In conclusion, the ring bromination of kojic acid derivatives takes place at the 6 position, but the reaction occurs only when the 5-hydroxyl is free.

Experimental Section

Bromination of Chlorokojic Acid (2) with NBS. A mixture of 1.54 g of **2**, 1.8 g of NBS, and 10 ml of C_6H_6 was refluxed for 1 hr and was concentrated under vacuum. The residue was washed with water and recrystallized twice from absolute C_2H_5OH to yield 0.49 g of **3**: mp 162–163°; positive $FeCl_3$; ir (Nujol) 3150, 1580 cm^{-1}.

Bromination of Kojic Acid Monoacetate (9) with NBS. The same procedure was used with 0.197 g of **9**, and yielded 0.217 g of **11** after recrystallization from CCl_4, mp 131–133°, ir (Nujol) 3350, 1740, 1640 cm^{-1}.

Anal. Calcd for $C_8H_7O_5Br$: C, 36.52; H, 2.66; Br, 30.39. Found: C, 36.29; H, 2.72; Br, 30.68.

Treatment of Kojic Acid Diacetate (5) with NBS. The same procedure was used with 2.13 g of **5**. There was no reaction, as shown by comparing the product (melting point, mixture melting point, tlc, and nmr) with the starting material and with the expected product **7**.

Bromination of Kojic Acid Monobenzoate (10) with NBS. The same procedure was used with 1 g of **10**. After recrystallization from CH_3OH there was obtained 0.450 g of **12**, mp 206–207°, ir (Nujol) 3350, 1720, and 1640 cm^{-1}.

Anal. Calcd for $C_{13}H_9O_5Br$: C, 48.01; H, 2.79; Br, 24.59. Found: C, 48.22; H, 2.78; Br, 24.48.

Treatment of Kojic Acid Dibenzoate (6) with NBS. The same procedure was used with 0.5 g of **6**. There was no reaction, as shown by direct comparison (melting point, mixture melting point, tlc, and nmr) with **6** and with the expected product **8**.

Treatment of Kojic Acid Diacetate (5) with Bromine. To a suspension of 0.872 g of **5** in 10 ml of water, 0.15 ml of Br_2 in 10 ml of H_2O was added dropwise with stirring at 0°. After an additional 12 hr of stirring at room temperature, the solid material was filtered, recrystallized from H_2O, and shown to be the starting material by direct comparison. Tlc analysis of the filtrate against an authentic sample showed the absence of **7**. Similarly, no reaction took place when the bromination was performed in the H_3PO_4–KH_2PO_4 buffer.

Treatment of Kojic Acid Dibenzoate (6) with Bromine. The above procedures were used with **6** and yielded the recovered starting material identified by tlc, melting point, mixture melting point, and nmr.

Bromination of Kojic Acid (1) in Water. To 2 g of **1** in 20 ml of H_2O, 0.8 ml of Br_2 in 10 ml of H_2O was added dropwise at 0° with stirring. After stirring for 12 hr at 10° the mixture was extracted with ether which was dried over $MgSO_4$ and evaporated. After recrystallization from EtOAc, there was obtained 0.036 g of **4**, mp 170–171°.

Bromination of 1 in Trifluoroacetic Acid. After a 2-hr reflux, a mixture of 5 g of **1**, 4 ml of Br_2, and 5 ml of CF_3COOH was chilled overnight. A black solid was separated and taken up in hot EtOAc. This solution was chilled and 6-bromokojic acid precipitated. After two recrystallizations from EtOAc there was obtained 0.12 g of **4**, mp 169–170°.

Bromination of 1 in H_3PO_4–NaH_2PO_4. A solution of 4 g of Br_2 and 13.2 g of NaH_2PO_4 in 150 ml of H_2O was added dropwise with stirring to 3 g of 1 in 30 ml of 50% aqueous H_3PO_4 at 0°. After stirring overnight at 10°, a pale orange solid was filtered and recrystallized from acetone. There was obtained 1.7 g of **4**, mp 171–172°.

Acetylation of 6-Bromokojic Acid (4). A mixture of 0.446 g of **4** and 5 ml of CH_3COCl was refluxed overnight, concentrated under vacuum, and treated with 10 ml of H_2O. It was neutralized with 10% aqueous $NaHCO_3$ and filtered. The precipitate was recrystallized several times from H_2O to yield 0.014 g of **7**, mp 69–70°, ir ($CHCl_3$) 1780, 1750, and 1660 cm^{-1}. The product completely decomposed upon standing at room temperature for 1 week.

Benzoylation of 4. A mixture of 0.614 g of **4**, 2 ml of C_6H_5COCl, and 20 ml of $CHCl_3$ was refluxed overnight, concentrated under vacuum, taken up in ether, and extracted with aqueous $NaHCO_3$ and with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated, and yielded an oil which was chromatographed over silica gel. Elution with $CHCl_3$ yielded **8**. After three recrystallizations from 50% aqueous ethanol there was obtained 0.304 g, mp 123–125°, ir ($CHCl_3$) 1734, 1754, and 1674 cm^{-1}.

Anal. Calcd for $C_{20}H_{13}O_6Br$: C, 55.90; H, 3.03; Br, 18.59. Found: C, 56.10; H, 3.20; Br, 18.46.

Bromination of 1 in H_3PO_4–NaH_2PO_4. A solution of 4 g of Br_2 **KH_2PO_4.** A solution of 3 g of KH_2PO_4 and 0.4 ml of Br_2 in 20 ml of H_2O was added dropwise with stirring at 0° to 0.5 g of **9** in 10 ml of 50% aqueous H_3PO_4. After further stirring overnight at room temperature, the solution was extracted twice with 10 ml of $CHCl_3$, which was washed with water, dried, and concentrated. The solid residue was recrystallized from CCl_4 and yielded 0.1 g of **11**, mp 131–133°, identical with the sample prepared with NBS.

Bromination of Chlorokojic Acid (2) in H_3PO_4–KH_2PO_4. The same procedure was used on 0.422 g of **2** and yielded 0.180 g of **3**, mp 162–163° after two recrystallizations from EtOH, which was identical with the product obtained with NBS.

Registry No.—**1**, 501-30-4; **2**, 7559-81-1; **3**, 40838-36-6; **4**, 40838-32-2; **7**, 51568-23-1; **8**, 51568-24-2; **9**, 25552-08-3; **10**, 33777-42-3; **11**, 51568-25-3; **12**, 51568-26-4.

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(5) The ring opening of 4-pyrones and their conversion into triketones susceptible of undergoing decomposition, condensation, or cyclization reactions is well known. For example, it was used in 1893 by Collie in his pioneering work on the synthesis of phenolic compounds by the polyacetate route, and leading references in this area may be found in T. Money, *Chem. Rev.*, **70**, 553 (1970), and W. E. Hillis and Y. Yazaki, *Phytochemistry*, **10**, 1051 (1971).
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Optically Active Amines. XVII.[1] Partial Kinetic Resolution of α-Phenylbutyric Acid Using Chiral Primary Amines and Their Salts[2]

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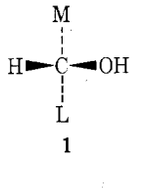
Received February 25, 1974

The kinetic resolution procedure of Horeau has been applied successfully to correlate the configurations of chiral secondary alcohols and in certain cases can be used to determine their absolute configurations.[5] The chiral alcohol is allowed to react with excess racemic α-phenylbutyric anhydride, and if the configuration of the alcohol is as shown in **1**, where L is a group with a larger steric requirement than M, partially resolved (*R*)-(−)-α-phenylbutyric acid [(*R*)-**2a**] will be recovered. The empirical nature of the method becomes evident when two of the carbinol substituents are not greatly different in steric requirement and other effects may be important. An example is the alkylphenylcarbinols, for which the phenyl group has an apparent steric requirement larger than any alkyl group, including the *tert*-butyl group.[6]



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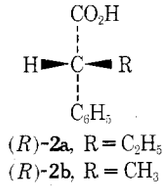


(*R*)-**2a**, R = C_2H_5
(*R*)-**2b**, R = CH_3

The method should be applicable to correlation of the absolute configurations of chiral primary and secondary amines, but few examples are available. Weidmann and Horeau[6] noted that excess racemic α-phenylethylamine [(±)-**3a**], α-benzylethylamine [(±)-**4**], and isobornylamine

Table I
Partial Asymmetric Resolution of α-Phenylbutyric Acid (2a) with Optically Active Amines

Amine[a] Compd	Amine[a] $[\alpha]^{19-26}D$, deg	Asymmetric synthesis $\alpha^{22-28}D$ of isolated **2a**, deg[b]	Asymmetric synthesis Optical yield, %[c]
(*R*)-α-Phenylethylamine [(*R*)-**3a**][d]	+39.9 (neat)	+0.28	2.3
(*S*)-α-Benzylethylamine [(*S*)-**4**][d]	+34.1 (neat)	−0.37	2.9
(*S*)-α-(1-Naphthyl)ethylamine [(*S*)-**5a**][e]	−75.4 (neat)	−0.14	1.1
(*S*)-*sec*-Butylamine [(*S*)-**6a**][d]	+6.3 (neat)[f]	−0.20	1.6
(*R*)-α-Phenyl-*n*-propylamine [(*R*)-**7a**][e]	+21.2 (neat)	−0.07	0.5
(*R*)-α-Phenylisobutylamine [(*R*)-**8a**][g]	+8.5 (*c* 2.1, C_6H_6)[h]	−0.59[i]	5.7
(*R*)-α-Cyclohexylbenzylamine [(*R*)-**9a**][j]	+9.8 (*c* 2.0, C_6H_6)	−1.07[i]	5.4
(*R*)-α-Phenylneopentylamine [(*R*)-**10**][e]	+5.2 (neat)	−1.25	8.1
Menthylamine [(3*R*)-**11**][k,l]	−37 (*c* 2.0, $CHCl_3$)	+1.31[i]	8.3
Neomenthylamine [(3*S*]-**12**][k,l]	+15.5 (neat)	−0.58	4.6
Isothujylamine [(3*S*)-**13a**][m]	+114 (*c* 2.4, 95% C_2H_5OH)	−0.19	1.3
Neoisothujylamine [(3*R*)-**14a**][k,m]	+52.2 (*c* 2.2, 95% C_2H_5OH)	+0.42[n]	3.4

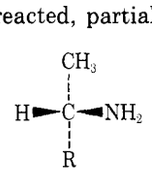
[a] References for sources of compounds, further characterization, and absolute configuration are footnotes. [b] One decimeter in benzene. (*S*)-**2a** is dextrorotatory. [c] Based on 100% amide formation and complete recovery of optically active **2a**. [d] H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2265 (1964). [e] M. E. Warren, Jr., and H. E. Smith, *J. Amer. Chem. Soc.*, **87**, 1757 (1965). [f] Partially racemic. Maximum value reported in ref *d* is $[\alpha]^{25}D$ + 8.1° (neat). Optical yield is corrected by a factor of 8.1/6.3. [g] O. Cervinka, V. Dudek, and L. Hub, *Collect. Czech. Chem. Commun.*, **35**, 724 (1970). [h] Partially racemic. Maximum value reported in ref *g* is $[\alpha]D$ +13° (*c* 2.5, C_2H_5OH). Optical yield is corrected by a factor of 13/8.5. [i] Reaction time 1 hr. [j] V. Ghislandi and D. Vercesi, *Farmaco, Ed. Sci.*, **26**, 474 (1971). [k] E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966). [l] J. Read and R. A. Storey, *J. Chem. Soc.*, 2761 (1930). [m] H. E. Smith, J. C. D. Brand, E. H. Massey, and L. J. Durham, *J. Org. Chem.*, **31**, 690 (1966). [n] Reaction time 9 hr.

Table II
Partial Asymmetric Resolution of α-Phenylbutyric Acid (2a) with Optically Active Amine Salts

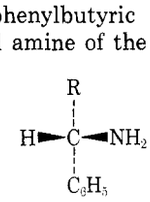
Amine salt[a] Compd	Amine salt[a] $[\alpha]^{25-26}D$, deg	Asymmetric synthesis $\alpha^{24-25}D$ of isolated **2a**, deg[b]	Asymmetric synthesis Optical yield, %[c]
(*R*)-α-Phenylethylamine hydrochloride [(*R*)-**3b**][d]	+6.7 (*c* 2.0, absolute C_2H_5OH)	+0.35	2.8
(*S*)-α-(1-Naphthyl)ethylamine hydrochloride [(*S*)-**5b**][e]	−10 (*c* 2.0, absolute C_2H_5OH)	−0.57	5.0
(*R*)-α-Phenyl-*n*-propylamine hydrochloride [(*R*)-**7b**][d]	+5.1 (*c* 2.0, absolute C_2H_5OH)	+0.14	1.2
(*R*)-α-Phenylisobutylamine hydrochloride [(*R*)-**8b**][e]	*f*, *g*	+1.10[h]	12
(*R*)-α-Cyclohexylbenzylamine hydrochloride [(*R*)-**9b**][e]	*f*	+1.11[h]	7.0
Isothujylamine nitrate [(3*S*)-**13b**][i]	+72 (*c* 1.0, H_2O)	+0.11	0.7
Neoisothujylamine *p*-toluenesulfonate [(3*R*)-**14b**][i]	+26 (*c* 0.6, H_2O, 2 dm)	−0.08	0.5

[a] References for source of compounds, further characterization, and absolute configuration are footnotes. [b] In benzene. (*S*)-**2a** is dextrorotatory. [c] Based on 100% amide formation and complete recovery of optically active **2a**. [d] H. E. Smith, M. E. Warren, Jr., and L. I. Katzin, *Tetrahedron*, **24**, 1327 (1968). [e] This work. [f] Not measured. [g] As shown in Table I, the amine [(*R*)-**8a**] from which this salt was prepared was partially racemic. Optical yield is corrected by a factor of 13/8.5. [h] Reaction time 1 hr. [i] E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966).

on treatment with (*S*)-(+)-α-phenylbutyric anhydride gave unreacted, partially resolved amine of the configura-



(*S*)-**3a**, R = C_6H_5
(*S*)-**4**, R = $C_6H_5CH_2$
(*S*)-**5a**, R = 1-$C_{10}H_7$
(*S*)-**6a**, R = C_2H_5



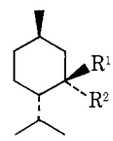
(*S*)-**7a**, R = C_2H_5
(*S*)-**8a**, R = $CH(CH_3)_2$
(*S*)-**9a**, R = c-C_6H_{11}
(*S*)-**10**, R = $C(CH_3)_3$

tion predicted assuming group steric requirements of phenyl and benzyl > methyl, and R_3C > RCH_2. This was in agreement with an earlier observation[7] that treatment of (*S*)-**3a** with excess α-phenylbutyric anhydride gave (*R*)-**2a** in about 3% optical yield. However, a recent report[8] on the kinetic resolution of several chiral anhydrides with the optical isomers of **3a** and of α-(1-naphthyl)ethylamine (**5a**) presents an anomaly with **3a**. Reaction of the cyclic anhydride of *threo*-2-methyl-3-propylsuccinic acid with (*R*)-**3a** and (*R*)-**5a** both gave the predicted (*S*)-*threo*-2-methyl-3-propylsuccinic acid. Reaction of (*R*)-**5a** with α-phenylbutyric anhydride also gave (*S*)-**2a**. However, it was reported[8] that with the latter anhydride (*R*)-**3a** gave (*R*)-**2a**, and (*S*)-**3a** gave (*S*)-**2a**.

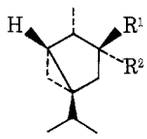
Anomalous behavior of α-phenylethylamine (**3a**) and its *N*-methyl derivative on amide formation with racemic α-phenylpropionic acid [(±)-**2b**] in the presence of dicyclohexylcarbodiimide (DCC) has been noted earlier by Cervinka.[9] Kinetic resolution with (*R*)-**3a** gave (*S*)-**2b**, but use of the *N*-methyl derivative of (*R*)-**3a** gave (*R*)-**2b**. Also, treatment of an excess of (±)-**3a** and its *N*-methyl derivatives with (*S*)-**2b** in the presence of DCC showed **3a** to be exceptional.[10] For other amines, and for all of their *N*-methyl derivatives, the configuration of the partially resolved isolated amine indicated group steric requirements of 1-naphthyl and phenyl > methyl, and benzyl, *o*-tolyl, and 1-naphthyl > phenyl. Partially resolved **3a**, however, was of the configuration indicating an apparent group steric requirement of methyl > phenyl.

In order to assess the general utility of the Horeau procedure for the establishment of the absolute configuration of chiral amines as well as to clarify the ambiguous case of α-phenylethylamine (**3a**), we now report the partial asymmetric resolution of α-phenylbutyric acid using a number of optically active disubstituted carbinamines (Table I) of known absolute configuration. Since amine salts are easier

to handle experimentally, we have also investigated a number of these (Table II) for comparison with the respective amines.



(3*R*)-**11**, $R^1 = NH_2$; $R^2 = H$
(3*S*)-**12**, $R^1 = H$; $R^2 = NH_2$



(3*S*)-**13a**, $R^1 = NH_2$; $R^2 = H$
(3*R*)-**14a**, $R^1 = H$; $R^2 = NH_2$

The optical yield (2.3%) of (*S*)-α-phenylbutyric acid [(*S*)-**2a**] using (*R*)-**3a** is the maximum obtained from 15 experiments under a variety of conditions (variations of reaction time and of molar ratios of anhydride to amine and pyridine to anhydride). The range of optical yields in these experiments was 0.9–2.3% and (*S*)-**2a** was always obtained. Thus the earlier conclusion[6,7] that the phenyl group exceeds the methyl group in steric requirement is verified. Alkylarylcarbinamines (*S*)-**4** and (*S*)-**5a** also give the expected result that in steric requirements the benzyl and 1-naphthyl groups are larger than the methyl group. Also the observed extent of asymmetric synthesis with the alkylphenylcarbinamines gives an order of group steric requirement: *tert*-butyl > cyclohexyl ≅ isopropyl > ethyl ≅ phenyl > methyl.

For the alkylarylcarbinamine hydrochlorides evaluated, it also appears that the 1-naphthyl group is effectively larger than the methyl group, and the phenyl group has an apparent steric requirement greater than that of the methyl, ethyl, isopropyl, and cyclohexyl groups, similar to that observed with the corresponding carbinols.[6]

Each chiral alkylamine gave partially resolved α-phenylbutyric acid (**2a**) of the configuration predicted on the basis of group steric requirements of ethyl > methyl, and R_2CH > RCH_2. However, isothujylamine nitrate [(3*S*)-**13b**] and neoisothujylamine *p*-toluenesulfonate [(3*R*)-**14b**] gave **2a** of opposite configuration to that obtained using the respective amines.

These observations show that, while in certain cases correlation of absolute configuration of chiral amines with results from the Horeau procedure is possible, there are cases in which steric requirement of the substituents of the carbinamine carbon atom is not the decisive factor in the kinetic resolution. Consequently, assignment of absolute configuration to chiral amines by this method is hazardous and such assignment must be substantiated by direct chemical correlation or by unambiguous circular dichroism measurements.[1]

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Boiling points are not corrected. Optical rotations were obtained using a visual polarimeter and a 1-dm sample tube. The elemental analysis was done by Galbraith Laboratories, Inc., Knoxville, Tenn.

(*S*)-α-(1-Naphthyl)ethylamine hydrochloride [(*S*)-**5b**] was prepared in ether from (*S*)-**5a**, $[\alpha]^{24}D$ −74.5° (neat) [lit.[11] $[\alpha]^{24}D$ −74.5° (neat)], and dry hydrogen chloride and was recrystallized from methanol. (*S*)-**5b** sublimed without melting near 175° and had $[\alpha]^{26}D$ −10° (*c* 2.0, absolute C_2H_5OH).

Anal. Calcd for $C_{12}H_{14}ClN$: Cl, 17.07. Found: Cl, 17.11.

(*R*)-α-Phenylisobutylamine hydrochloride [(*R*)-**8b**] **and (*R*)-α-cyclohexylbenzylamine hydrochloride** [(*R*)-**9b**] were prepared in ether from (*R*)-**8a**, $[\alpha]^{19}D$ +8.5° (*c* 2.1, C_6H_6) and (*R*)-**9a**, $[\alpha]^{24}D$ +9.8° (*c* 2.0, C_6H_6), respectively, and dry hydrogen chloride. The precipitated salts were collected by filtration, dried, and used without further purification.

Reaction of an Optically Active Amine or Amine Salt with (±)-α-Phenylbutric Anhydride. A weighed amount of amine or amine salt (0.73–0.99 mmol) was added to a 40–90% excess of (±)-α-phenylbutyric anhydride (1.18–1.62 mmol), bp 105–108° (8 mm), prepared by the procedure reported for acetic propionic anhydride,[12] in pyridine (6.6–9.8 mmol). After thorough mixing, the mixture was allowed to stand at room temperature for 4 hr. It was then diluted with benzene (5 ml) and water (5 ml) and stirred for 10–15 min. Solid sodium hydroxide was added until the mixture was basic, the benzene layer was removed, and the aqueous layer was extracted three times with benzene. The aqueous layer was acidified with hydrochloric acid and extracted three times with benzene. These latter benzene solutions were combined, dried (Na_2SO_4), and evaporated to 1.0 ml for determination of the optical rotation. In the few cases where approximately 2-mmol quantities of amine or amine salt and correspondingly larger quantities of anhydride and pyridine were used, the volume of the benzene solution used for determination of the optical rotation was adjusted to 2.0 ml.

Assuming 100% reaction of the amine and total recovery of the optically active α-phenylbutyric acid, the per cent asymmetric synthesis was calculated as

$$\text{asymmetric synthesis, \%} = \frac{(\alpha D)(\text{volume of benzene solution, ml})}{(\pm 158°)(\text{moles of amine or amine salt})}$$

In the equation, ±158° is the molecular rotation of optically pure α-phenylbutyric acid in benzene.[13]

Acknowledgment. We thank the National Science Foundation for a grant (GP-5772) supporting part of this work.

Registry No.—(±)-**2a**, 7782-29-8; (*R*)-**2a**, 938-79-4; (*S*)-**2a**, 4286-15-1; (*R*)-**3a**, 3886-69-9; (*R*)-**3b**, 10277-86-8; (*S*)-**4**, 51-64-9; (*S*)-**5a**, 10420-89-0; (*S*)-**5b**, 51600-24-9; (*S*)-**6a**, 513-49-5; (*R*)-**7a**, 3082-64-2; (*R*)-**7b**, 19068-33-8; (*R*)-**8a**, 23844-66-8; (*R*)-**8b**, 51600-25-0; (*R*)-**9a**, 32908-33-1; (*R*)-**9b**, 32908-34-2; (*R*)-**10**, 3082-71-1; (3*R*)-**11**, 51743-63-6; (3*S*)-**12**, 20706-69-8; (3*S*)-**13a**, 5033-81-8; (3*S*)-**13b**, 51731-30-7; (3*R*)-**14a**, 5033-82-9; (3*R*)-**14b**, 51600-26-1; (±)-α-phenylbutyric anhydride, 1519-21-7.

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(2) Taken in part from the Ph.D. Dissertation of A. W. G., Vanderbilt University, June 1968, and the M.S. Thesis of A. F. B., Murray State University, May 1972.
(3) (a) Vanderbilt University; (b) Murray State University.
(4) Supported by NIH Grant HD-05797.
(5) For a discussion and leading references see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 30–35.
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Axially Disposed Phenyl Groups in Geminally Substituted Cyclohexanes

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Received February 14, 1974

The common assignment of the aromatic groups of 1,4-disubstituted cyclohexanes to the equatorial position rests on the relatively large free-energy difference (3.0 ± 0.1 kcal/mol)[1] between axial and equatorial phenyl. There is evidence that the introduction of additional substitution