus forms the strongest intramolecular hydrogen bonds of all the halogens. In passing from chlorine to bromine to iodine, the effects of the repulsive interaction between the orbitals is more important than the increasingly smaller interacting distance. This produces an increasing perturbation on the O–H group but decreases the strength of the hydrogen bond. Furthermore, the repulsion appears to be generated also by electron levels lower than the valence shell and becomes particularly evident in iodine with the filling of the extended 4d orbitals.

These data are supported in part by the dipole moment data of Anzilotti and Curran.[17] They concluded from a comparison of the difference in the dipole moments of the *o*-halophenols in benzene and dioxane that the order of hydrogen bond strength is O–H—F > O–H—Cl > O–H—Br > O–H—I. This order, which puts fluorine first, assumes that the acidity of all four phenols is equal. However, it has been shown more recently[10] that a *p*-fluorosubstituent decreases the acidity of the phenolic OH group whereas all of the other *p*-halogens increase it.[18] The same probably is true for the *o*-halogens since it has been demonstrated that there are only small differences between the polar properties of *o*- and *p*-halogens. Therefore, it is entirely possible that the change in phenol acidity is sufficient to alter the true order of the halogens in the dipole moment measurements.

Temperature Effects.—A recent publication[19] has expressed the belief that the $\Delta\nu_{OH}$ shifts in compounds such as the *o*-halophenols probably are due to electrostatic effects and not to the formation of hydrogen bonds such as occur between O–H and either O or N groups. Although this subject will be considered at length in a future publication, a brief discussion is pertinent at this point.

The two principal contributions to the energy of intermolecular hydrogen bonds are now well recognized to be electrostatic interaction and charge transfer effects. It is quite probable that hydrogen bonds of weak or moderate strength are due mainly to electrostatic effects, particularly in intramolecular associations involving five-membered rings. Charge transfer effects, which are largely responsible for the increase in band intensities, are of only secondary importance in these cases of highly bent hydrogen bonds whether the receptor atom is halogen, oxygen or certain types of nitrogen groupings. Therefore, it is not surprising that the band intensities of O–H groups involved in these hydrogen bonds are only slightly greater than those of the free O–H groups. The authors feel that there is no reason to rename the hydrogen bonding interactions simply because one of the two contributions to the energy is unusually weak. The electrostatic attraction results in a majority of the OH groups bonding to the halogen in *o*-halophenols and to the halogen of greater energy of interaction in the dihalophenols. The presence of two bands of comparable intensity in the dihalophenols is compatible only with a specific interaction to each halogen involving their lone pair electrons. This interaction is, therefore, due to hydrogen bonding particularly since the approximate frequencies can all be predicted from the spectra of the mono-*o*-halophenols. Moreover, the $\Delta\nu_{OH}$ shifts bear no relationship to the C–X dipole moments of the phenyl halides. This argues against a strict dipole–dipole association effect.

For hydrogen bonding in the dihalophenols, one would predict that the relative intensity of the two

---

(17) W. F. Anzilotti and B. C. Curran, THIS JOURNAL, **65**, 607 (1943).

(18) This is supported by the pKa data of Baddeley, *et al.*, (*J. Chem. Soc.*, 1827 (1935)), who showed that the acidity of *p*-fluorophenol is less than that of phenol.

(19) M. St. C. Flett, *Spectrochim. Acta*, **10**, 21 (1957).

bands in each compound would tend to become equal as the temperature is raised. This does indeed occur as shown in Table II, thus lending strong support to the above conclusions. The samples were run as described except that hexachlorobutadiene was used as a solvent. Since the dielectric properties of this solvent are similar to those of carbon tetrachloride, the O–H spectra obtained from both solvents are nearly identical, but the temperature can be extended well beyond the liquid range of carbon tetrachloride with hexachlorobutadiene.

Finally, as will be shown in a future publication, the association bands of *o*-halophenols are approximately the same width as the associated bands of some compounds containing O–H—N or O–H—O hydrogen bonds. In these latter compounds, the interacting distances and rotational configurations must be just as restricted as in the *o*-halophenols.

TABLE II

Halogen substituents			
2	6	T, °C.	Absorbance ratio (peak)
F	Cl	36	0.61
		139	.68
F	Br	33	.68
		125	.74
Cl	I	35	2.73
		139	2.08
Br	I	29	1.9
		138	1.5

This means that for these compounds, the ΔS term involved in formation of the hydrogen bond must be nearly zero, as it is for the halophenols. This is the principal reason for the narrowness of these types of bands.

PITTSBURGH, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Multiple Intermediates in Steady State Enzyme Kinetics.[1,2] I. The Mechanism Involving a Single Substrate and Product

BY LEONARD PELLER AND ROBERT A. ALBERTY

RECEIVED JUNE 2, 1959

The method of Christiansen has been employed to derive the general steady-state rate equation for an enzymatically catalyzed reversible reaction involving a single substrate and a single product but with an arbitrary number of intermediates. The observable kinetic parameters (Michaelis constants and maximum velocities) define lower limits to the rate constants for the unimolecular and bimolecular steps. The magnitude of the latter for a number of enzyme systems suggests that a diffusion controlled combination of enzyme and substrate is being observed. The kinetic behavior of the intermediates during the steady-state period is examined. A particular model for the *p*H variation of the rate as applied to the *n*-intermediate system is also considered.

Introduction

In studies of the kinetics of enzymatic reactions under steady-state conditions, it is generally impossible to assign values for the rate constants for specific steps in a mechanism which involves even a reasonable number of intermediates. For a reversible system involving a single substrate and a single product which can be described in terms of one intermediate, the four measurable kinetic parameters (two Michaelis constants and two maximum velocities) suffice to determine the four rate constants. However, such a mechanism if not requiring revision by studies of the influence of other variables, *e.g.*, *p*H, generally falls far short of providing an adequate description of the chemical steps involved.

A number of years ago Christiansen[3] proposed a method for dealing in a straightforward fashion with the steady-state kinetics of complex reaction schemes. Use has been made of this approach in treating multi-barrier kinetic processes by Eyring and associates.[4] It has been applied to sequences of enzymatic reactions by Christiansen,[5] Hearon[6] and Lumry.[7] Most recently Hearon has pointed out some of the complexities which may have to be taken into consideration in dealing with the effect of inhibitors on the kinetics of complex enzymatic mechanisms.[8]

It is the purpose of this paper to develop a general steady-state rate equation by the use of Christiansen's method for an enzymatically catalyzed reversible reaction involving a single substrate and product but with an arbitrary number of intermediates. The resulting expression permits a ready definition of Michaelis constants and maximum velocities. The equations for these parameters are put in such a form that certain general arguments can be made concerning their relation to the actual rate constants in the mechanism. Moreover, such an approach clearly indicates which conclusions commonly drawn from

---

[1] This research was supported by grants from the National Science Foundation and from the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation.

[2] Presented in part before the 135th National Meeting of the American Chemical Society, Boston, April 5–10, 1959.

[3] J. A. Christiansen, *Z. physik. Chem.*, **28B**, 303 (1935); **33B**, 145 (1936).

[4] B. J. Zwolinski, H. Eyring and C. E. Reese, *J. Phys. Colloid Chem.*, **53**, 1426 (1949); R. B. Parlin and H. Eyring in "Ion Transport Across Membranes," ed. by H. T. Clarke, Academic Press, Inc., New York, N. Y., 1954, p. 103.

[5] J. A. Christiansen, *Acta Chem. Scand.*, **3**, 493 (1949).

[6] J. Z. Hearon, *Physiol. Rev.*, **32**, 499 (1952).

[7] R. Lumry, *Disc. Faraday Soc.*, **20**, 257 (1955).

[8] J. Z. Hearon, S. A. Bernhard, S. L. Friess, D. F. Botts and M. F. Morales in "The Enzymes," Vol. I, 2nd Ed., Academic Press, Inc., New York, N. Y., 1959, pp. 89–108.