1,14-Dihydroxy-3,12-dibenzyl-3,12-diaza-6,9-dioxatetradecane (1). A mixture of 18.7 g (0.1 mol) of **11**, 32 g (0.21 mol) of *N*-benzylethanolamine, and 25 g of anhydrous sodium carbonate was stirred in 200 mL of xylene under reflux for 3 days on a Dean–Stark apparatus to remove water. The insoluble inorganic salts were filtered and the filtrate was evaporated under reduced pressure. The residue was distilled to give 35 g (84%) of product, bp 233–236 °C/0.5 mm; ^{1}H NMR ($CDCl_3$) δ 2.76 (m, 8 H), 3.2 (s, 2 H), 3.55 (m, 12 H), 3.72 (s, 4 H), 7.24 (s, 10 H); IR 3460, 1100, 730, 690 cm^{-1}; MS, *m/z* (relative intensity) 540, 91 (100). Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.20; H, 8.71. Found: C, 68.98; H, 8.62.

Compound **1** was also prepared by refluxing a mixture of 1.18 g (0.005 mol) of 1,14-dihydroxy-3,12-diaza-6,9-dioxatetradecane,[16] 2.5 g (0.011 mol) of benzyl bromide, and 5 g of potassium carbonate in 100 mL of toluene for 20 h on a Dean–Stark apparatus to remove water. The product was isolated as above to give a 76% yield of **1**.

1,17-Dihydroxy-3,15-dibenzyl-3,15-diaza-6,9,12-trioxaheptadecane (2). A mixture of 11.55 g (0.05 mol) of **12**, 16 g (0.11 mol) of *N*-benzylethanolamine, and 13 g of anhydrous sodium carbonate was reacted as above for **1**. The residue was chromatographed on a short alumina column and then on a silica gel column (ethyl acetate/ethanol/triethylamine, 95:4:1) to give 15 g (65%) of an oil: ^{1}H NMR δ 2.72 (m, 8 H), 3.0 (s, 2 H), 3.54 (m, 16 H), 3.68 (s, 4 H), 7.28 (s, 10 H); IR 3400, 1100, 705, 670 cm^{-1}. Anal. Calcd for $C_{26}H_{40}N_2O_5$: C, 67.80; H, 8.75. Found: C, 67.89; H, 8.78.

1,14-Dihydroxy-3,12-diethyl-3,12-diaza-6,9-dioxatetradecane (3). A mixture of 18.7 g (0.1 mol) of **11**, 20 g (0.22 mol) of 2-(ethylamino)ethanol, and 25 g of anhydrous potassium carbonate was reacted as above for **1**. The residue was distilled to give 23 g (79%) of **3** as an oil, bp 140 °C/0.05 mm: ^{1}H NMR δ 1.0 (t, 6 H), 2.63 (m, 12 H), 3.5 (m, 14 H); IR 3400, 1100 cm^{-1}. Anal. Calcd for $C_{14}H_{32}N_2O_4\cdot{}^1/_2H_2O$: C, 55.79; H, 11.03. Found: C, 56.04; H, 10.51.

1,10-Dibenzyl-1,10-diaza-3,7-dioxadecane (4). To a solution of 50 g (0.47 mol) of benzylamine and 25 g of sodium carbonate in 100 mL of toluene under reflux was added 23.0 g (0.12 mol) of **11** over a 5-h period. The mixture was refluxed for 20 h on a Dean–Stark apparatus to remove the water. The insoluble inorganic salts were filtered and the filtrate was evaporated. The residue was distilled twice (bp 183–185 °C/0.1 mm) to give 33 g (82%) of **48** which was identical with that reported.[2]

7,16-Diaza-10,13-dioxadocosane (5). Compound **11** (25.7 g, 0.14 mol) was slowly added to a refluxing solution of 50.6 g (0.5 mol) of hexylamine and 10 g of sodium hydroxide in 100 mL of toluene over a 5-h period. The mixture was refluxed for 10 h on a Dean–Stark apparatus, cooled, and filtered and the filtrate was evaporated. The residue was dissolved in 100 mL of chloroform, and the organic layer was washed twice with 50-mL portions of water. The water was extracted with 100 mL of chloroform. The combined chloroform layers were dried over anhydrous magnesium sulfate and evaporated and the residue was distilled to give 29.9 g (69%) of **5**, bp 135–140 °C/0.1 mm: ^{1}H NMR δ 0.86 (t, 6 H), 1.22 (m, 18 H), 2.56 (m, 8 H), 3.48 (m, 8 H); IR 3520, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{40}N_2O_2$: C, 68.30; H, 12.74. Found: C, 68.12; H, 12.57.

1,20-Dihydroxy-6,15-dibenzyl-6,15-diaza-3,9,12,18-tetraoxaicosane (6). A mixture of 3.28 g (0.01 mol) of **4**, 4 g (0.032 mol) of 2-(2-chloroethoxy)ethanol, 5 g of sodium carbonate, and 100 mL of xylene was reacted as above for **1**. The low boiling material of the residue was distilled (to 200 °C/0.01 mm) and the resulting residue was chromatographed first through a small alumina column and then through silica gel, using ethyl acetate/ethanol/triethylamine (95:4:1) as eluant, to give 4.0 g (79%) of **6** as an oil: NMR δ 2.76 (m, 8 H), 2.95 (s, 2 H), 3.6 (m, 24 H), 7.28 (s, 10 H); IR 3600, 1100, 715, 680 cm^{-1}; MS, *m/z* (relative intensity) 504, 429 (100). Anal. Calcd for $C_{28}H_{44}N_2O_6$: C, 66.64; H, 8.79. Found: C, 66.42; H, 8.74.

7,13-Dibenzyl-7,13-diaza-1,4,10-trioxacyclopentadecane (7). Tosyl chloride (1.95 g, 0.01 mol) in 125 mL of dioxane was added to a mixture of 300 mL of *tert*-butyl alcohol, 0.82 g (0.02 mol) of potassium metal, and 4.16 g (0.01 mol) of **1** during a 5-h period at 60 °C. The mixture was refluxed for 12 h. The mixture was then filtered and evaporated and the residue was passed through an alumina column (toluene/ethanol, 60:1) to give 3.1 g (78%) of compound **7** as an oil. The NMR and IR spectra were the same as reported by Gokel and co-workers.[2]

The above reaction was repeated except 3.70 g (0.01 mol) of ethylene glycol ditosylate was used instead of tosyl chloride. The product, 2.9 g (73%), proved to be compound **7**.

10,16-Dibenzyl-10,16-diaza-1,4,7,13-tetraoxacyclooctadecane (8). To a solution of 1.12 g (0.02 mol) of powdered potassium hydroxide and 2.3 g (0.005 mol) of **2** in 200 mL of dioxane at 60 °C was slowly added 0.95 g (0.005 mol) of tosyl chloride in 100 mL of dioxane over a 3-h period. The mixture was stirred for 12 h and then filtered and the solvent was evaporated. The residue was passed through an alumina column using toluene/ethanol (60:1) as eluant to give 1.5 g (68%) of **8** as an oil: ^{1}H NMR δ 2.80 (t, 8 H), 3.64 (m, 20 H), 7.28 (s, 10 H); IR 2860, 1100, 730, 695 cm^{-1}; MS, *m/z* (relative intensity) 442, 351 (100). Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 70.56; H, 8.65. Found: C, 70.56; H, 8.58.

10,19-Dibenzyl-10,19-diaza-1,4,7,13,16-pentaoxacyclohenicosane (9). A mixture of 0.9 g of metallic cesium and 1 g (0.002 mol) of **6** in 100 mL of *tert*-butyl alcohol was slowly added to 0.74 g (0.002 mol) of ethylene glycol ditosylate in 50 mL of dioxane at 60 °C during a 3-h period. The mixture was refluxed for 18 h and then filtered and evaporated. The residue was chromatographed on alumina (toluene/ethanol, 50:1) to yield 0.52 g (54%) of **9** as an oil: ^{1}H NMR δ 2.82 (t, 8 H), 3.65 (m, 24 H), 7.32 (s, 10 H); IR 1120, 735, 695 cm^{-1}; MS, *m/z* (relative intensity) 486, 395 (100). Anal. Calcd for $C_{28}H_{42}N_2O_5\cdot{}^1/_4H_2O$: C, 68.43; H, 8.71. Found: C, 68.37; H, 8.71.

Compound **9** was also prepared by adding 2.13 g (0.005 mol) of **1** to a mixture of 0.41 g (0.01 mol) of potassium metal dissolved in 200 mL of *tert*-butyl alcohol. Diethylene glycol ditosylate (2.12 g, 0.005 mol) in 125 mL of dioxane was added to the above mixture over a 5-h period at 60 °C. The resulting mixture was refluxed for 5 h and a small portion of product **9** was isolated as above. No yields were obtained for this reaction.

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Registry No. **1**, 113585-52-7; **2**, 113585-53-8; **3**, 113585-54-9; **4**, 66582-26-1; **5**, 105399-99-3; **6**, 113585-55-0; **7**, 94195-16-1; **8**, 105399-96-0; **9**, 94195-17-2; **11**, 112-26-5; **12**, 638-56-2; *N*-benzylethanolamine, 104-63-2; 1,14-dihydroxy-3,12-diaza-6,9-dioxatetradecane, 50977-92-9; 2-(ethylamino)ethanol, 110-73-6; benzylamine, 100-46-9; hexylamine, 111-26-2; 2-(2-chloroethoxy)ethanol, 628-89-7; diethylene glycol ditosylate, 7460-82-4.

Why Are Carboxylic Acids and Phenols Stronger Acids than Alcohols?

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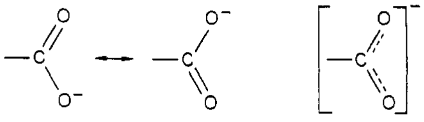
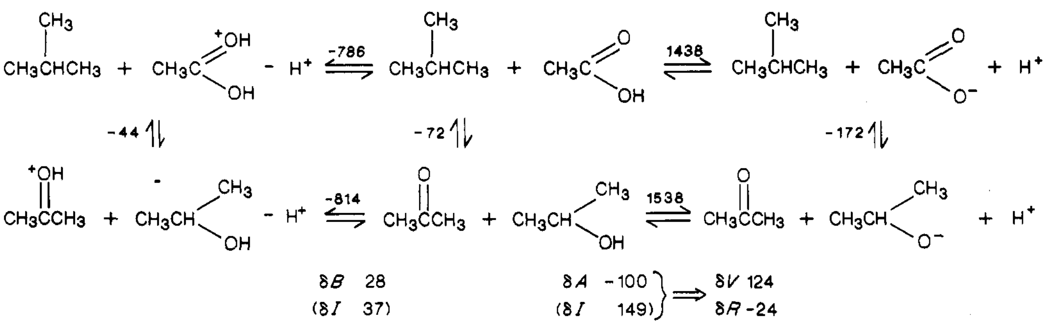
Carboxylic acids and phenols are relatively strong acids, e.g., stronger than simple alcohols, both in the gas phase and in solution. In contemporary textbooks the difference is attributed to a low energy content of the anions. In terms of organic chemistry it is said that these anions are stabilized by conjugation or by mesomeric (resonance) interaction as pictured by the formulas **1** ↔ **2** or by **3** in the case of carboxylate anion, and by similar well-known formulas for phenolate anion.



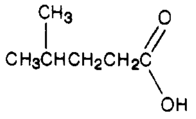
1 2 3

Chart I[a]



[a] Values in kJ mol^{-1}.

The energy difference between the actual structure **3** and hypothetical structure **1** has received the name mesomeric (resonance) energy. This generally accepted interpretation was recently challenged by Siggel and Thomas[1] who attributed the acidity to an unusually high energy content of the undissociated acid molecule. This conclusion was based on quantum chemical calculations of charge distribution and on comparison of experimental gas-phase acidities[2] and oxygen 1s ionization energies[3] in terms of electrostatic theory.[4] In order to prevent further proliferation of this misunderstanding I present in this paper (a) simple thermodynamical considerations which are at variance with the above claim,[1] confirming the classical interpretation, and (b) possible explanation of the error by neglecting intrinsic substituent effects in the electrostatic theory.



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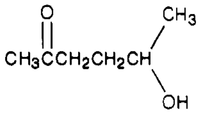

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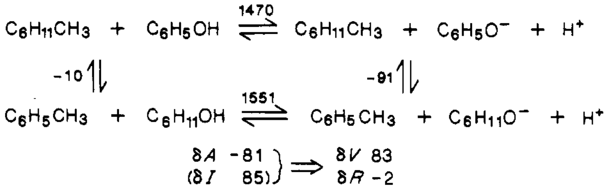
As in ref 1, we shall deal only with relative values and compare molecules of almost equal size: acetic acid to 2-propanol and phenol to cyclohexanol. The respective difference will be denoted by the operator δ. The simple difference of Gibbs energies of formation, $\delta\Delta G_f{}^\circ{}_{298}$, of acetic acid and 2-propanol does not correspond to their stabilities since the compounds are not isomeric. The simplest and most telling proof would be to compare two isomers like **4** and **5**. Since the data are not available, we can use the additivity principle[5] of thermodynamic properties to calculate δG with a sufficient accuracy. In other terminology, but with the same numerical results, we can calculate ΔG of the isodesmic reaction of acetone and 2-propanol (Chart I) from tabulated values[5,6] of $\Delta G_f{}^\circ{}_{298}$. The result, −72 kJ, reveals that the molecule of acetic acids is rather strongly stabilized by the neighborhood of the carbonyl and hydroxyl groups. The stabilization energy of the acetate anion, −172 kJ, follows from a thermodynamic cycle. This extraordinary low energy is thus evidently responsible for the high acidity of the acid: although even the neutral acid is stabilized, its anion is stabilized much more. Of course, the derived values of the stabilization energy cannot be taken as mesomeric (resonance) energies of the respective species since they are affected still by electrostatic interactions, in terms of organic chemistry by the inductive effect. Any attempt to separate the two effects is rather speculative and approximate; it is also not relevant for further conclusions.[7]

Chart II[a]



[a] Values in kJ mol^{-1}.

When the same line of reasoning is applied to phenol as compared to cyclohexanol, a similar result is obtained (Chart II). The acidity is again controlled by the extraordinarily low energy of the anion. The inductive effect is presumably rather small.

The contradictory results of Siggel and Thomas[1] were based on an electrostatic model[4] which describes the molecule as a polarizable medium encompassing the oxygen atom. By proton removal the charge on this oxygen is changed from q to $q - 1$ and the respective energy change may be represented as sum of two negative terms pertinent to the initial charge distribution (δV) and to relaxation (δR) (eq 1).

$$\delta A = -\delta V - \delta R \qquad (1)$$

Similarly the core ionization is viewed as a change of charge to $q + 1$ and the energy needed expressed as eq 2.

$$\delta I = \delta V - \delta R \qquad (2)$$

From experimental δA and δI one can calculate δV and δR. As shown above, this procedure is ultimately at variance with thermodynamic data, but it is not easy to show where the mistake is. In our opinion neglecting the changes of geometry, e.g., bond lengths in the carboxylate ion as compared to the carboxylic acid molecule, is im-

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[5] Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969.

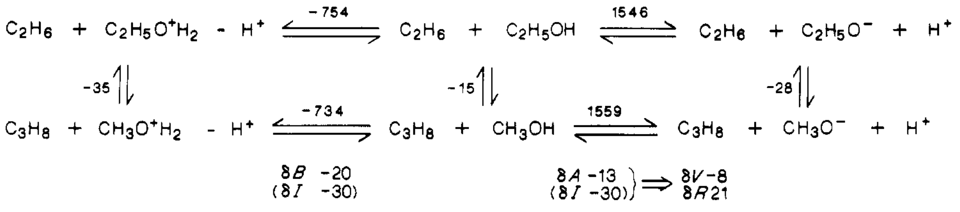
[6] All ΔG values given have been corrected with statistical factors. With ΔH very similar results were obtained in all cases.

[7] With reference to 1,1-dialkoxy derivatives[8] we can estimate the inductive effect in acetic acid to some 20 kJ, in the acetate anion say twice more. The mesomeric contribution (thermochemical resonance energy[9]) prevails in any case.

[8] Marsh, K. N.; Månsson, M. *J. Chem. Thermodyn.* **1985**, *17*, 995–1002.

[9] Shaik, S. S.; Hiberty, P. C.; Lefour, J.-M.; Ohanessian, G. *J. Am. Chem. Soc.* **1987**, *109*, 363–374.

Chart III[a]



[a] Values in kJ mol^{-1}.

portant. In spite of some calculations,[1] the energy difference must be large. Also the charge redistribution could be poorly expressed by a unique polarizability, e.g., the same in both phenolate anion and cation. In organic chemistry terms the above theory neglects the mesomeric effects, while the inductive effects should be included in δV. The core ionization as a vertical process can be affected only by the latter effect, but ionization equilibrium is affected by both. Hence the two quantities δA and δI cannot be directly compared. Inherent approximations of the model remain in its quantum chemical verification[1] which follows the same reasoning and calculates δV and δR from the potentials at the hydrogen and oxygen atoms. However, for the acid–base equilibrium the energies of the whole molecules are deciding. Their quantum chemical calculation would also be possible, but it could give nothing more than replacing the experimental quantities in Chart I by calculated ones.

We tested still the above model by extending it to basicities[10] (acetic acid relative to acetone, Chart I, left). Now the changes of charge due to addition of proton or to removal of a 1s electron are equal, but the pertinent energies are not (28 and 37 kJ, respectively). Substituent effects on basicities and on core ionization energies are generally not equal[11] and it is not warranted to assume a closer similarity in the case of acidities. A further test was application to the pair ethanol–methanol (Chart III), where assumptions of the theory should be met much better since the differences both in acidity and basicity are due mainly to polarizability effects.[12] From the experimental[3,13] δA and δI one gets $\delta V = -8$ kJ and $\delta R = 21$ kJ, confirming the view that the greater polarizability in the ethanolate anion is decisive. However, even here the agreement of δI with δB is quite poor. The stabilization energies of the anion and cation are rather similar, in agreement with the view[12] that the polarizability of the methyl group stabilizes both the anion and the cation equally well.

Regardless of the better or worse approximation of the electrostatic model it follows from the above examples that the energy content of the anion is the controlling factor in most cases while that of the acid controls in some other cases. This will depend on the structure of the examined acid and of the reference compound. In a similar approach[14] acidities of substituted phenols were evaluated with reference to phenol, using STO-3G calculated energies instead of experimental $\Delta G_f°_{298}$. The observed effects were smaller than in this paper, and the stability of the anion was the controlling factor in most cases but not in all (substituent 4-F). Returning to carboxylic acids and phenols we may state that the title question cannot be answered in a simple way. All available experimental facts have to be taken into account and a decomposition into various "effects", as inductive or mesomeric, must be largely artificial. Nevertheless, the terms energy content of the acid and of the anion have a physical meaning, and for their evaluation the thermodynamic quantities are deciding. Hence it is, in my opinion, experimentally proven that the acidity of carboxylic acids and phenols—as compared to alcohols—is conditioned by a low energy content of their anions.

Acknowledgment. I thank to Professor T. Darrah Thomas for a fair and valuable discussion, although a complete agreement was not reached.

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Isodesmic Reaction Energies and the Relative Acidities of Carboxylic Acids and Alcohols

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The greater acidity of carboxylic acids relative to alcohols has traditionally[2] been explained as being due to extra stability of the carboxylate anion, which is enhanced by resonance delocalization of the negative charge over the two oxygens of the carboxylate group. Similar stabilization has been thought to be of little importance in alcohols because such resonance forms cannot be drawn for the alkoxide anion.

This traditional view has been challenged by Siggel and Thomas,[3] who have used comparisons of oxygen core-ionization energies with gas-phase acidities as well as theoretical calculations to show that the differential stabilization of the carboxylate anion relative to the alkoxide anion is not the major factor responsible for the greater acidity of carboxylic acids relative to alcohols. Rather this arises primarily because of differences in the charge distribution in the neutral molecules, which lead to a potential at the acidic proton of the carboxyl group that is more positive than the potential at the hydroxyl hydrogen in alcohols. These conclusions receive further support from calculations[4] of charge distributions in formic acid and ethanol and of the charge flow when the hydroxyl proton

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