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o-PHTHALALDEHYDE AMIDE ADDUCTS—I

THE "ORTHO PARADOX" IN PHTHALALDEHYDE—BENZAMIDE ADDUCTS

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Abstract—Primary amides add to *o*-phthalaldehyde to form phthalans and/or isoindolines. The final product distribution is governed by the steric requirement of the carbonamides. Small R groups favor isoindolines, and larger R groups lead to phthalans. We have found that, in the aliphatic series, this steric control is quite general and applies to all adducts so far studied. In the aromatic series, phthalans have been predicted because cyclization to isoindolines is sterically hindered by the ortho hydrogens. In most cases, benzamides in fact produced the expected phthalans. However, with strongly electron-withdrawing ortho substituents, we have found that isoindolines were the predominant products.

o-Phthalaldehyde (PA) forms heterocyclic adducts with a variety of reagents.[1a-e] Recently, Reynolds *et al.* reported a facile cycloaddition with primary amides to form two types of adducts.[2] Simple amides with small or elongated substituents gave isoindolines (I), whereas bulky amides gave phthalans (P). Examples of bulky amides were pivalamide (R=t-Bu) and, interestingly, benzamide along with a number of its derivatives.

A mechanism based on a steric model was proposed in which the first step involves attack by the amide anion on the PA CO to give intermediate **A**, which equilibrates with intermediate **B** as shown in Scheme 1.

Intermediate **B** is considered to be more stable than **A**; consequently, ring closure of **B** to isoindoline is more favorable. If, however, isoindoline formation is sterically hindered, an alternative ring closure of **A** to phthalan is expected to predominate.

For adducts with benzamides, Reynolds *et al.*[2] suggested that the *ortho* hydrogens might create sufficient hindrance to prevent cyclization to isoindolines.

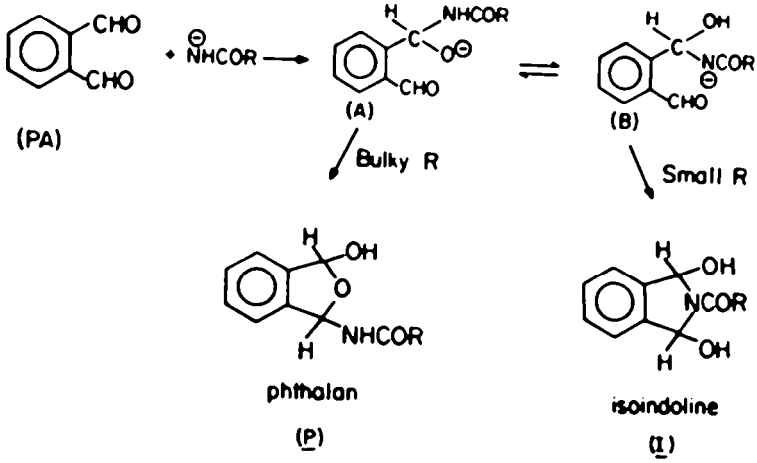
In most adducts, we have found that the Reynolds model seems to be valid. Thus, with the simple amides listed in Table 1, steric control indeed is clearly indicated. In agreement with Reynolds' prediction, we found that the I/P preference decreased from acetamide **1** to isobutyramide **2** and dramatically dropped with pivalamide **3** (series I). A similar trend was observed for the chlorosubstituted acetamides **4–6** (series II).[3]

The ortho paradox

In the benzamide series we found an exception which could not be explained on the basis of Reynolds' steric model. To our surprise, reaction of PA with more sterically hindered 2,6-dichlorobenzamide yielded only isoindoline **17** instead of the expected phthalan.[3] This suggests a situation where an overriding electronic effect may obscure a steric trend.

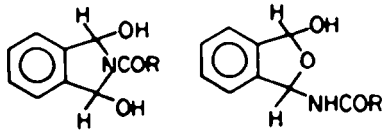
To substantiate this hypothesis, various ring-substituted aromatic amides were reacted with PA, and the structures of the adducts were then characterized by both ^{13}C and ^{1}H NMR.[3]

Table 2 shows that *meta*- and *para*-substituted benzamides, without exception, gave only phthalans, independent of the nature of the substituents. With *ortho*-substituted benzamides, again phthalans were formed exclusively when the substituents are electron donating



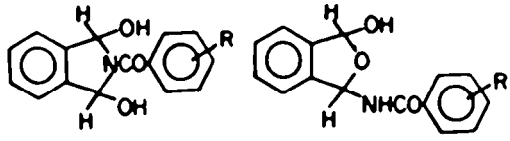
Scheme 1. Mechanism of cycloaddition

Table 1. Adducts with simple amides. Product distribution governed by steric effects of substituents



Adduct	R	% Isoindoline	% Phthalan
series I: methyl-substituted acetamides			
1	$-CH_3$	100	0
2	$-CH(CH_3)_2$	87	13
3	$-C(CH_3)_3$	0	100
series II: chloro-substituted acetamides			
4	$-CH_2Cl$	90	10
5	$-CHCl_2$	62	38
6	$-CCl_3$	0	100

Table 2. Adducts with benzamides. Product distribution governed by position and electronic effect of substituents



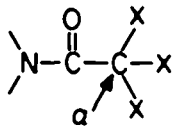
Adduct	R	% Isoindoline	% Phthalan
series III: benzamides			
para			
7	p-H	0	100
8	p-CH_3	0	100
9	p-OCH_3	0	100
10	p-Cl	0	100
11	p-NO_2	0	100
meta			
12	m-NO_2	0	100
ortho			
13	o-CH_3	0	100
14	o-OCH_3	0	100
15	o-NO_2	100	0
16	o-Cl	50	50
17	o,o-diCl	100	0
18	o-F	0	100
19	per-F	50	50

(R=Me, OMe). However, benzamides with electron-withdrawing *ortho*-substituents (R=NO_2, Cl) unexpectedly produced the isoindolines. Thus *o*-chlorobenzamide and perfluorobenzamide led to equimolar mixtures of both isomers, but *o*-nitrobenzamide and 2,6-dichlorobenzamide gave 100% isoindolines.

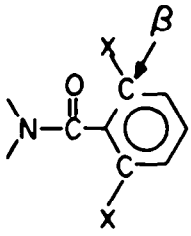
A modified Reynolds model

Evidently the overriding factor in these instances is not steric. Intuitively, the steric effect due to 2,6-dichloro substitution may seem severe. This, however, is more apparent than real because, unlike adducts in series I and II, the substituents in series III are located at the β-

carbon, which is one atom farther from the cyclizing center.



α substituents
(Series I and Series II)



β substituents
(Series III)

Table 3. Ortho effect in benzoic acid ionization[4]

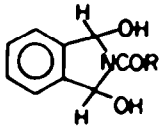
Substituent	Relative acid strength[a] ortho	meta	para
H	1.0	1.0	1.0
F	8.6	2.2	1.2
Cl	18.2	2.4	1.7
NO_2	107.0	5.2	6.0

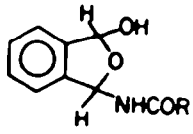
[a]Ratio of ionization constants K_A.

Furthermore, the planarity of a benzene ring with 2,6-substituents may introduce steric hindrance only in certain orientations. We suggest, however, that the electron-withdrawing effect of these substituents increases markedly as they go from a *para* to an *ortho* position. A precedent for this is the ionization of benzoic acids, which has been known to be greatly enhanced because of an "ortho" or "proximity" effect. Dippy and Lewis reported that benzoic acids with *ortho* electron-withdrawing substituents ionized about an order of magnitude more readily than their *para* or *meta* counterparts[4] (Table 3).

By analogy, our results favor a modified Reynolds model for benzamides with electronegative *ortho* substituents. These compounds, by virtue of enhanced acidity, may shift the equilibrium in favor of intermediate **B**, leading to isoindolines. Even though the Hammett σ values for *ortho* substituents have not been determined, our data suggest that an electron-withdrawing power comparable to that of chloro ($\sigma_p = 0.23$) is required to

Table 4. Melting point, yield, and selected chemical shifts for adducts with simple amides

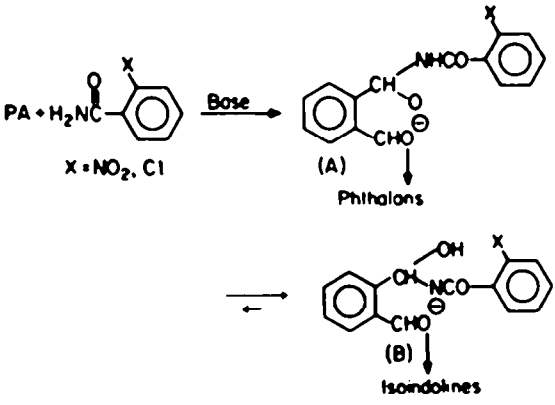




Adduct	R	Isoindoline	Phthalan	m.p., °C	% Yield
		^{13}C NMR (ppm)[a]			
series I: methyl-substituted acetamides					
1[2]	$-CH_3$	80.6, 82.6	none	157.158	78
2	$-CH(CH_3)_2$	82	80.8; 92	116-118	54
3[2]	$-C(CH_3)_3$	none	81.4; 82.5; 99, 99.5	140-141	62
series II: chloro-substituted acetamides					
4	$-CH_2Cl$	81.6	81, 82; 96, 97	159	73
5	$-CHCl_2$	82.1	81.5, 82.9; 99.5, 99.9	121-123	71
6	$-CCl_3$	none	82.9, 84.3; 92.5, 92.7	126-133	62

[a]Chemical shifts for C_1 and C_3 which for (I) are 80-83 ppm, but for $(P)C_1$ are 92-100 ppm and $(P)C_3$ 81-83 ppm. Pairs of figures are due to magnetic nonequivalence or cis-trans isomerization.[3]

produce a substantial effect. Thus, fluoro ($\sigma_p = 0.06$) is inadequate, whereas perfluoro or chloro leads to 50% isoindoline, and nitro ($\sigma_p = 0.78$) or 2,6-dichloro results in 100% isoindoline.



CONCLUSION

o-Phthalaldehyde and primary amides form two types of cyclic adducts which are sterically controlled. Small alkyl groups produce isoindoline, but large alkyl or aryl groups produce phthalan. Exceptions to this steric rule are benzamides with electron-withdrawing *ortho* substituents, which favor isoindoline over phthalan.

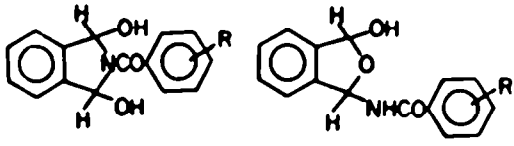
EXPERIMENTAL

Uncorrected m.p. determinations were done on a Thomas–Hoover apparatus. The TLC analyses were done on either glass plates (Uniplate, Blue Hen Industrial Park, Newark, Delaware) or Kodak Chromagram sheets coated with silica gel with hexane containing 5% EtOAc. NMR and IR spectra were obtained on a Varian EM 360A NMR spectrometer and a Perkin–Elmer IR spectrophotometer. ^{13}C NMR measurements and in special cases ^1H NMR were carried out on a JEOL JNM-FX60Q Fourier-transform spectrometer, a 90-Hz Perkin-Elmer R-32 spectrometer, and a Nicolet Fourier-transform spectrometer. Unreported IR and NMR data were consistent with assigned structures.

The procedure for **6** exemplifies our synthesis for adducts in Tables 1, 2, 4 and 5. This procedure, adapted from Reynolds,[2] has been used successfully to prepare more than 70 adducts, including ~25 new adducts with sulfonamides.[5] Products often consisted of an equimolar mixture of *cis* and *trans* isomers of one type of adduct. In some rare instances, various mixtures of isoindoline and phthalan were also obtained. No attempt was made to isolate these isomers in their pure forms. However, their presence and relative ratios were readily identified by NMR, especially by the ^{13}C technique.[1] Tables 4 and 5 also contain melting points, yields, and relevant ^{13}C NMR data[1] for the adducts investigated. All new adducts gave acceptable elemental analyses.

Preparation of 1-*hydroxy*-3-*trichloroacetamidophthalan* (**6**). Phthalaldehyde (PA, 67 g, 0.5 mol, Aldrich) that had been ground in a mortar was added to a stirred mixture of trichloroacetamide (81 g, 0.5 mol) in water (3 l). The suspension was stirred vigorously for 10 min and then cooled to 10°. A 20-ml portion of

Table 5. Melting point, yield, and selected chemical shifts for adducts with benzamides



Adduct	R	Isoindoline ^{13}C NMR (ppm)[a]	Phthalan	m.p., °C	Yield, %
series III: benzamides					
para					
7	p-H		81.6, 82.8; 99.3, 99.8	135-136	69
8	p-CH_3		81.6, 82.8; 99.2, 99.7	107-108	89
9	p-OCH_3		81.6, 82.8; 99.2, 99.6	127-129	45
10	p-Cl		81.6, 82.8; 99.3, 99.8	162-163	36
11	p-NO_2		81.6, 82.7; 99.4, 100.0	158	80
meta					
12	m-NO_2		81.6, 82.8; 99.4, 100.0	131-132	75
ortho					
13	o-CH_3		81.2, 82.2; 99.2, 99.6	120-125	62
14	o-OCH_3		81.4, 82.5; 99.3, 99.7	145-148	72
15	o-NO_2	81.2, 83.1		130-131	62
16	o-Cl	81.2, 82.9	82.2, 83.5; 99.8	88-90	86
17	o,o-diCl	81.1, 83.2		146-147	75
18	o-F		81.3, 82.4; 99.5, 99.9	111-112	54
19	per-F	81.6, 83.3	81.3, 92.4; 99.6, 100.2	111-112	63

[a] See Table 4, footnote a.

1 N KOH was added over 10 min, and vigorous stirring was continued for 1.5 hr at room temp. The suspension, initially white, turned tan and was weakly alkaline to indicator paper. An additional 5 ml of 1N KOH was added, and stirring was continued for 3.5 hr. The tan solids were collected and washed three times with 1:1 acetonitrile/water. The damp filter cake was dissolved in acetone (1 l); the soln was stirred for 10 min with Nuchar (10 g) and filtered immediately through a bed of Celite, which was washed with acetone (300 ml). The filtrate was diluted with 1.3 l water and chilled in an ice bath for 2 hr with occasional scratching of the sides of the flask. The pale-tar solids were collected, washed with water (300 ml), and dried under vacuum for 48 hr: 92.5 g (62%), m.p. 126–133°. A single spot by TLC showed the absence of PA. (Found: C, 40.5; H, 2.5; N, 4.7. Calc for $C_{10}H_8Cl_3NO_3$: C, 40.5; H, 2.7; N, 4.7%).

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[3]See D. D. Giannini, L. W. Kelts, T. DoMinh and M. H. Stern, *Tetrahedron* **39**, 1673 (1983).

[4]J. F. J. Dippy and R. H. Lewis, *J. Chem. Soc.* 1425 (1937).

[5]All adducts with sulfonamides so far investigated are isoindolines. T. DoMinh, M. H. Stern, D. D. Giannini and L. W. Kelts, unpublished.