Communications to the Editor

Sir:

The inductive effects of dipolar substituents on both experimental and theoretically calculated gas-phase acidities have been found to be generally consistent with the $p$ values obtained from the double proton-transfer equilibria, $\text{eq 1}$ and $\text{eq 2}$

$$\text{eq 1:} \quad \text{ROH}_2^+ + \text{CH}_3\text{OH}_2^+ \rightleftharpoons \text{RO}^- + \text{CH}_3\text{O}^- + \Delta G^0(1)$$

$$\text{eq 2:} \quad \text{ROH}_2^- + \text{CH}_3\text{OH}^- \rightleftharpoons \text{RO}^- + \text{CH}_3\text{O}^- + \Delta G^0(2)$$

where $R$ is any group derived by substitution for the H's of the CH$_3$ group.

The results obtained from our combined studies by the pulsed ion cyclotron resonance equilibrium constant method$^7$ are given in Table I. It is immediately apparent that the values of $\Delta G^0$ obtained from the double proton-transfer equilibria, eq 5, are in the classical inductive order. The quantitive correlation of the $\Delta G^0$ values is shown in Figure 1. For alkyl substituents the inductive effect of $R$ relative to CH$_3$ is substantial, i.e., up to $0.12$ kcal/mol for t-Bu, but, nonetheless, these are three to seven times smaller than for the corresponding predominant polarizability ($P$) effects. As expected for inductive electron-donating substituents, $I$ values are negative but $P$ values are positive.$^8$

We report a separation of polarizability and inductive effects contributing to the values of $\Delta G^0$ for reactions 1 and 2. The polarizability effect$^3$ ($P$) for $R$ relative to CH$_3$ arises from greater charge-induced dipole stabilization of both the cation or anion, i.e., ROH$_2^+$ relative to CH$_3$OH$_2^+$ and RO$^-$ relative to CH$_3$O$^-$. An inductive electron-releasing effect of $R(I)$ will stabilize ROH$_2^+$ relative to CH$_3$OH$_2^+$ but will destabilize RO$^-$ relative to CH$_3$O$^-$. We make the simplifying assumption (in view of the nature of reactions 1 and 2) that the magnitudes of these effects will be approximately equal,$^6$ i.e., for reaction 1

$$\Delta G^0(1) = I + P$$

and for reaction 2

$$\Delta G^0(2) = -I + P$$

where $I$ is the inductive effect of $R$ compared to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

Regarding the Separation of Polarizability and Inductive Effects in Gas- and Solution-Phase Proton-Transfer Equilibria$^4$

Sir:

The inductive effects of dipolar substituents on both experimental and theoretically calculated gas-phase acidities have been found to be generally consistent with the $p$ values obtained from the double proton-transfer equilibria, eq 5, are in the classical inductive order. The quantitive correlation of the $\Delta G^0$ values is shown in Figure 1. For alkyl substituents the $p$ values used are based upon the method of Ingold$^5$ and Taft$^5b$ involving alkaline- and acid-catalyzed ester (RCH$_2$CO$_2$Et) hydrolysis transition states.

For alkyl substituents, the electron-releasing inductive effects of $R$ relative to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

The results obtained from our combined studies by the pulsed ion cyclotron resonance equilibrium constant method$^7$ are given in Table I. It is immediately apparent that the values of $\Delta G^0$ obtained from the double proton-transfer equilibria, eq 5, are in the classical inductive order. The quantitive correlation of the $\Delta G^0$ values is shown in Figure 1. For alkyl substituents the $p$ values used are based upon the method of Ingold$^5$ and Taft$^5b$ involving alkaline- and acid-catalyzed ester (RCH$_2$CO$_2$Et) hydrolysis transition states.

For alkyl substituents, the electron-releasing inductive effects of $R$ relative to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

$\Delta G^0(1) = I + P$

and for reaction 2

$\Delta G^0(2) = -I + P$

where $I$ is the inductive effect of $R$ compared to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

$\Delta G^0(1) = I + P$

and for reaction 2

$\Delta G^0(2) = -I + P$

where $I$ is the inductive effect of $R$ compared to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

$\Delta G^0(1) = I + P$

and for reaction 2

$\Delta G^0(2) = -I + P$

where $I$ is the inductive effect of $R$ compared to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.

$\Delta G^0(1) = I + P$

and for reaction 2

$\Delta G^0(2) = -I + P$

where $I$ is the inductive effect of $R$ compared to CH$_3$ (opposite in sign for reactions 1 and 2) and $P$ is the stabilizing polarizability effect of $R$ compared to CH$_3$ (+ for both reactions 1 and 2). Subtracting (2) from (1) gives an equilibria (hypothetical) between four ions, for which the polarizability effect has been minimized or eliminated, i.e., $(1) - (2) = (5)$.
I values are nearly additive in the two series:9 Me, Et, i-Pr, t-Bu, and Et, CH2CH2F, CH2CF3, whereas P values show that saturation occurs in the former series (increments of 3.8, 2.7, and 2.0 kcal/mol10,11) and in the latter series P is approximately constant. The introduction of CH3 substituents for H on the β carbon gives I values which are the same within the combined experimental errors, whereas P values increase substantially.10 Evidently, the conformations with α-alkyl substituents “bent around” are favored to obtain optimal stabilization by the polarizability effect (giving, for example, Ph-Ph ≈ Pneopent).

The regression line of Figure 1 may be used to define inherent σ values, which are free from solvation effects: σi = (I + 2.84)/70.0. The values obtained are in the last column of Table I. However, eq 5, −ΔGo(5) ≈ 2I, is not applicable to the H substituted on oxygen, i.e., for HO, since there is hyperconjugative stabilization of alcohols compared with hydroxides. Small differential stabilizations of the alkoxide ions due to differing C–H and C–C hyperconjugative interactions probably contribute to −ΔGo(2) values, but these and P contributions have evidently nearly cancelled in the −ΔGo(5) (or σ) values.

While the substituent effects for reactions 1 and 2 are composites of I and P effects, corresponding or analogous proton transfer equilibria for alkoxide ions or ammonium ions in aqueous solutions have been shown by correlations with only σa values13,14 to involve predominant but reduced inductive effects. The correlations are as follows. For reaction 2, −ΔGo(1) = −70.0(Δη) + (1.0)P (R = 0.999, n = 11); −ΔGo(2) = −23.2(Δη) − 0.03 (R = 0.990, n = 4). For the reaction

\[
\text{RNH}2 + \text{CH}_3\text{NH}_3^+ \rightarrow \text{RNH}_3^+ + \text{CH}_3\text{NH}_2
\]

−ΔGo(1) = −64.2(Δη) + (0.67)P (R = 0.998, n = 10); −ΔGo(2) = −38.9(Δη) − 0.40 (R = 0.975, n = 10); ΔHeq = −25.6(Δη) − 0.01 (R = 0.980, n = 9).

The dependence on Δσ values is reduced by factors of 2–3 in aqueous solution compared with the corresponding gas-phase values. The dependence on P values is reduced to such an extent in aqueous solution as to be negligible. These results may be understood in terms that the specific binding of solvent molecules to the ions acts to disperse charge to the H-bonded solvent, attenuating both the I and P effects. A much larger solvent attenuation factor for P than for I effects is anticipated by the simple electrostatic models for these effects: charge-induced dipole interaction, \( E = -ae^2/2Dr^4 \) and charge-dipole interaction, \( E = \pm e\mu\cos \theta/Dr^2 \), respectively.

The dispersal of charge accompanying specific binding of H-bonded solvent molecules leads to an appreciable increase in the distance \( r \) between the centroids of change (\( e \)) and polarizability (\( \alpha \)) or dipole moment (\( \mu \)). Since P effects fall off with the fourth power of distance (\( r \)), whereas I effects fall off only with the second power of distance, the consequence is a much larger solvent attenuation factor for P than I effects.

The solvent effect differentiation for oxonium, ammonium, and alkoxide ions provides an important means for identifying these structural effects. The reverse order of acidities of aliphatic alcohols in the gas phase and in hydroxyl solvents is explained since P effects determine the gas phase acidity order,3 but the I effects of the opposite order (reduced but not eliminated by solvation) determine the solution acidity order.13

The values of −ΔGo(1) for benzyl and for branched-chain alcohols have been obtained indirectly since their ROH2+ are too unstable for direct equilibrium constant determination. Using methane as a chemical ionization source, mixtures of 2-propanol with a series of reference bases, B, of increasing strength, were utilized in the spectrometer to form i-PrOH2+ and BH+. It was determined using double resonance that propanethiol did not deprotonate i-PrOH2+, but ethyl formate and propionitrile did. Based upon these results,15 a value of −ΔGo(1) for i-PrOH of 9.0 ± 0.5 kcal can be assigned. More generally, −ΔGo(1) values have been obtained (as given in Table I) from the highly precise linear relationships between the relative gas-phase basicities for aliphatic ethers, ROMe (relative to Me2O),17 and aliphatic amines, RNH2 (relative to MeNH3),24 compared with ROH (relative to MeOH). The conjugate acids of the branched-chain members of the former two series are stable and their gas-phase basicities have been directly determined. The results for these compounds are converted to −ΔGo(1) values, using the slopes of the linear correlations obtained from the results for the straight-chain alkyl groups in all three series.

Ab initio molecular orbital calculations of −ΔGo(1) values have been carried out at the 4-31G level18 (cf. Table I, note g, and ref 19). The calculated values are in very satisfactory agreement with the results obtained above for the series Me, Et, i-Pr, t-Bu, but (inexplicably) in poor agreement for the series n-Pr, i-Pr, neopent.

# Acknowledgment

We are pleased to acknowledge the helpful comments of Dr. Leo Radom.

## References and Notes

(1) This work was supported in part by grants from the National Science Foundation.


Communications to the Editor


The I and P effects for reaction 1 are probably more accurately proportional to rather than equal to the corresponding I and P effects for reaction 2. However, the assumption of equality expressed in eq 3 and 4 is simpler and is sufficiently adequate for all of the major points of concern in this paper.


(9) The opposite directions of the effects of CH3 and F substituents are in accord with the greater first ionization potential and electron affinity of -F than -H, and the smaller of both of these quantities for CH3 than H.

(10) These P values are well within the order of magnitude calculations based upon the relative polarizabilities of CH3 and H substituents; cf. D. H. Aue, H. M. Webb, and M. T. Bowers, J. Am. Chem. Soc., 89, 311 (1967).

(11) This assessment of alkyl structural effects on I and P values appears to be more reliable than that inferred by the effects on proton affinities of substitution of alkyl substituents in the CH3 group of OrgNa; cf. R. W. Taft and L. S. Levitt, J. Org. Chem., 42, 916 (1977).


(19) The calculations were carried out at the split valence shell 4-31G level. Fully optimized MeOH and MeOH2+ were used as skeletons upon which the remaining species were built up with standard model alkyl groups" depicted in the theoretical lowest energy conformations.


Department of Chemistry, University of California, Irvine, Irvine, California 92717
Received June 22, 1978

A Stereoscopic Total Synthesis of
(s)-Pentenomycin I, (s)-Pentenomycin II, and Dehydropentenomycin I Exploiting a Versatile Latent a-Ketovinyl Anion Equivalent

Sir:

In this communication we report an efficient, stereospecific total synthesis of three novel cyclopentenone antibiotics, pentenomycin I (1), pentenomycin II (2), and dehydropentenomycin I (3) exploiting a versatile latent a-ketovinyl anion equivalent. Pentenomycins I and II were isolated by Umino and co-workers in 1973 from culture broths of Streptomyces eurythmus and assigned structures 1 and 2, respectively, based on a combination of spectroscopic techniques including X-ray crystallographic analysis of the derived bromotriacetate 4. More recently (1978) Noble et al. reported the isolation of antibiotic G-2201-C (3), a simple oxidation product of pentenomycin I, from Streptomyces cattleya which we have termed dehydropentenomycin 1.5,6 Our interest in these synthetic targets was prompted both by their demonstrated activity against Gram-positive3 and Gram-negative1,4 bacteria including Neisseria gonorrhoeae as well as by the potential pharmacological importance of the cyclopentenone structural unit recently suggested to be the reactive functionality in a variety of structurally complex antitumor agents.7 Our synthetic route is particularly attractive in that it is short, stereospecific, highly efficient (i.e., proceeds in 25, 22, and 11% overall respectively, for 1-3 from cyclopentenone) and has led to the development of new methodology for a,b-eneones.

From a retrosynthetic perspective, a-hydroxymethylcyclopentenone 5 appeared to be an ideal intermediate for the elaboration of 1-3. Although merely an olefinic position isomer of the enolic form of a-formylcyclopentanone, examination of the literature revealed, somewhat surprisingly, no previous report for this compound. Furthermore, a-hydroxymethyl-a,b-eneones are, in general, not common to the chemical literature. With these considerations in mind we set out to devise a viable approach to 5.

Initial successful construction of 5,9 albeit expensive and multistep, employed the low-temperature Dibal reduction of ketal 69 followed by careful deketalization (HOOCCH2OH/ aqueous CH2C2). Ketal 6 in turn was readily available in 82% yield9 from 2-carbethoxy-2-cyclopentene (7) (1.2 equiv HOCH2CH2OH/catalyst:HOOCCH2OH/C6H6/ -H2O via the Dean-Stark procedure).10 the latter prepared from commercially available 2-carbethoxy-2cyclopentanone as reported by Reich and co-workers (i.e., a-phenylselenenylation followed by oxidative-elimination).11 Although available in 59% yield from 7, the demand for large quantities of 5 coupled with the expense of phenylselenenyl chloride necessitated the development of an alternate route. To this end we envisioned the hypothetical reaction illustrated below. Equivalent to this transformation appeared to be metalation17 of bromo ketal 8; addition of CH2O and deketalization would then afford 5. Indeed, treatment of 8,13 with n-butyllithium (−78 °C, THF) led to vinyl anion 9, which could be efficiently captured with a variety of electrophilic reagents; for the case at hand careful addition of predistilled gaseous CH2O and subsequent deketalization afforded 5 (mp 68−69 °C) in 84% yield.8,14 The efficiency of this approach to 5 demonstrates, we believe, that...