amino)benzoyl chloride.[8,9] Platinum(IV) oxide ($PtO_2 \cdot H_2O$, Adams catalyst) was purchased from Alfa Products (Thiokol/Ventron Division, Danvers, MA). All solvents were HPLC grade (Mallinckrodt, Inc., Paris, KY).

HPLC was performed on a Waters Associates (Milford, MA) liquid chromatograph consisting of a Model 6000A solvent delivery system, a Model M45 solvent delivery system, a Model 660 solvent programmer, and a Model 440 absorbance (254 nm) detector. Samples were injected via a Valco Model N60 loop injector (Valco, Houston, TX). Reversed-phase HPLC was performed by using a DuPont Zorbax ODS column (25 cm × 4.6 mm i.d.) and water/methanol (1:3, v/v) as the elution solvent at 1.2 mL/min. Normal-phase HPLC was carried out on a DuPont Golden Series Zorbax SIL column (6.2 mm i.d. × 8 cm) with ethyl acetate/hexane (1:3, v/v) containing 0.4% (v/v) of methanol as the elution solvent at 2 mL/min. The enantiomers of **1**, **2a**, and **2e** were separated with an HPLC column (4.6 mm i.d. × 25 cm; Regis Chemical Co., Morton Grove, IL) packed with an (*R*)-*N*-(3,5-dinitrobenzoyl)-phenylglycine ionically bonded to spherical particles of 5-μm diameter of γ-aminopropylsilanized silica gel. This chiral column is commonly known as Pirkle type IA column. Separation of enantiomeric diols was achieved isocratically with a flow rate of 2 mL/min by using premixed solvents of ethanol/acetonitrile/hexane (2:1:17, volume ratio) at ambient temperature.

Mass spectral analysis was performed on a Finnigan Model 4000 gas chromatograph–mass spectrometer–data system by electron impact with a solid probe at 70 eV and 250 °C ionizer temperature. Ultraviolet–visible absorption spectra of samples in methanol were determined on a 1-cm path-length quartz cuvette with a Varian Model Cary 118C spectrophotometer.

The proton NMR spectra were obtained on a Bruker WM-300 spectrometer equipped with an ASPECT 3000 minicomputer. The conventional 1D Fourier transform NMR spectra were collected with 32K data points. This yielded a digital resolution of 0.368 Hz/point. The spectral width was 6000 Hz. Each spectrum was obtained by an accumulation of 256 scans.

Phase-sensitive 2D NMR spectroscopy (both COSY and NOESY)[12] was performed. The spectral window for 2D spectra was 2500 Hz and data points were 1K for both frequency dimensions (F1 and F2). However, 256 points were taken in the F1 domain. Up to 64 scans were accumulated in each F1 domain. Sine bell function was applied on the Fourier transform in F1 domain to eliminate the spin–lattice relaxation noice.[16] The mixing time of 2D NOESY was 1 s. All samples were dissolved in 99.8% acetone-d_6 with a trace of D_2O to exchange the hydroxyl protons and all spectra were taken at 25 °C. Chemical shifts (in ppm) are relative to that of tetramethylsilane.

CD spectra of samples (dissolved in methanol) in quartz cell of 1-cm path length at room temperature were measured on a JASCO Model 500A spectropolarimeter equipped with a Model DP-500 data processor. The concentration of the sample is indicated by $A_{\lambda 2}$/mL (absorbance units at wavelength $\lambda 2$ per mL of solvent). CD spectra are expressed by ellipticity ($\Phi_{\lambda 1}/A_{\lambda 2}$, in millidegrees) for solutions that have an absorbance of $A_{\lambda 2}$ unit (usually ≤ 1.5) per mL of solvent at wavelength $\lambda 2$ (usually the wavelength of maximal absorption). Under conditions of measurements indicated above, the molecular ellipticity ($[\Theta]_{\lambda 1}$, in deg·cm^2·dmol^{-1}) and ellipticity ($\Phi_{\lambda 1}/A_{\lambda 2}$, in millidegrees) are related to the extinction coefficient ($\epsilon_{\lambda 2}$, in cm^{-1} M^{-1}) as follows:

$$[\Theta]_{\lambda 1} = 0.1\epsilon_{\lambda 2}(\Phi_{\lambda 1}/A_{\lambda 2})$$

1,2-Dihydrobenzo[*b*]fluoranthene-*trans*-1,2-diol (1). Compound 1 obtained from the Chemical Repository of the National Cancer Institute was purified by normal-phase HPLC on a DuPont Golden Series SIL column. MS: *m/z* (relative intensity) 286 (M^+, 23), 268 (100).

1,2,3,3a-Tetrahydrobenzo[*b*]fluoranthene-*trans*-1,2-diols (2a and 2e). Diastereomeric conformers **2a** and **2e** were obtained by catalytic hydrogenation (THF, PtO_2, 1 atm, 30 min) of 1 and were separated by normal-phase HPLC on a DuPont Golden Series SIL column. The enantiomers of **2a** and **2e** were separated with a Pirkle type IA chiral column as described above. **2a**: MS, *m/z* (relative intensity) 288 (M^+, 23), 270 (18), 255 (6), 253 (8), 252 (7), 244 (33), 228 (36), and 215 (100). **2e**: MS, *m/z* (relative intensity) 288 (M^+, 26), 270 (10), 255 (3), 253 (5), 252 (5), 244 (39), 228 (51), and 215 (100).

Acknowledgment. We thank Mr. Henri Weems for mass spectral analyses.

(16) Bax, A. *Two Dimensional Nuclear Magnetic Resonance in Liquids*; Delft University Press, D. Reidel Publishing Co.: Dordrecht, Holland, 1982.

On the Regioselectivity of Metal Hydride Reductions of 3-Substituted Phthalic Anhydrides

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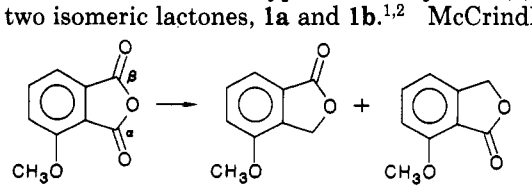
A problem of 3-methoxyphthalide reduction by metal hydrides was reinvestigated. Various effects controlling selectivity of reductions in 3-substituted phthalides were studied, and a qualitative interpretation of the results is now proposed. Methods for obtaining enhanced yields of one or the other lactonic product were developed.

The reduction of 3-methoxyphthalic anhydride (1) can yield two isomeric lactones, **1a** and **1b**.[1,2] McCrindle et



1 **1a** **1b**

al.[3] have reported highly regioselective formation of lactone **1a** (**1a**:**1b** = 87:13) in the reduction of 3-methoxyphthalic anhydride (1) by sodium borohydride. A similar pattern of regioselectivity (preferred reduction at the β-carbonyl group) was reported for the borohydride reduction of 3-(dimethylamino)phthalic anhydride, while the reduction of 3-methylphthalic anhydride was found to be nonselective.[3]

The above findings suggest that the regioselectivity of these reactions could be due to the preferential reduction of chelates formed by complexation of an appropriate

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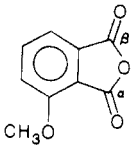
(1) McAlees, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans 1* **1977**, 2030–2036.
(2) Brewster, J. H.; Fusco, A. M. *J. Org. Chem.* **1963**, *28*, 501.
(3) McAlees, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans 1* **1977**, 2037–2038.

0022-3263/87/1952-0129$01.50/0

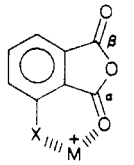
Table I. Reductions of 3-Methoxyphthalic Anhydride (1)



expt	reducing agent	temp, °C	time, h	% reduction[a]	lactonic products ratio 1a (α)	1b (β)
1	$LiBH_4$	−10→20	2	90	50	50
2	$NaBH_4$	−10→0	2	100	77 (60)[b]	23 (40)[b]
3	KBH_4	−10→0	2	no redn		
4	KBH_4	22	48	no redn		
5	$Zn(BH_4)_2$	−10→20	72	100	70	30
6	$NaBH_4(ZnCl_2)$	−10→20	72	100	70	30
7	$NaBH_4(CdSO_4)$	−10→20	72	91	75	25
8	$NaBH_4$(15-crown-5)	20	72	94	38	62
9	$LiAlH_4$	−78→−30	2	100	30	70
10	$NaAlH_4$	−10→22	72	50	50	50
11	$NaAlH_4$	−10→22	113	80	50	50
12	$Na(AlH_4)$(15-crown-5)	−78→20	109	30	33	67
13	Li-Selectride	−78→30	2	100	9	91
14	Na-Selectride	−78→−30	2	93	11	89
15	K-Selectride	−78→−30	2	81	14	86
16	Na-Selectride + $ZnCl_2$	−78→−30	2	87	10	90
17	Na-Selectride (15-crown-5)	−78→−30	20	40	21	78
18	DIBAL-H	30	2	100	20	80

[a] 100% reduction means that no starting anhydride could be detected on GC or in the NMR spectrum of the crude product. The isolated yields of reduced compounds were only slightly lower. [b] The ratio **1a**:**1b** = 60:40 was obtained with fresh $NaBH_4$ not dried under vacuum.

substituent X (e.g., methoxy) and the ortho carbonyl function, as shown in **2**.[4]



2

More recently, Makhlouf and Rickborn[5] reported rather different patterns of selectivity in metal hydride reductions of anhydride **1**.

The reduction of $NaBH_4$ was shown to be devoid of selectivity (**1a**:**1b** = 53:46), while L-Selectride (Aldrich) reduction gave **1b** as a major product (**1a**:**1b** = 1:9). The authors noted a similar regioselectivity in reductions of 1-methoxy-2,3-naphthoic anhydride. In all reactions, simple metal hydrides ($NaBH_4$, $LiBH_4$) appeard to be nonselective, while bulky Selectride reagents favored reduction at the β-carbonyl group. The results were rationalized on steric grounds, although the authors noted that electronic factors could also be involved.

Since the regioselectivities observed by the two groups[3,5] were significantly different, and the proposed steric control[5] appeared unconvincing in the perspective of our experience with Selectride reductions of maleic anhydrides,[6] and the results of Krepelka and Holubek (Figure 1[7]), we decided to reexamine the problem.

A number of 3-substituted phthalic anhydrides was prepared as described in the Experimental Section. Using these substrates we carried out a systematic study of the regioselectivity of reductions by various metal hydrides

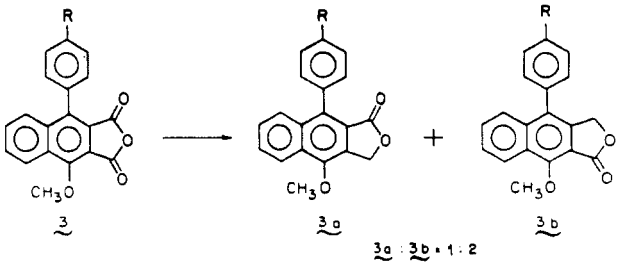


Figure 1. Reduction of 4-aryl-1-methoxynaphthalene-2,3-dicarboxylic anhydride (**3**) gave lactone **3b** as a major product, **3a**:**3b** = 1:2.

(MBH_4, $MAlH_4$, Selectrides, DIBAL-H). The experiments were designed, and the results examined, with a specific goal in mind, namely, to shed some light on the importance of the nucleophile's reactivity and the effect of counterions on the selectivity of these reactions.

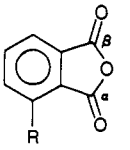
Since the manipulation of a crude product can significantly alter the ratio of the two lactones obtained, the analyses (by ^1H NMR and GLC) were performed on crude mixtures before any attempt was made at the separation and purification of individual lactones. The results are listed in Tables I–III. The lactones were separated on a chromatotron (see Experimental Section) and purified by sublimation. The *isolated yields* corresponded closely to the yields reported in Tables I–III.

Discussion

The examination of Table I shows that while reductions of 3-methoxyphthalic anhydride with $NaAlH_4$ and $LiBH_4$ exhibit no selectivity, the reductions with Selectrides occur preferentially at the β-carbonyl function to give 7-methoxyphthalic lactone as a major product. The above observations also apply reasonably well to 3-halophthalides (Table II). The results listed in Tables I–III show that careful choice of the reducing agent and the reduction conditions permits preparation of one or the other lactone as a principal product. Furthermore, the experimental

(4) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 2484–2490.
(5) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 4810–4811.
(6) Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P.; Ip, H. S. *Can. J. Chem.* **1986**, *64*, 104–109.
(7) Krepelka, J.; Holubek, J. *Collect. Czech. Chem. Commun.* **1981**, *46*, 2123–2128.

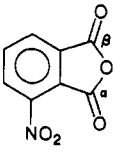
Table II. Metal Hydride Reductions of 3-Halophthalic Anhydrides 4, 5, 6, 7



conad	R	reducing agent	temp, °C	time, h	% redn[a]	lactonic products ratio α	lactonic products ratio β
4	F	$LiBH_4$	22	72	100	60	40
		$NaBH_4$	22	20	100	61	39
		$Zn(BH_4)_2$	0→22	60	100	66	34
		$LiAlH_4$	−30→22	2	100	25	75
		$NaAlH_4$	22	96	76	40	60
		Li-Selectride	0→22	20	87	30	70
		Na-Selectride	0→22	20	83	32	68
		K-Selectride	0→22	22	89	33	67
		$(CH_3)_4N^+BH_4^-$	22	96	40	56	44
		DIBAL-H	−78→−60	2	87	10	90
5	Cl	$LiBH_4$			96 (40% diol)	10	90
		$NaBH_4$	22	20	91	60	40
		$Zn(BH_4)_2$	22	48	100	70	30
		$LiAlH_4$	22	24	98	36	64
		$NaAlH_4$	22	96	98	33	67
		Li-Selectride	0→22	24	90	18	82
		Na-Selectride	0→22	24	90	20	80
		K-Selectride	0→22	24	80	18	82
		DIBAL-H	−78→−60	2	61	12	88
6	Br	$LiBH_4$			99 (50% diol)	20	80
		$NaBH_4$	22	20	96	72	28
		$Zn(BH_4)_2$	22	24	98	76	24
		$LiAlH_4$	0→22	20	79	53	47
		$NaAlH_4$	22	96	91	54	46
		Li-Selectride	0→22	20	71	15	85
		Na-Selectride	0→22	20	73	20	80
		K-Selectride	0→22	22	70	24	76
		DIBAL-H	−78→−60	2	81	10	90
7	I	$LiBH_4$					
		$NaBH_4$	22	48	99 (20% diol)	60	40
		$Zn(BH_4)_2$			90	84	16
		$LiAlH_4$	−30→0	4	96	55	45
		$NaAlH_4$	0	4	77	43	57
		Li-Selectride	0	4	72	15	85
		Na-Selectride	0	4	85	12	88
		K-Selectride	0	4	31	12	88
		DIBAL-H	−78→−60	2	40 (17% diol)	29	71

[a] 100% reduction means that no starting anhydride could be detected on GC or in the NMR spectrum of the crude product. The isolated yields of reduced compounds were only slightly lower.

Table III. Metal Hydride Reductions of 3-Nitrophthalic Acid Anhydride

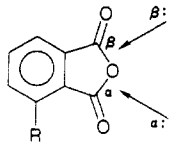


		reducing agent	temp, °C	time, h	% redn	lactonic products ratio α	lactonic products ratio β
8	NO_2	$NaBH_4$	−30	2	75	83	17
		$LiAlH_4$	−30	2	91	71	29
		Li-Selectride	−30	2	87	23	77
		Na-Selectride	−30	2	85	18	82

data suggest that no single factor can account for regioselectivity control in the reduction of phthalides. Rather, the net effect of several factors determines the relative ratio of two lactones.

Electronic Effects. Extended Hückel and ab initio calculations (Table IV) show that in the presence of an electron-releasing substituent the highest LUMO coefficient is located on the carbon atom of the β-carbonyl group of **9**.[8] Thus, the β-carbonyl is a better target for nucleo-

(8) The geometry for phthalic anhydride was adapted from the crystallographic data: Ito, K.; Moriya, K.; Kashino, S.; Haisa, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3078. Bates, R. B.; Cutler, R. S. *Acta Crystallogr., Sect. B: Struct. Sci.* **1977**, *33*, 893.



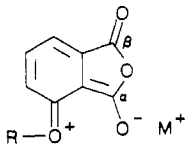
9

higher LUMO coefficient ("intrinsically" more reactive) for R = OH, Cl, F

higher LUMO coefficient for R = CN

philic attack.[9] When the substituent is an electron-attracting group, the preferred reduction at the α-carbonyl might be expected. This, in fact, is supported by the general drift observed in the selectivity of reductions by $LiAlH_4$ (Table V).

A similar conclusion can be reached when resonance effects in the counterion–anhydride complex are considered. It has been well established that the cation actively participates in the metal hydride reductions of carbonyl compounds.[10,11] In the absence of a counterion, aliphatic aldehydes and ketones are *not* reduced by metal hydrides (10), aromatic and conjugated compounds *can* be reduced, but the reactions are slower and the yields considerably reduced.[12] Thus, the cation, although not essential for the reduction of aromatic carbonyl compounds, is nonetheless implicated in these reactions in a catalytic fashion. In phthalic anhydrides substituted with an electron-donating group, the contribution of the canonical form **10**

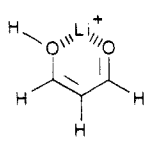


10

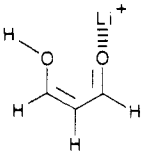
stabilizes the complex with a cation but simultaneously deactivates the α-carbonyl function toward the nucleophilic attack (the enol effect). Hence, by default, the β-carbonyl becomes the more likely target.

Chelating Effect. When a stable chelate (**2**) can be formed, the contribution of structure **10** is diminished as a nonbonded electron pair on the substituent is engaged in chelate formation. At the same time, the chelated function is activated vis-à-vis a nucleophile.

Ab initio calculations performed for the model compound **11**[13] confirm that the chelated complex **11a** is energetically preferred to a straight line complex **11b**.



11a
-29 kcal/mol

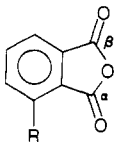


11b
0 kcal/mol

Theoretically, therefore, the formation of a chelate is favored. Practically, an appropriate cation suitably free to form a chelate is necessary. The experimental results show a slight but consistent increase in selectivity for the α-carbonyl function (the one which is capable of chelate formation) on changing the counterion from Li^+ to Na^+, Zn^{2+}, or Cd^{2+}. (See Table VI.)

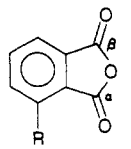
Which counterion will form the most stable chelate depends not only on the nature of the cation but also on the solubility and solvation of the reducing agent (and/or the added salt, where applicable) and the competition between solvation and chelation of the cation. $LiAlH_4$ is quite soluble in THF (13 g/100 g of THF at 25 °C).[14] $NaBH_4$ is very slightly soluble (0.1 g/100 g of THF) while KBH_4 is essentially insoluble in ethers. Accordingly, under anhydrous, nonprotic conditions, even after 48 h at room temperature, KBH_4 does not reduce phthalic anhydrides, the reduction by $NaBH_4$ takes more than 12 h, and the

Table IV. Calculations on 3-Substituted Phthalic Anhydrides



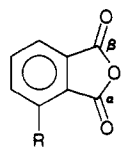
R	LUMO coefficients Cα	Cβ
	Ab Initio	
CH_3	0.329	−0.328
OH	0.309	−0.340
Cl	0.309	−0.314
F	0.309	−0.324
CN	0.251	−0.063
	Extended Hückel	
CH_3	0.520	−0.528
Cl	0.510	−0.534
F	0.509	−0.535
CN	0.552	−0.477
NO_2	0.130	−0.007

Table V. Relationship between LUMO Coefficients and Regioselectivity of Reduction with $LiAlH_4$ in THF



R	LUMO Cα	% redn at α	LUMO Cβ	% redn at β
F	0.309	25	−0.324	75
OCH_3	0.309	30	−0.340	70
Cl	0.309	36	−0.314	64
NO_2	0.130	71	−0.007	29

Table VI. % Reduction at α-Carbonyl Group



reducing agent	R OCH_3	F	Cl	Br	I
$LiBH_4$	50	60			
$NaBH_4$	60	62	60	72	60
$Zn(BH_4)_2$	70	66	70	76	84

(9) Kayser, M. M.; Eisenstein, O. *Can. J. Chem.* **1981**, *59*, 2457–2462.
(10) Brown, H. C.; Ichikawa, K. *J. Am. Chem. Soc.* **1961**, *83*, 4372–4377.
(11) Pierre, J. L.; Handel, H. *Tetrahedron Lett.* **1974**, 2317. Pierre, J. L.; Handel, H.; Perraud, R. *Tetrahedron* **1975**, *31*, 2795–2798. Handel, H.; Pierre, J. L. *Ibid.* **1975**, *31*, 2799–2802.
(12) Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* **1976**, 1677.
(13) The structure of chelate was calculated by using the GAUSSIAN 70 program with a minimal STO-3G basis set (Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. GAUSSIAN 70, QCPE No. 236, Bloomington, IN). Standard bond lengths and bond angles were used (Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*, McGraw-Hill: New York 1970, p 111).
(14) Gaylord, N. G. *Reduction with Complex Metal Hydrides*; Interscience: New York, 1956.

reductions by $LiAlH_4$ are completed within 2 h even at low temperatures.

Conductance studies of $LiAlH_4$, $NaAlH_4$, and $LiBH_4$ indicate that in THF at 25 °C $LiAlH_4$ exists predominantly in solvent-separated ion pairs, $NaAlH_4$ as a mixture of solvent-separated and contact ion pairs, and $LiBH_4$ in intimate contact ion pairs. NMR studies show the formation of a 4:1 THF solvate with Li^+ cation from $LiAlH_4$ and the formation of a 2:1 THF solvate with Li^+ from $LiBH_4$.[15]

The entropies of activation indicate that the Li^+ cation binds more strongly to carbonyl oxygen than Na^+.[17] Hence, the solvent-separated Li^+ cation, more available (higher solubility in THF) and mobile (solvent separated), can effectively seek out the "intrinsically" more reactive carbonyl function, form an activated complex, and assist in the hydride transfer. The chelation process by the THF-solvated Li^+ (4:1) is somewhat less efficient. In order to form a chelate, another molecule of THF on Li^+ must be replaced by an electron pair from the substituent in position 3. This is not particularly favorable since THF is a better electron donor than a methoxy or a halo substituent on an aromatic ring.

Thus, it appears that although Li^+ is more effective than Na^+ in catalyzing reductions of carbonyl groups in general, it is less effective in forming chelates with 3-substituted phthalic anhydrides. In the presence of 15-crown-5, both $NaBH_4$ and $NaAlH_4$ reduce preferentially the β-carbonyl group, suggesting that BH_4^- as well as AlH_4^- "recognize" the intrinsically more reactive site in the absence of the modifying influence of a cation.

The experimentally demonstrated change in selectivity from β- to α-carbonyl reduction in the presence of Na^+, Zn^{2+}, or Mg^{2+} cations is observed and reproducible only under strictly anhydrous conditions. Traces of moisture provoke partial or total loss of selectivity for the α-carbonyl group and in addition catalyze the reduction to the point where stopping at a lactone stage may be difficult.

Even scrupulously dried equipment and solvent do not prevent such complications if $NaBH_4$ and $LiBH_4$ are not dry (both reagents are hygroscopic). In the early stages of our work we found it difficult to obtain reproducible results. This problem was eventually linked to the difference in the reductions with "older" and "newer" batches of reducing agents ($NaBH_4$ and $LiBH_4$). Not only were we obtaining different proportions of lactones, but, in addition, variable and unpredictable quantities of diols were a frequent minor product. Traces of water not only catalyze the reduction but also appear to solvate the cation and, thus, in the case of Na^+, prevent it from effective chelate formation, hence decreasing the possibility of reduction at the α-carbonyl.

It is the degree of "dryness" of the $NaBH_4$ reagent which quite likely was the cause for the discrepancies in the ratios of lactones produced in the reductions of 3-methoxy phthalic anhydrides reported in the literature.[3,5]

Steric Effects. Reactions with bulky Selectride and DIBAL-H reagents give 7-substituted phthalides as major products. Such selectivity cannot be entirely linked to steric interaction with the 3-substituent on phthalic anhydride. In 3-fluorophthalic anhydride, where the substituent exerts minimal steric influence, reductions with Selectrides give product ratios identical with those observed in $LiAlH_4$ reductions. Thus, the steric effect depends on the size and charge of the 3-substituent, being negligible for a 3-fluoro and quite important for a 3-nitro group. (See Table: II and III.)

In conclusion we would like to point out that although several different factors influence regioselectivity of these reactions, it is now possible to predict which effects are going to be dominant and consequently by choosing appropriate reagents and conditions to obtain an excellent yield of the desired lactone.

Experimental Section

General Methods. Melting points were measured with a Fisher Scientific microscope melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with either a NT-360NB (Atlantic Region NMR Centre) or a Varian EM-360-L spectrometer. Analyses by mass spectrometry were carried out at the Ottawa–Carleton Mass Spectrometry Centre. Infrared spectra were measured with a Perkin-Elmer 1420 spectrophotometer. A DANI 7070 gas chromatograph was used for reaction monitoring and simple GC analyses.

Tetrahydrofuran (500 mL) was refluxed under dry nitrogen with sodium metal (5–10 g) and benzophenone (10 g) until the blue color persisted, and then it was distilled into oven-dried flasks containing a dry reducing agent and was used immediately. The general procedures for the reductions were as follows: Lithium aluminum hydride (0.004 mol) was placed in an oven-dried, three-neck flask into which 60 mL of tetrahydrofuran was subsequently distilled. The flask was fitted with an inlet post for syringes, gas outlet tube, thermometer, and magnetic stirrer. The suspension, swept with a slow stream of nitrogen, was stirred for 15 min at room temperature and then cooled in a dry ice–acetone bath. An anhydride (0.008 mol), dissolved in freshly distilled tetrahydrofuran (40 mL), was injected slowly into the reaction flask. The temperature of the reaction mixture was maintained below −50 °C throughout the addition process. The stirred solution was allowed to warm to 0 °C over a period indicated in the tables. The flask was then cooled again to −20 °C and 10 mL of water and 3 N HCl were added until pH 1. The reaction mixture was stirred overnight. The THF was evaporated and the acidic aqueous layer extracted repeatedly with ether. The combined organic layers were dried, the solvent was evaporated, and the product was analyzed by ^1H NMR and GLC equipped with 50-cm, $^1/_8$ in. OV-101 5% column.

Reductions with sodium borohydride were carried out as follows: The suspension of crushed $NaBH_4$ (0.005 mol, dried at 120 °C in vacuum), in dry tetrahydrofuran (60 mL), was refluxed for 15 min and then cooled in an ice bath. A solution of an anhydride (0.008 mol) in dry tetrahydrofuran (40 mL) was added dropwise to a stirred, ice-cold suspension of $NaBH_4$. The stirring was continued for 12–20 h. After quenching with 3 N HCl (to pH 1), 10 mL water was added and stirring continued overnight. The workup procedure was the same as in the procedure described for $LiAlH_4$ reductions.

The Selectride reductions were carried out as follows: An anhydride (0.003 mol) was dissolved in dry, freshly distilled THF (100 mL). The mixture, flushed with a constant slow stream of dry N_2, was cooled in a dry ice–acetone bath. Li-, Na-, or K-Selectride (1 M in THF, 10 mL) was injected slowly into the reaction flask. The reaction was stirred for 2 h while the temperature was allowed to rise slowly to −30 or −20 °C. At that time NaOH (4 N, 2 mL) and 30% H_2O_2 (3 mL) were added and stirring was continued overnight. The reaction mixture was acidified with 3 N HCl, reduced on a rotatory evaporator, and extracted several times with chloroform and diethyl ether. The combined organic layers were evaporated to dryness.

Reductions in the presence of the 15-crown-5 were modified in the following manner: The reducing agent and the crown ether (in molar ratio 1:2) were refluxed in dry THF for 3–4 h prior to addition of an anhydride. The two lactones were separated on a chromatotron (a preparative centrifugally accelerated, radial, thin-layer chromatograph, Model 79247, Harrison Research, Palo Alto, CA) on silica gel using toluene–ethyl acetate (9:1) as elutant. The *isolated yields* of the reduced product were very close to the yields reported as % reduction. Convenient syntheses of 3-methoxy- and 3-halophthalic anhydrides are described below.

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3-Methoxyphthalic Anhydride (1). 3-Methoxyphthalic acid was prepared according to the procedure described in the literature.[17] It was cyclized to the corresponding anhydride, mp 160 °C, as described for 3-fluorophthalic anhydride.

3-Fluorophthalic Anhydride (4). 2,3-Dimethylfluorobenzene was prepared according to the method described by Flood.[18] ^{1}H NMR: δ ($CDCl_3$) 2.05 (s, 3 H), 2.08 (s, 3 H), 6.77 (m, 3 H). 2,3-Dimethylfluorobenzene (34.1 g), water (300 mL), and cetyltrimethylammonium bromide (0.05 g) were placed in a round-bottom flask (1 L) equipped with a condenser. $KMnO_4$ (174.0 g, 4 equiv) as added in several portions to the reaction mixture and vigorously stirred at 60 °C. The reaction took approximately 4 days. MnO_2 was filtered and the filtrate acidified at 0 °C with concentrated HCl until pH 1. Repeated extractions with ether gave 3-fluorophthalic acid (24.7 g) mp 180 °C. The acid (24.0 g) was refluxed for 1 h with acetic anhydride (24.0 g) and then cooled in an ice–bath. Nearly white crystals were filtered, washed with cold ether, and then sublimed, yielding 18 g, mp 162–163 °C: ^{1}H NMR δ 7.58 (t, 1 H)8 7.86 (d, 1 H), 7.95 (m, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 162.2, 159.5, 157.2 (J_{CF} = 242 Hz), 139.4, 133, 123, 121, 118; ν_{max} 1865, 1790 cm^{-1} (CO–O–CO anhydride); MS, *m/e* 166 (M^+), 122, 94.

3-Chlorophthalic anhydride (5) was similarly prepared in 66% yield from 2,3-dimethylaniline by a Sandmeyer reaction.[19] The intermediate 2,3-dimethylchlorobenzene (27.0 g) was oxidized by 4 equiv of $KMnO_4$ as described above. The reaction was carried out for 24 h at 50–60 °C until the color of permanganate disappeared. The yield of 3-chlorophthalic acid was 40%, mp 184–186 °C (lit.[20] mp 186 °C). The acid (14.0 g) was refluxed with acetic anhydride (14.0 g) for 1 h. After the mixture had been cooled, a pale brown crystalline material was obtained (12.7 g). 3-Chlorophthalic anhydride (**5**) was purified by sublimation at reduced pressure to give white crystals in 95% yield, mp 126–127 °C (lit.[20] mp 124–125 °C): ^{1}H NMR ($CDCl_3$) 7.85 (d, 2 H), 7.94 (m, 1 H); ν_{max} 1860, 1785 cm^{-1}.

3-Bromophthalic anhydride (6) was prepared in three steps from 2,3-dimethylphenol by reaction with triphenylphosphine and Br_2 in acetonitrile according to the method described previously.[21] The yield of 2,3-dimethylbromobenzene was 60%. Oxidation of this intermediate under the conditions described above gave 3-bromophthalic acid in 37% yield, mp 186–188 °C (lit.[22] mp 188 °C). The acid was refluxed with acetic anhydride for 1 h. When the reaction mixture had been cooled in a refrigerator, 3-bromophthalic anhydride (**6**) crystallized. Sublimation at reduced pressure gave white crystals, mp 132–134 °C (lit.[23] 132–134 °C), in 88% yield: ^{1}H NMR ($CDCl_3$) δ 7.75 (t, *J* = 8 Hz 1 H), 8.00 (dd, *J* = 8 Hz, 2 H); ν_{max} 1860, 1785 cm^{-1}; MS, *m/e* 226, 228 (M^+), 182, 184, 75; ^{13}C NMR ($CDCl_3$) 161, 160, 140, 136, 133, 129, 124, 120.

3-Iodophthalic Anhydride (7). 2,3-Dimethyliodobenzene was prepared from 2,3-dimethylaniline according to the procedure described by Vogel.[19] The oxidation with $KMnO_4$ was carried out as described before to give 3-iodophthalic acid, mp 205 °C (lit.[23] mp 206 °C), which was subsequently dehydrated to the corresponding anhydride. The best yield (72%) was obtained when the oxidation was carried out on small portions (2 g) of 2,3-dimethyliodobenzene. Sublimation under vacuum gave white crystalline compound in 88% yield, mp 159–160 °C (lit.[23] 159–161 °C): ^{1}H NMR ($CDCl_3$) δ 7.56 (t, *J* = 8 Hz, 1 H) 8.01 (dd, 1 H) 8.30 (dd, 1 H); ν_{max} 1860 cm^{-1}; MS, *m/e* 274 (M^+) 230, 103, 75; ^{13}C NMR ($CDCl_3$) δ 161, 160.7 147, 136, 133, 125, 91, 79.

Lactone Identification. Individual isomers were isolated by chromatography on silica gel (chromatron) with petroleum ether (bp 30–60 °C)/diethyl ether) and were sublimed under vacuum. The melting points and spectroscopic data for all lactones are listed below:

4-Methoxyphthalide (1a): mp 129–131 °C (lit.[24] mp 126–128 °C); ^{1}H NMR δ ($CDCl_3$) 3.90 (s, 3 H), 5.22 (s, 2 H), 7.2 (m, 1 H), 7.5 (m, 2 H); δ (Me_2SO-d_6) 3.90 (s, 3 H), 5.33 (s, 2 H) 7.4 (m, 3 H); ν_{max} 1785 cm^{-1} (CO) lactone).

7-Methoxyphthalide (1b): mp 102–103 °C (lit.[25] 103–105 °C); ^{1}H NMR δ ($CDCl_3$) 3.97 (s, 3 H), 5.22 (s, 2 H), 6.95 (m, 2 H), 7.65 (m, 1 H); δ (Me_2SO-d_6) 3.90 (s, 3 H) 5.27 (s, 2 H) 7.1 (m, 2 H), 7.7 (m, 1 H); ν_{max} 1760 cm^{-1} (CO lactone).

4-Fluorophthalide (4a): mp 99–100 °C (lit.[26] 99–100 °C); ^{1}H NMR δ ($CDCl_3$) 5.37 (s, 1 H, CH_2) 7.36 (t, *J* = 8 Hz, 1 H), 7.56 (m, 1 H), 7.73 (d, *J* = 8 Hz, 1 H); ν_{max} 1775 cm^{-1} (CO lactone).

7-Fluorophthalide (4b): mp 166–168 °C (lit.[26] mp 169–170 °C); ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 1 H, CH_2), 7.16 (t, *J* = 8 Hz, 1 H), 7.27 (d, *J* = 8 Hz, 1 H), 7.67 (m, 1 H); ν_{max} 1780 cm^{-1} (CO lactone).

4-Chlorophthalide (5a): mp 87–88 °C (lit.[27] mp 87 °C); ^{1}H NMR ($CDCl_3$) δ 5.30 (s, 1 H, CH_2), 7.51 (t, *J* = 8 Hz 1 H), 7.65 (d, *J* = 8 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 1 H); ν_{max} 1775 cm^{-1} (CO lactone).

7-Chlorophthalide (5b): mp 148–150 °C (lit.[27] 149 °C); ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 1 H, CH_2), 7.39 (d, *J* = 8 H, 1 H), 7.49 (d, *J* = 8 Hz, 1 H), 7.60 (t, *J* = 8 Hz, 1 H); ν_{max} 1775 cm^{-1} (CO lactone).

4-Bromophthalide (6a): mp 103–104 °C (lit.[27] 103–104 °C); ^{1}H NMR ($CDCl_3$) δ 5.23 (s, 1 H, CH_2), 7.45 (t, *J* = 8 Hz, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.88 (d, *J* = 8 Hz, 1 H); ν_{max} 1775 cm^{-1} (CO lactone).

7-Bromophthalide (6b): mp 141–143 °C (lit.[27] mp 143 °C); ^{1}H NMR ($CDCl_3$) δ 5.27 (s, 1 H, CH_2), 7.44 (dd, *J* = 8 Hz, 1 H), 7.52 (t, *J* = 8 Hz, 1 H), 7.69 (d, *J* = 8 Hz, 1 H); ν_{max} 1770 cm^{-1} (CO lactone).

4-Iodophthalide (7a): mp 134 °C (lit.[27] mp 141–142 °C); ^{1}H NMR ($CDCl_3$) δ 5.11 (s, 1 H, CH_2), 7.32 (t, *J* = 8 Hz, 1 H), 8.92 (d, *J* = 8 Hz, 1 H), 8.02 (d, *J* = 8 Hz, 1 H); ν_{max} 1760 cm^{-1} (CO lactone).

7-Iodophthalide (7b): mp 137 °C (lit.[27] mp 137 °C); ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 1 H, CH_2), 7.33 (t, *J* = 8 Hz, 1 H), 7.48 (d, *J* = 8 Hz, 1 H), 7.99 (d, *J* = 8 Hz, 1 H); ν_{max} 1765 cm^{-1} (CO lactone).

4-Nitrophthalide (8a) and **7-nitrophthalide (8b)** were described before.[4]

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