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Acidities of Indenes and Their Radical Cations. Homolytic Bond Dissociation Energies of the Benzylic C-H Bonds in Indenes

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Abstract: Equilibrium acidities of the benzylic C-H bonds (pK_{HA}), oxidation potentials ($E_{OX}(HA)$), and oxidation potentials of the conjugate bases ($E_{ox}(A^-)$) have been measured in DMSO for 23 indenes. Homolytic bond dissociation energies of the benzylic C-H bonds in these indenes (BDE_{HA}) and acidities ($pK_{HA^{\bullet+}}$) of the corresponding radical cations were estimated by a suitable combination of these data. Donor groups, such as MeO and R_2N, were observed to cause sizable increases in the pK_{HA} values for 2- or 3-substituted indenes relative to indene, whereas in 9-substituted fluorenes these substituents caused decreases in pK_{HA} values relative to fluorene. The increases in pK_{HA} values in indenes are caused by ground-state effects, which are related to Hine's C=C double-bond stabilization parameters. These increases in pK_{HA} led to increased BDE_{HA} values for 2-substituted indenes relative to the parent, but no increases were observed for 3-substituted indenes. In fluorenes, the presence of the powerful donor 2-Me_2N and 2,7-$(Me_2N)_2$ groups caused small increases in pK_{HA} and BDE_{HA} values that are believed to be due to ground-state effects.

Introduction

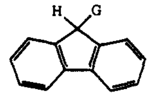
9-Substituted fluorenes **1** provided excellent indicators for the development of a DMSO acidity scale over the range from $pK_{HA} = 6.5$ for 2,7-dibromo-9-(methoxycarbonyl)fluorene to $pK_{HA} = 24.35$ for 9-*tert*-butylfluorene.[1] These same indicators played an important role in developing a method of estimating homolytic bond dissociation energies (BDEs) of weak acids, HA, by combining pK_{HA} values with the oxidation potentials of their conjugate bases.[2] Literally hundreds of BDE values for acidic C-H, N-H, O-H, and S-H bonds have been estimated by using eq 1 or the like.[3] Comparisons indicate that BDEs estimated by using eq 1 usually agree to within ±2 kcal/mol with the best gas-phase

$$BDE_{HA}\ (\text{kcal/mol}) = 1.37pK_{HA} + 23.1E_{ox}(A^-) + 73.3 \qquad (1)$$

(enthalpy) values.[3] (Henceforth kcal/mol will be abbreviated as kcal.) In the present paper, studies of this kind have been extended to a number of indenes.

Results and Discussion

Comparison of Acidities of Substituted Fluorenes and Indenes. It was of interest to compare the acidities of 9-substituted fluorenes **1** with those of the 1-, 2-, and 3-substituted indenes, a closely related family. Studies of 1-substituted indenes are difficult or impossible, however, because they rearrange rapidly to 3-substituted indenes under the conditions used for acidity measurements. A comparison of acidity data for fluorenes (9-G-FlH) and indenes (3-G-InH and 2-G-InH) is shown in Table I.



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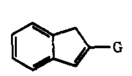

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Examination of Table I shows that indene is 2.5 pK_{HA} units more acidic than fluorene in DMSO. It is 2.1 units less acidic than cyclopentadiene, however, the acidity order being CpH_2 ($pK_{HA} = 18.0$) > InH_2 (20.1) > FlH_2 (22.6).[1] This order may seem surprising, since benzofusion onto the double bond of cyclopentadiene should enhance the possibilities for delocalization of charge in the anion and increase the acidity. Indeed, the reverse order is observed for the corresponding nitrogen acids in DMSO, i.e., pyrrole (23.0) < indole (20.95) < carbazole (19.9).[1] Gas-phase acidity measurements have shown that the latter order is the *intrinsic order for both this series of nitrogen acids and for the analogous series of carbon acids*. It follows that the order observed for the carbon acids in DMSO is reversed by stronger solvation forces that stabilize the smaller anions.[4]

Table I. Acidities of Substituted Fluorenes and Indenes in DMSO

G	pK_{HA}[a] 9-GFlH	ΔpK_{HA}[c] (kcal)	pK_{HA}[d] 3-GInH	DBSP[e] (kcal)	ΔpK_{HA}[c] (kcal)	pK_{HA}[d] 2-GInH
H	22.6	(0.0)	20.1	(0.0)	(0.0)	20.1
Me	22.3	0.82	22.1	3.3	−2.7	
t-Bu	24.35	−1.9	22.6		−3.4	
MeO	22.1	1.1	23.85	5.2	−5.1	
MeS	18.0	6.7	18.0	3.2	2.9	
c-C_4H_8N	22.2[b]	0.96	24.5	8.2	−6.0	24.5
c-$C_5H_{10}N$	22.5[b]	0.55	23.6	8.2	−4.8	23.95
c-OC_4H_8N	22.4	0.50	23.1	8.2	−4.1	23.2
PhS	15.4	10				17.3
Ph	17.9	6.8	17.2	4.9	4.0	19.35
$CONH_2$	11.9	15.0	13.8		8.6	
COOMe	10.35	17.0	10.4	3.2	13	15.4
CN	8.3	20.0	9.0	2.6	15	

[a] Reference 2 unless otherwise noted. [b] Bordwell, F. G.; Lynch, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558-7562. [c] Statistically corrected for the number of acidic hydrogen atoms. [d] Measured against two indicators. [e] Double bond stabilization parameters.[5]

Comparison of the effects on ΔpK_{HA} of donor groups on the acidities of 9-G-FlH and 3-G-InH in Table I shows *opposite* effects in most instances. The effects of substituents from 9-substituted fluorenes (and other weak acids) have generally been rationalized in terms of their ability to stabilize or destabilize the anions formed on dissociation. For example, the increase in acidity caused by a 9-methyl group is believed to be caused by a polarizability effect, and the increases caused by 9-MeO and 9-Me_2N groups have been attributed to their electron-attracting field/inductive effects on the anions. The acidity decrease caused by a 9-*t*-Bu group has been attributed to steric inhibition of solvation in the anion. The reversal or attenuation of these effects for the corresponding 3-substituents in indenes must be due to the presence of an opposing effect. Stabilization of the undissociated acid (the initial or ground state) by the interaction of G with the C=C bond is the likely cause. Hine has identified double-bond stabilizing parameters (DBSP) of this type on ground-state stabilities by substituents and has estimated their relative sizes to be as follows (kcal): H (0.0) < Br (0.3) < MeS(O) (0.7) < Cl (1.8) < CN (2.6) < MeS, CO_2Me (3.2), F, Me (3.3) < Ph (4.9) < MeO (5.2)

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Table II. Homolytic Bond Dissociation Energies for the Acidic C–H Bonds in 2- and 3-Substituted Indenes. Acidities of Radical Cations Derived from Indenes

G	pK_{HA}[a]	$E_{ox}(A^-)$[c]	$E_{OX}(HA)$[c]	$pK_{HA^{\cdot+}}$[d]	BDE[e]
H	20.1	–0.950	1.305	–18	78.7
3-Me	22.0	–1.105	1.285	–18	77.6
6-NO_2-3-Me	13.4[b]	–0.545[b]	1.565	–22	78.4
3-*t*-Bu	22.6	–1.109			78.5
3-MeO	23.85	–1.275	0.935	–13	76.4
3-MeS	18.0	–1.032	0.335	–5	74.1
3-c-C_4H_8N	24.5	–1.580	–0.072	–8	70.3
2-c-C_4H_8N	24.5	–1.010	–0.120	+9	83.5
3-c-$C_5H_{10}N$	23.6	–1.440	0.210	–4	72.3
2-c-$C_5H_{10}N$	23.95	–1.018	–0.105	+4	82.5
3-c-OC_4H_8N	23.1	–1.360	–0.070	–5.4	73.4
2-c-OC_4H_8N	23.2	–0.960	0.000	+7	82.8
3-Ph	17.3	–0.835	1.062	–16	75.3
2-Ph	19.35	–0.903	0.940	–13	79.3
1,2,3-Ph_3	15.2	–0.785	1.175	–20	75.8
2-(4-$MeOC_6H_4$)	20.1	–0.933			79.3
2-(4-MeC_6H_4)	19.7	–0.915			79.1
2-PhS	17.3	–0.729	0.755	–8	80.2
3-$CONH_2$	13.8	–0.623	1.455	–21	77.7
3-COOMe	10.4	–0.428	1.505	–22	77.6
3-CN	9.0	–0.328	1.795	–27	77.9
2-Br	17.2	–0.685	1.280	–16	80.9
2-CO_2Me	15.4	–0.661			79.2

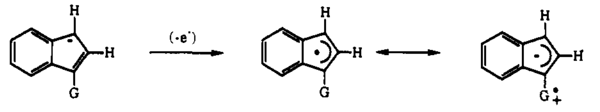
[a] Measured in DMSO against two indicators. [b] 5-Nitro-1-methylindene was used, but this rapidly isomerizes to 6-nitro-3-methylindene under the experimental conditions. [c] Measured by cyclic voltammetry under the conditions previously described,[3] and referenced to the Fc/Fc^+ couple. Oxidation potentials greater than 0.825 were measured in acetonitrile. [d] Calculated using eq 2. [e] Calculated using eq 1.

< Me_2N (8.2).[5] These DBSP effects in 3-substituted indenes are evidently large enough to overshadow the stabilizing effects on the anion for Me, MeO, and R_2N substituents and to cause a reversal of their acidity effects by 2.7, 5.1, and 4.1–6.0 kcal, respectively, compared to those observed in 9-substituted fluorenes. The acidifying effects for MeS and Ph substituents in 3-indenes are too large to be overshadowed by DBSP effects, but nevertheless these DBSP effects must cause attenuation of their acidifying effects. Examination of Table I shows that the DBSPs for the acceptor groups $CONH_2$, CO_2Me, and CN also cause attenuation of their acidifying effects in 3-substituted indenes relative to 9-substituted fluorenes, but the effects are small.

The pK_{HA} values of 2-c-C_4H_8N-, 2-c-$C_5H_{10}N$-, and 2-c-OC_4H_8N-indenes are substantially higher than that of indene, and these indenes also must be subject to acid-weakening ground-state effects, which are larger than 5–6 kcal when their field/inductive effects are taken into account. 2-Phenylindene is a weaker acid than 3-phenylindene by 2.15 pK_{HA} units and only 0.75 pK_{HA} unit stronger than indene itself. Here, too, it is clear that stabilization of the ground state of these molecules by interaction of the phenyl groups with the C=C bond has introduced an appreciable acid-weakening effect. These ground-state effects must, of course, also be present in the anion, but here the negative charge, which is concentrated in the 1- and 3-positions of indene, negates stabilization by electron-donor groups and tends to level the effects of electron-withdrawing groups.

Homolytic Bond Dissociation Energies (BDEs) for the Benzylic C–H Bonds in 2- and 3-Substituted Indenes. The pK_{HA} data and corresponding electrochemical data for the benzylic C–H bonds in indene and 22 of its 2- and 3-substituted derivatives are summarized in Table II.

The benzylic C–H bonds in indene and fluorene have almost the same BDEs, i.e., 79 and 80, respectively. This is not surprising, since indene differs structurally from fluorene in that a C=C bond has replaced a benzene ring and the delocalizing effects on odd electrons is nearly the same for allyl and benzyl radicals.[6] Steric and saturation (leveling) effects on the BDEs are expected to be similar, but the substituent effects differ in that the 2-and 3-substituents in indenes are attached to an sp^2 carbon atom whereas the 9-substituents in fluorenes are attached to an sp^3 carbon atom. The evidence in Table I suggests that donor substituents in the 2- or 3-positions in indenes can stabilize the ground state by as much as 6 kcal (for the c-C_4H_8N group). If lowering of the ground-state energy causes strengthening of the benzylic C–H bond,[7] as expected, then this should be observed most clearly in 2-substituted indenes wherein there is little inherent ability to lower the BDEs by delocalizing the odd electron to the substituent in the corresponding radicals. Indeed, we see in Table II that the presence of 2-CO_2Me, 2-Ph, 2-PhS, 2-Br, 2-c-OC_4H_8N, 2-c-$C_5H_{10}N$, and 2-c-C_4H_8N substituents cause an increase in the BDE of the acidic C–H bond by about 0.5, 0.5, 1, 2, 4, 4, and 5 kcal, respectively. On the other hand, 3-substituents all *decrease* the BDE of the benzylic C–H bond by amounts varying from 1 to 8 kcal. Evidently the delocalizing effects illustrated in formulas **6a•–6b•** for donor substituents in the radicals derived from anions 5^- are large enough to overshadow the bond-strengthening ground-state effects. The effects on BDEs of like substituents in GCH_2–H methanes, 9-GFl–H fluorenes, and 2- and 3-GIn–H indenes are compared in Table III.



5^- $6a^\bullet$ $6b^\bullet$

Table III. Homolytic Bond Dissociation Energies (ΔBDEs) for Methanes (GCH_2H), Fluorenes (9-GFlH) and Indenes (3-GInH)

G	ΔBDE[a] GCH_2H	ΔBDE[c] 9-GFlH	ΔBDE[d] 3-GInH	DBSP[e]	ΔBDE[d] 2-GInH
H	(0.0)	(0.0)	(0.0)[d]		(0.0)
Me	7	4.5	1.0	3.3	
MeO	12	7.0	2.3	5.2	
MeS	12[b]	5.4	4.7	3.2	–1.3 (PhS)
c-C_4H_8N	21[b]	11	8.4	8.2	–4.8
c-$C_5H_{10}N$	21[b]	9	6.4	8.2	–3.8
Ph	17	5.9	3.4	4.9	–0.6
CO_2Me	10	3.9	1.1	3.2	
CN	12	5.7	0.8	2.6	
Br					–2.2

[a] Related to CH_3H BDE (105 kcal); ref 6. [b] Reference 9. [c] Related to HFlH BDE (80 kcal). [d] Related to HInH BDE (79 kcal). [e] Double-bond stabilization parameters (ref 5).

The ΔBDEs of substituted methanes, which are included in Table III as a benchmark, are believed to provide the best measure of the radical stabilization energies (RSEs) of the corresponding $GCH_2^\bullet$ radicals.[6] The ΔBDEs of the benzylic C–H bonds in the corresponding 9-substituted fluorenes are only about one-half those in GCH_2–H methanes. The diminished ΔBDEs are the result of saturation and steric effects.[10] The ΔBDEs for 3-substituted indenes would be expected to be similar to those of 9-substituted fluorenes in that saturation, steric, and delocalization effects should be similar. The appreciably smaller effects observed are believed to be a consequence of bond-strengthening ground-state effects, which parallel for the most part Hine's double-bond stabilizing parameters (DBSP). The ΔBDEs for 2-substituted indenes are all negative because the DBSP effects overshadow the bond-weakening delocalizing effect when such are present.

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Ground-State Energy Effects on Remote Substituent Effects. Recently, appreciable ground-state effects have been observed for para substituents on the BDEs for the C–Br bonds in benzylic bromides; stabilizing ground-state effects of ca. 0.2 kcal were reported for *p*-Me and *p*-*t*-Bu, and destabilizing effects of ca. 0.5, 1.8, 2.8, and 5 kcal were reported for *p*-F, *p*-Br, *p*-CF_3, and *p*-CN, respectively. These effects were explained in terms of substituent interactions with the polar $C^{\delta+}$–$Br^{\delta-}$ bond.[11] In the present paper, we have seen in previous sections that pK_{HA} measurements have revealed sizable ground-state effects caused by the interaction of donor and acceptor substituents with the C=C bond in indenes (Table I) and that these effects lead to appreciable perturbations on BDEs (Table III).

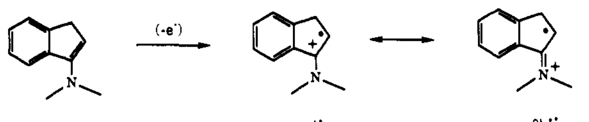
The largest ground-state double-bond stabilizing parameter observed by Hine was that for the Me_2N group (8.2 kcal).[5b] It seems reasonable to expect similar, but smaller ground-state stabilizations to occur between this powerful donor group and the C=C bonds in aromatic systems. Such ground-state effects, if present, should reveal themselves in effects on pK_{HA} values in the same way as was observed for indenes, i.e., the acid-weakening ground-state effects caused by this conjugative interaction should overshadow the acid-strengthening electron-withdrawing effect on the Me_2N group, leading to a pK_{HA} increase. An example of such an effect has indeed been found for 2-Me_2N and 2,7-$(Me_2N)_2$ fluorenes, which have pK_{HA} values 2.2 and 3.8 kcal *higher*, respectively, than that of fluorene.[12a] Furthermore, the estimated BDE values for the benzylic C–H bonds in these (dimethylamino)fluorenes are 1.0 and 1.5 kcal higher than that of fluorene, as expected from the results with the 2- and 3-R_2N-substituted indenes (Tables I and III). Smaller ground-state effects should be observed with weaker donor substituents, and indeed the pK_{HA} values for 2-MeO and 2,7-$(MeO)_2$ fluorenes were found to be 0.14 and 0.48 kcal higher, respectively, than that of fluorene.[12a] The BDEs for the acidic C–H bonds in these methoxyfluorenes were also slightly higher than that of fluorene.[12a] It seems likely, then, that small ground-state effects are present for substituents in other weakly acidic aromatic families that we have studied, such as arylacetonitriles[12b] and phenols,[12c] but the 1–2-kcal effects on the (dimethylamino)fluorenes should place an upper limit on the size of such effects in aromatic systems, and there is no reason to believe that acidities or BDEs in GCH_2H methanes will be subject to ground-state effects.

Acidities of the Radical Cations Derived from 2- and 3-Substituted Indenes. Table II also contains estimates of the acidities of the radical cations of the indenes calculated from eq 2.[13a] Most

$$pK_{HA}{}^{\bullet+} = pK_{HA} + [E_{ox}(A^-) - E_{OX}(HA)]23.1/1.37 \quad (2)$$

of the E_{OX}(HA) values used in making these estimates were measured in acetonitrile because the ease of oxidation of the solvent precluded measurements in DMSO. Previous experience has shown that the E_{OX}(HA) values obtained in DMSO and MeCN[12a] usually differ but little, and this proved to be true also in the present instance of 2-morpholinyl-, 2-piperidinyl, 2-pyrrolidinyl, and 3-pyrrolidinylindenes.

The acidities of benzylic hydrocarbon radical cations have generally been found to be in the range similar to that now observed for indenes ($pK_{HA^{\bullet+}}$ = −13 to −27).[12,13] But the presence of 2-Me_2N and 2,7-$(Me_2N)_2$ groups in fluorene has been shown to decrease the acidities of the fluorenyl radical cations by 25 and 33 kcal, respectively.[12a] The effects are similar for introducing 3-cycloamino substituents into the indenyl radical cation (14–19 kcal acidity decreases). The ability of nitrogen atoms to stabilize the positive charge in the initial states of the radical cations $\mathbf{8}^{\bullet+}$



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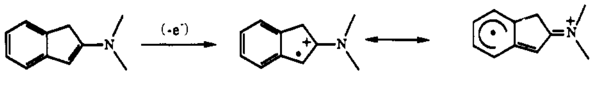
$8a^{\bullet+}$

$8b^{\bullet+}$

are believed to be responsible for these large acidity decreases. The introduction of cycloamino groups into the 2-position of the indenyl radical cation $\mathbf{10}^{\bullet+}$ causes even larger acidity decreases (30–37 kcal). Here, loss of the electron occurs again in a manner so as to allow delocalization of the positive charge to nitrogen, but now the odd electron can also be delocalized to the adjacent benzene ring, leading to further stabilization of the initial state of the radical cation and further decrease in the radical cation acidity.



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$10a^{\bullet+}$

$10b^{\bullet+}$

Summary and Conclusions

A comparison of the pK_{HA} values of 9-substituted fluorenes and 3-substituted indenes has shown that for six donor substituents, the ΔpK_{HA} values relative to the parent averaged 0.255 for the fluorenes compared to −4.35 kcal for the indenes (Table I). The large negative values for the indenes were traced to sizable ground-state effects that stabilized the undissociated indenes and lowered their acidities. The higher pK_{HA} values caused by ground-state effects for indenes led to lower ΔBDEs (Table III). Ground-state effects also raised the pK_{HA}s and lowered ΔBDEs for 2-substituted indenes and caused large decreases in the radical cation acidities of 2- and 3-substituted indenes. Finally, ground-state effects in 2-Me_2N and 2,7-$(Me_2N)_2$ fluorenes caused 2.2- and 3.8-kcal increases, respectively, in pK_{HA} values and 1- and 1.5-kcal increases, respectively, in BDEs. It seems that 1–2 kcal will be the upper limit of the ground-state effects present in aromatic systems, and there is no reason to believe that ground-state effects will perturb acidities or BDEs in GCH_2H systems.

Experimental Section

General. ^1H NMR spectra were recorded on Varian EM-390 or XLA-400 spectrometers using $CDCl_3$ as solvent and Me_4Si as internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All known compounds were identified by comparison of their NMR spectra and melting points with literature data. The procedures for electrochemical measurements have been described earlier.[3] All potentials are reported with reference to the formal potential ($E_{1/2}$) of ferrocene/ferrocenium couple.

Materials. Literature procedures were used for the prepn. of 3-methoxyindene[14a] [bp 95–100 °C (5–10 mm) (lit.[14b] bp 116–117 °C (20 mm))], 3-(methylthio)indene [bp 67–70 °C (0.03 mm) (lit.[15] bp 80 °C (0.01 mm))], 3-pyrrolidinylindene [bp 88–92 °C (0.05 mm) (lit.[16] bp 140 °C (2 mm))], 2-pyrrolidinylindene [mp 120–121 °C (lit.[17] mp 120–121 °C)], 2-piperidinylidene [mp 96–99 °C (lit.[17] mp 98–99 °C)], and 2-morpholinylindene [mp 196–197 °C (lit.[17] mp 197–198 °C)]. The crude 2-(phenylthio)indene obtained by reaction of 2-indanone, chlorotrimethylsilane, and thiophenol as described in ref 15 was purified by column chromatography over silica gel. The middle fraction on solvent removal gave white crystals that showed NMR and IR spectra in agreement with literature data and structure [mp 31–32 °C (lit.[15] mp 41 °C)]. Esterification[18a] of indene-3-carboxylic acid gave an oily liquid that was purified by Kugelrohr distillation. The fraction collected below 88 °C (0.07 mm) gave NMR in agreement with the structure of 3-carbomethoxy-indene (lit.[18] bp 76 °C (0.1 mm)). The crude 1*H*-indene-3-carboxamide obtained by the method described in ref 18b was crystallized from a benzene–ethanol mixture [mp 177–178 °C (lit.[18b] 195–212 °C dec (for the crude 1*H*-indene-3-carboxamide))]. A sample of 2-carbo-

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methoxyindene, kindly provided by Prof. F. D. Lewis, was crystallized from ethanol [mp 79-80 °C (lit.[19] 78-80.5 °C)]. The preparations of 3-phenyl-, 2-phenyl-, and 1,2,3-triphenylindenes have been described earlier.[20] We thank Dr. Olle Matsson for samples of 3-methylindene and 5-nitro-1-methylindene.

3-*tert*-Butylindene. Reaction of 1-indanone with *tert*-butylmagnesium chloride and subsequent dehydration as described by Weidler[21] gave a mixture of 1-indanone and 3-*tert*-butylindene. Purification by column chromatography over silica gel gave 3-*tert*-butylindene, which was 97% pure by GLC analysis: ^{1}H NMR δ 7.75-7.10 (m, 4 H), 6.21 (m, 1 H), 3.29 (m, 2 H), 1.38 (s, 9 H); MS *m/e* (relative intensity) 173 (3), 172 (18), 157 (15), 142 (9), 116 (27), 57 (100).

3-Cyanoindene. Dehydration of 1*H*-indene-3-carboxamide to 3-cyanoindene was accomplished following the procedure described by Casini:[22] bp 120 °C (0.5 mm) (lit.[22] bp 135-137 °C (7 mm)).

3-Piperidinylindene. This enamine was prepared by azeotropic removal of water from a mixture of 1-indanone and piperidine (2 equiv) in benzene. The crude residue obtained after removal of solvent was distilled under reduced pressure. The 3-piperidinylindene was collected between 83-88 °C (0.05 mm): ^{1}H NMR δ 7.60-7.08 (m, 4 H), 5.51 (m, 1 H), 3.29 (m, 2 H), 3.06 (t, 4 H, 5 Hz), 1.69 (m, 6 H).

3-Morpholinylindene was prepared from 1-indanone and morpholine as described above: bp 100 °C (0.08 mm); ^{1}H NMR δ 7.52-7.06 (m, 4 H), 5.50 (t, 1 H, 2.5 Hz), 3.87 (t, 4 H, 5 Hz), 3.30 (m, 2 H), 3.05 (t, 4 H, 5 Hz). Enamines obtained from 1-indanone are extremely air sensitive.

2-Bromoindene. Indene was converted to indene bromohydrin and further dehydrated to 2-bromoindene following the procedure described by MacDowell:[23] bp 66 °C (0.08 mm) (lit.[23] bp 135 °C (18 mm); ^{1}H NMR δ 7.45-6.80 (m, 4 H), 6.73 (s, 1 H), 3.38 (s, 2 H); MS *m/e* (relative intensity) 196 (19), 194 (19.6), 116 (10), 115 (100).

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Stereochemistry of C-3 Deoxygenation of Sugar Nucleosides: Formation of Pentopyranine C from [3-^{2}H]-D-Glucose by *Streptomyces griseochromogenes*

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Abstract: Cytosylglucuronic acid (CGA) has previously been shown to be the first intermediate in the biosynthesis of the antibiotic blasticidin S (BS), produced by *Streptomyces griseochromogenes*. Addition of aminooxyacetic acid (AOAA), an inhibitor of pyridoxal phosphate/pyridoxamine phosphate-dependent transaminases, to *S. griseochromogenes* fermentations led to substantial accumulations of CGA and pentopyranine C (PPNC, a shunt metabolite which has undergone decarboxylation at C-5′, deoxygenation at C-3′, and epimerization at C-4′) and to substantial reductions in the production of BS and *N*-demethylBS. In contrast, inhibitors of glutamine-dependent amidotransferases had little effect. [3-^{2}H]-D-Glucose was fed to a fermentation of *S. griseochromogenes* containing arginine hydroxamate, an inhibitor of arginine biosynthesis, and a large quantity of cytosine—currently the best conditions for maximum production of CGA and PPNC. This yielded cytosyl[3′-^{2}H]glucuronic acid, an 85:15 mixture of [3′-2H$_{\text{axial}}$]- and [3′-^{2}H$_{\text{equatorial}}$]PPNC, and a small amount of a 46:54 mixture of [3′-^{2}H$_{\text{axial}}$]- and [3′-^{2}H$_{\text{equatorial}}$]pentopyranone (the immediate precursor to PPNC). The relationship of this C-3 sugar deoxygenation to blasticidin S biosynthesis and to the pyridoxamine phosphate-dependent CDP-4-keto-6-deoxy-D-glucose-3-dehydrase reaction which is central to cell-wall lipopolysaccharide biosynthesis of Gram-negative bacteria is discussed.

Blasticidin S (**1**), an antifungal antibiotic produced by *Streptomyces griseochromogenes* that is used commercially for the control of *Piricularia oryzae* (rice blast), was first isolated by Takeuchi et al. in 1958.[1] Its structure and absolute stereochemistry were elucidated by chemical means[2-5] and confirmed by X-ray diffraction.[6,7] Seto et al.[8] established that **1** is biosynthesized from cytosine (**2**), D-glucose (**3**), L-α-arginine (**4**), and L-methionine (**5**). Isolation of a number of structurally related metabolites from *S. griseochromogenes* has also been reported.[9-14] We have shown that **4** is converted to L-β-arginine (**6**) and have established the stereochemistry of the arginine 2,3-aminomutase reaction.[15] We have also demonstrated,[16] using cell-free extracts

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