A STUDY OF THE MECHANISM OF AROMATIC CYCLODEHYDRATION

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An Abstract

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A Study of the Mechanism of Aromatic Cyclodehydration

An Abstract.

A kinetic study of the acid catalyzed cyclodehydration of o-benzylbenzophenones to give 9-substituted anthracenes led Bradsher and Vingiello (1) to the conclusion that the rate of the reaction was determined by two steps. Referring to Chart I, it can be seen that the first step is the reversible addition of a proton to the carbonyl group, and the second step is the attack of the resulting carbonium ion on the ortho position of the benzene ring into which cyclization takes place. The third step, the dehydration of the dihydroanthracene to give the fully aromatic anthracene, is not believed to be rate controlling.

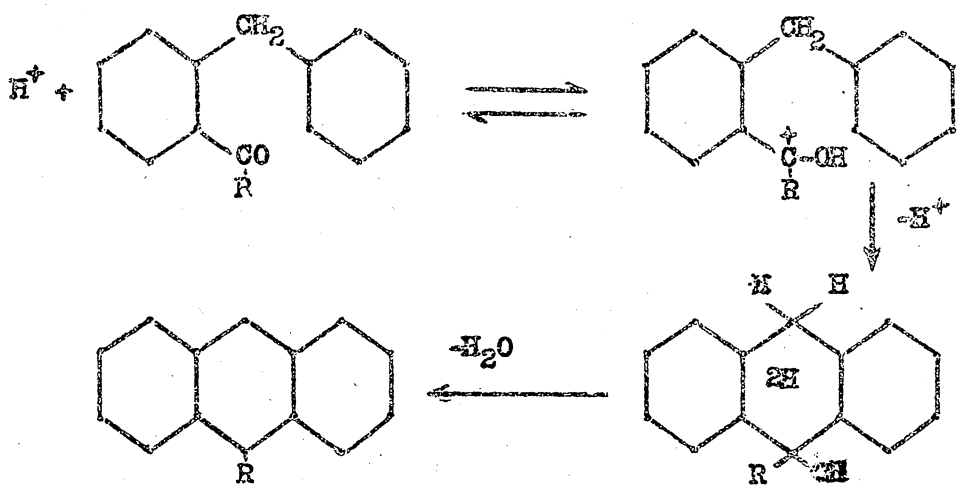


CHART I

Berliner (2) had suggested that the rate controlling step was only the second step, and based his argument on some experiments of debatable validity, in which he showed that the rate of cyclization decreased when increasingly electron releasing alkyl substituents were attached to the carbonyl group. He pointed out that such an electron release would decrease the electropositive character of the carbonium ion and thus decrease the rate at which this ion would attack the benzene ring. One of the debatable points of these experiments was that the same result could also depend upon the steric nature of the substituent.

By the use of para substituted phenyl groups, Bradsher and Vingiello could vary the electronic effect of the substituent on the carbonium ion, but at the same time maintain the steric factor essentially constant. The results of these experiments showed that neither an electron releasing group (methyl), nor electron attracting groups (chlorine and bromine) caused a change in the rate of reaction from that of the unsubstituted o-benzylbenzophenone. Since the first step of the reaction would be facilitated by an electron releasing group, while the second step would be retarded by the same substituent, and vice versa for an electron attracting group, it is concluded that both of these steps were rate controlling: any change in rate caused by a substituent on the first step would be nullified by the opposing electrical requirement of the second step. The outstanding discrepancy in this series of rate measurements was the case of the para fluoro compound, which cyclized at a significantly

slower rate than the remainder of the compounds. The reasons for this discrepancy were not clear at the time.

The present investigation has satisfactorily explained, it is believed, the reasons for the slower rate at which the fluoro ketone cyclizes, and has given a more detailed picture of the electronic mechanism of the reaction. This investigation was undertaken with the following thoughts in mind.

Fluorine, being the most electronegative element in the periodic table, exerts a very powerful electron attraction along the line of valence bond (the inductive effect, $-I_E$). But at the same time there is an overwhelming array of experimental facts which show that, despite its high electronegativity and consequent strong hold on its electrons, fluorine will release its electrons more readily in a tautomeric shift (in which the electrons change their octet affiliations) than any other of the halogens. Dipole moment studies (3), the strengths of acids (4), anilines and phenols, (5, 6), and the rates of hydrolysis of various halogenated benzyl chlorides (5) all require that fluorine release its electrons more easily in this tautomeric (T) shift than any of the other halogens. This T effect may manifest itself as a permanent polarization of the molecule (M, the Mesomeric effect) or as a polarizability effect (E, the Electromeric effect) brought into play at the moment of reaction, and then only at the demand of the attacking reagent. These effects are described in more detail by Remick (7).

Since the T effect is known to operate strongly from the <u>para</u>

position, but only very weakly from the meta position (7), the effect of fluorine in the meta position on the rate of cyclization would be due to the -I effect only, divorced from the opposing T effect. Consequently, a series of ketones with substituents in the meta position (3'-substituted-2-benzylbenzophenones, where the substituent is fluoro, chloro, bromo, methyl, and trifluoromethyl) was synthesized, and the rates of cyclization to the m-substituted phenyl anthracenes were measured. These rates were compared with the values obtained for the corresponding para substituted compounds, and the values for the rate constants are given in the appendix. The fact that the two sets of values were comparable was shown by the redetermination of two of the values found in the first series. The methods of syntheses, the yields and the analyses for new compounds are also given in the appendix.

One of the outstanding features of this series of rate constants is that there is very little numerical difference in the rate constants when substituents with such widely differing electronic effects as the trifluoromethyl group and the methyl group are present. (It will be shown below that the substitution of these groups in another ring of the compound cause a tremendous retarding and accelerating effect, respectively, on the rate.) This fact corroborates the statement of Bradsher and Vingiello (1) that the overall rate of the reaction was dependent on two rate determining steps of opposing electrical requirements; the compensating electrical requirements of these two steps would serve to nullify any retardation or acceleration due to

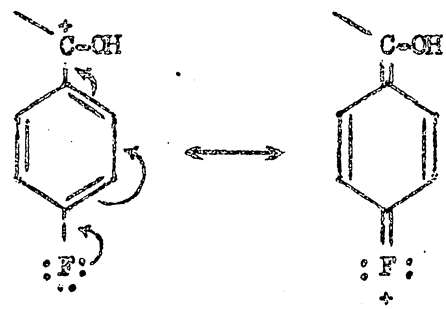
an electron attracting or electron releasing group, and the rate of the overall reaction would remain essentially unchanged.

There is, however, a slight general trend in the reaction rates shown by the compounds studied. It is to be noted that in those cases where a +T effect can operate, the rate is slower than in those cases where this effect cannot operate. Moreover, as we progress from the unsubstituted ketone to the meta-halogenated ketones to the m-trifluoromethyl to the p-trifluoromethyl we find a general increase in the rate; this order of substituents also corresponds to an increase in electron attraction (-I effect, and -I, -T effect in the last group). This fact would lead one to believe that the second step in the reaction is slightly more susceptible to the effects of substituents than the first step is. Now it must be pointed out that these differences are indeed small, whereas the differences in the electrical effects of the substituents are by comparison quite large. This point emphasizes again that it is the compensating nature of the two steps in the reaction which is the major factor; otherwise one would expect much larger differences in the rates than are actually found.

In the light of these new facts, the slower rate of cyclization found for the para-fluoro ketone is not out of line. The results of the present work show that fluorine in the meta position, with its large -I effect, actually increases the rate of cyclization slightly. Since the tautomeric effect does not operate significantly from the meta position, it follows that the presence of the tautomeric

effect operating from the para position would seem to be the cause of the slower rate. The objection to this argument is, of course, that if the +T effect slowed the second step, why then does it not correspondingly speed the first step (i.e., shift the equilibrium to the right) and thereby nullify any change in rate?

In answering this question, it is first to be noted that the +E effect of fluorine is not called into play in the second step, since it would not aid the reaction. The +M effect, being a permanent polarization of the molecule, would, however, serve to impede this step (Ref. 7, p. 59). It was pointed out above that the +M effect of the fluorine atom is larger than that of any of the other halogens in a neutral molecule. Moreover, in the present case, we find that there is a full positive charge on the carbonium ion, and the +M effect of the halogens is undoubtedly considerably enhanced by this charge. This would result in a relatively significant contribution of the form on the right below to the resonance hybrid of the carbonium ion:



It can be plainly seen that any contribution of such a form would lower the electropositive character of the central carbon atom, and hence slow the rate at which it would attack the benzene ring into

which cyclization takes place. The fact that fluorine is better able to donate its electrons in such a shift, coupled with the fact that the fluoro ketone cyclizes slower than the other halogenated ketones, would indicate that only in the case of fluorine is this above resonance form strong enough to overcome the compensating nature of the two steps in the reaction.

It must be further concluded that the magnification of the +M effect by this full positive charge is strong enough to reverse the normal electron attractive powers of the fluorine atom, so that in this case, fluorine exerts an electron release. There are cases comparable to this quoted by Alexander (8) where it was necessary to postulate that the M effect appeared to outweigh the inductive effect.

It may be possible that this same factor (increase in the +M effect) is partially responsible for the similarity in rates of the para-chloro, para-bromo, methyl and unsubstituted ketones, by acting in the halogenated ketones to nullify the large -I effect.

Since the M effect of the methyl group is of hyperconjugative origin, its magnitude is quite small by comparison to that of the halogens. This fact, and the fact that the +E effect is not called into play in the second step of the reaction, may be the reasons why no difference is noted in the rates for the m- and p-methyl ketones. Any small difference here, and between these ketones and the unsubstituted ketone is not noticed presumably because of the compensating action of the two steps in the reaction.

Bradsher and Vingiello (1) also showed that the rates of cyclization

of o-benzoyltriphenylmethane to 9, 10-diphenylanthracene, and of o-benzoyl-1, 1-diphenylethane to 9-methyl-10-phenylanthracene were faster than the rate of the unsubstituted o-benzylbenzophenone. This increase in the rate was explained on the basis of an increased electron density at the ortho position at which cyclization takes place, or, alternatively, in the case of the triphenylmethane derivative, on a statistical basis, since there are four ortho positions (instead of two) in this compound, leading to an increase in the probability of the reaction. The steric natures of these two compounds are also not the same as the other compounds studied, and this was thought also to have an effect upon the rate of cyclization. Thus the factors here which would have an effect upon the rates of cyclization of these ketones were postulated to be the electron density at the ortho position into which cyclization takes place, the number of such ortho positions, and the steric requirements of the molecule.

These conclusions were substantially verified in the present work. Substituents were placed in the ring into which cyclization takes place, and the effects of these substituents on the rate were noted. Again the syntheses of 2-(x-substituted-benzyl)-benzophenones are described in the form of a chart in the appendix. The yields, results of rate measurements, and analyses required are also reported in the appendix. These substituents were o-, m-, and p-methyl, m-trifluoromethyl, and p-fluoro.

As a consequence of their known electron release (+I) the methyl

groups in this ring cause a marked increase in the rate of cyclization, by increasing the electron density at the ortho position into which cyclization takes place. When the methyl group is para (also ortho) to the point of cyclization, moreover, we find that there is a tremendous increase in the rate. This is also to be expected, since from this position, the +E effect of the methyl group is called into play. It is this same effect of the methyl group which causes ortho-para direction in electrophilic substitution in aromatic compounds.

It was rather surprising to find that the ketone with a methyl group in the ortho position (only one ortho position free for cyclization) cyclized at a faster rate than the ketone with the methyl group in the para position (two ortho positions available for cyclization). In both of these ketones, the methyl group is meta to the point of cyclization, and hence the electronic effect of the two would presumably be the same. With the present information available, it is only possible to surmise that there must be some preferred orientation in the molecule which would aid the reaction, due to the ortho methyl group. The fact that the ortho methyl ketone is a solid, while the para ketone is a liquid, shows that there is some difference in the intramolecular forces in the two compounds. A comparison of the differences between these two compounds, and the difference between the meta-methyl ketone and these ketones, shows that the former difference is insignificant, and does not invalidate the electronic interpretation

given above. This slight discrepancy shows, however, that the steric requirements of the molecule are important.

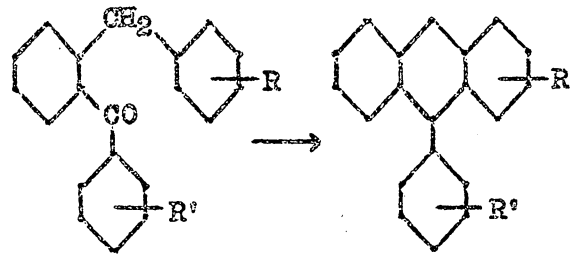
As a corollary to the fact that electron releasing groups in this ring accelerate the reaction is that electron attracting groups retard it. Numerous attempts to cyclize 2-(3-trifluoromethylbenzyl)-benzophenone and 2-(4-fluorobenzyl)-benzophenone failed. No cyclization product could be obtained from the reaction mixtures when the former compound was heated under reflux in the standard acid mixture for over ten days, nor from the latter after reflux for over three days. The material isolated from the reaction mixtures after reflux treatment was shown to be unchanged ketone by oxidation to the diketone (e.g., derivatives of o-dibenzoylbenzene) and comparison with the material obtained from the oxidation of the pure ketone. In both cases, the yields after treatment were only slightly less than the yields of the diketone from the oxidation of the pure ketone. These experiments show that the presence of the strongly electron attracting trifluoromethyl group para to, and the fluorine atom, also electron attracting, meta to, the point of cyclization strongly inhibits the cyclization reaction.

In conclusion, we may say that the present investigation (a) confirms the statement of Bradsher and Vingiello (1) that the rate of cyclization of the ketones is dependent upon the electron density at the ortho position in the ring into which cyclization takes place, (b) corroborates their statement that the rate is dependent upon two rate determining steps of opposing electrical requirements, but shows that these two steps are not exactly compensating, (c) explains why

4'-fluoro-2-benzylbenzophenone cyclizes at a slower rate than the other ketones studied by showing that the magnification of the +M effect of the fluorine by a full positive charge serves to slow the reaction by acting in step two of the reaction, and finally, (d) indicates that the steric requirements of the reaction are important.

APPENDIX I

Rates of Cyclization of Some Substituted o-Benzylbenzophenones.

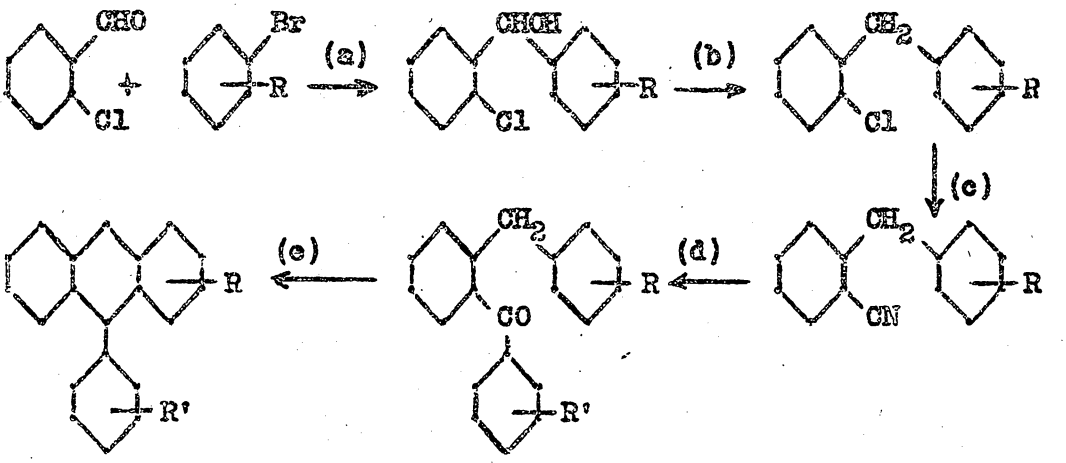


R:	R':	K x 10^{-2} $hrs.^{-1}$
H	p-F*	2.8
H	p-Cl*	4.1
H	p-Br*	4.2
H	p-CH_3*	4.2
H	m-CH_3	4.4
H	H*	4.4
H	m-Br	5.0
H	m-Cl	5.3
H	m-F	5.3
H	m-CF_3	6.4
H	p-CF_3	9.3
**o-CH_3	H	15.4
m-CH_3	H	200.
p-CH_3	H	13.8
m-CF_3	H	Does not cyclize in 10 days.
p-F	H	Does not cyclize in 3 days.

*Values from the earlier work. (1)
**The position here refers to the location in the ketone.

APPENDIX II

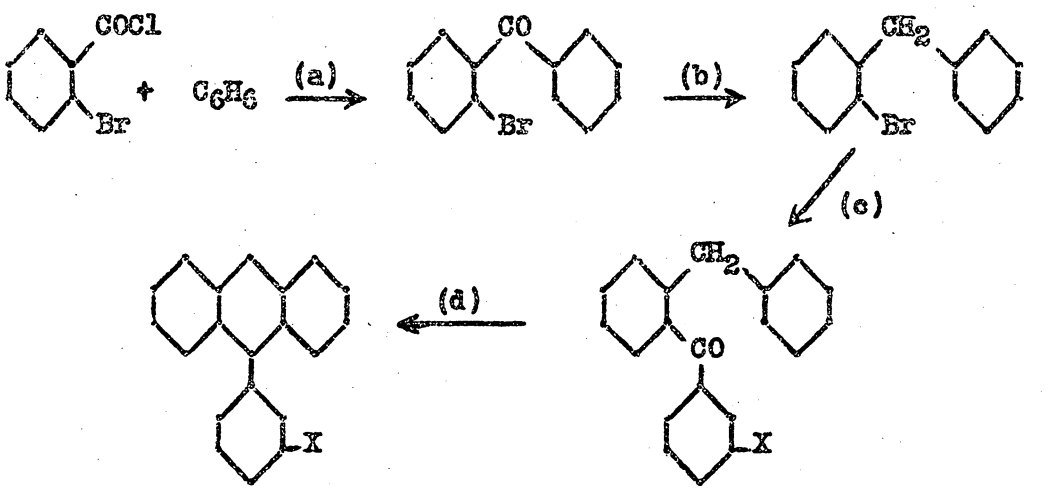
Charts showing the method of preparation of 2-(x-substituted-benzyl)-benzophenones and 2-benzyl-x'-substituted-benzophenones, and their cyclization to substituted 9-phenylanthracenes.



(a) Through Grignard, (b) I_2, red P, in Acetic acid, (c) $Cu_2(CN)_2$ in pyridine at 250°, (d) 1. Grignard. 2. HCl (2N) (e) HBr-HOAc.

R is o-, m-, p-CH_3; m-CF_3; p-F (R' is H).

R' is m-Cl, m-CH_3, m-CF_3, p-CF_3 (R is H).



(a) $AlCl_3$. (b) HI, red P. (c) Grignard, plus acid chloride.

(d) HBr-HOAc. **X is Br or F.**

APPENDIX III

Table of New Compounds

Name	% Yield	m.p. or b.p. °C	Analysis			
			Calculated		Found	
Name			C	H	C	H
2-chloro-2'-methyldiphenylcarbinol	67	113.5-114.5	72.25	5.63	72.24	5.73
2-chloro-3'-methyldiphenylcarbinol	76	56.5-57.5	72.25	5.63	72.36	5.76
2-chloro-3'-trifluoromethyldiphenylcarbinol	93	174-176/5.8 mm.	58.65	3.52	58.20	3.59
2-chloro-4'-fluorodiphenylcarbinol	72	175-178/6.8 mm.	65.97	4.26	66.00	4.18
2-chloro-2'-methyldiphenylmethane	77	159-159.5/9 mm.	77.59	6.05	77.84	6.13
2-chloro-3'-methyldiphenylmethane	78	151-153/7.5 mm.	77.59	6.05	77.80	6.10
2-chloro-4'-methyldiphenylmethane	59	146-147/5 mm.	77.59	6.05	77.85	6.01
2-chloro-3'-trifluoromethyldiphenylmethane	80	134-135/3.6 mm.	62.12	3.72	62.00	3.82
2-chloro-4'-fluorodiphenylmethane	66	149-154/11 mm.	70.75	4.57	70.75	4.55
2-cyano-2'-methyldiphenylmethane	77	174-175/6 mm.	86.91	6.32	86.86	6.42
2-cyano-3'-methyldiphenylmethane	67	165-165.5/4.5 mm.	86.91	6.32	87.05	6.27
2-cyano-4'-methyldiphenylmethane	60	170-171/4.5 mm.	86.91	6.32	87.20	6.28
2-cyano-3'-trifluoromethyldiphenylmethane	79	135.5-136/1 mm.	68.96	3.86	69.08	3.98
2-cyano-4'-fluorodiphenylmethane	62	171-173/8.2 mm.	79.60	4.77	80.00	4.73

Table of New Compounds (Cont'd)

Name	% Yield	m.p. or b.p. °C	Analysis Calculated C	Calculated H	Found C	Found H
2-(2-methylbenzyl)-benzophenone	84	85-86	88.08	6.33	88.48	6.31
2-(3-methylbenzyl)-benzophenone	86	191-191.5/1.5 mm.	88.08	6.33	87.98	6.47
2-(4-methylbenzyl)-benzophenone	95	194-196/1 mm.	88.08	6.33	88.42	6.36
2-(3-trifluoromethylbenzyl)-benzophenone	84	185-186.5/1 mm.	74.11	4.44	73.74	4.55
2-(4-fluorobenzyl)-benzophenone	89	193-195/2 mm.	82.74	5.21	83.07	5.14
1-methyl-10-phenylanthracene	90	104-104.5	93.99	6.01	93.70	6.14
3-methyl-10-phenylanthracene	88	117-118	93.99	6.01	93.86	6.05
2-benzoyl-3'-trifluoromethylbenzophenone	94	107.5-108	71.19	3.70	**71.20**	**3.77**
4'-trifluoromethyl-2-benzylbenzophenone	61	169-170/0.9 mm.	74.11	4.44	**74.20**	**4.52**
9-(4-trifluoromethylphenyl)-anthracene	61	205-206	78.18	4.07	**78.50**	**4.13**
3'-fluoro-2-benzylbenzophenone	44	174-176/1 mm.	82.74	5.21	82.78	5.53
9-(3-fluorophenyl)-anthracene	60	143.5-144.5	88.21	4.81	88.22	4.78
9-(3-methylphenyl)-anthracene	67	97-98.5	93.99	6.01	**93.84**	**6.10**

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