Through-Space Polar.pi. Effects on the Acidity and Hydrogen-Bonding Capacity of Carboxylic Acids

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Through-Space Polar–π Effects on the Acidity and Hydrogen-Bonding Capacity of Carboxylic Acids

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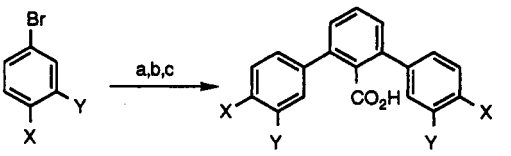
Acidity and hydrogen bonding capacity are crucial factors in molecular recognition[1] and biocatalysis.[2] The ability to design and create biomimetic catalysts depends on an understanding of the way these properties change as a function of environment. Environmental control of functional group reactivity is a principal mechanism by which the chemistry of active site residues is modified.[3] Given that the interaction between two simple phenyl derivatives contains a significant component that is transmitted electrostatically and through space (polar–π),[4] the question arises of whether this polar–π interaction can be used to affect the properties of a functional group like a carboxylic acid. This report presents our findings for a series of 2,6-bis(*p*-X-phenyl)benzoic acids (DPBA).

Benzoic acids, with flanking ortho phenyl rings, were chosen to maximize the polar–π effect by symmetry and proximity.[5] The flanking phenyl groups sandwich the carboxyl group, excluding solvent from the faces,[6,7] and the symmetry of the system amplifies the effect of substitution. Substituents are held distal to the reactive site to minimize local steric effects.

The series **1-9** was prepared by the Hart reaction of the desired X-phenyl Grignard with 2,6-dichloroiodobenzene; the resultant anion was quenched with CO_2 (Scheme 1).[8] Measurement of the pK_a values was done by titrating a solution (1×10^{-3} M) of the acid in 80% (w/w) methylcellusolve/water with a standardized potassium hydroxide solution (0.1 M) using a potentiometric microtitration apparatus.[6,9,10] The titration data were fitted using a nonlinear least squares regression analysis. Two runs were averaged to produce the reported pK_a (Table 1). Binding constants for **1**, **6**, and **7** with 9-ethyladenine (9-EA) were determined in dry chloroform-*d* by ^{1}H NMR (at 500 MHz) from a series of solutions of the acid (2×10^{-4} M) mixed with various proportions of 9-ethyladenine (2×10^{-4} to 2.5×10^{-2} M). The values for the binding constants were derived by nonlinear least squares analysis of the data between 20% and 80% saturation.[11]

A plot of pK_a vs $\Sigma\sigma^n_{para}$[12] for **1-7** shows a strong linear relationship with a ρ value of 1.1 (Figure 1).[10] Substituted benzoic acid, *cis*-cinnamic acid, 2-phenylbenzoic acid (2-PBA), and 4-phenylbenzoic acid in the same solvent display ρ values of 1.7, 0.86, 0.62, and 0.43, respectively.[7,10,13] The through-space nature of the interaction is demonstrated by the pK_a values of the meta-substituted methoxy and acetyl compounds. Within experimental

Scheme 1[a]



	X	Y
1	OMe	H
2	Me	H
3	H	H
4	F	H
5	Cl	H
6	Br	H
7[d]	C(O)Me[d]	H
8	H	OMe
9[d]	H	C(O)Me[d]

[a] (a) Mg, THF; (b) 2,6-dichloroiodobenzene; (c) CO_2; (d) prepared as cyclic acetal, deprotected with acidic wet silica in dichloromethane.

Table 1. Values for pK_a and Binding Constants with 9-EA for **1–9**

compd	X	σ_n[a]	pK_a[b]	K_b (M^{-1})[c]
1	*p*-OMe	–0.28	6.61	830
2	*p*-Me	–0.14	6.50	
3	H	0.00	6.39	
4	*p*-F	0.15	6.14	
5	*p*-Cl	0.24	5.97	
6	*p*-Br	0.26	5.98	1560
7	*p*-C(O)Me	0.47	5.87	1930
8	*m*-OMe	0.10	6.61	
9	*m*-C(O)Me	0.36	5.87	

[a] See ref 12. [b] Measured by microtitration in 80% methyl cellusolve/water. [c] Measured by ^{1}H NMR titration in chloroform-*d*.

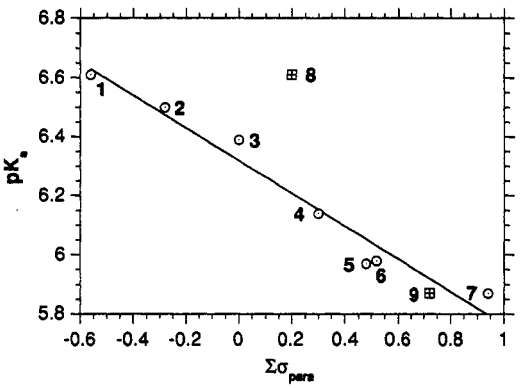


Figure 1. Plot of $\Sigma\sigma^n$ vs pK_a for Acids **1-9**.

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(5) Empirical force field and semiempirical calculations using the AM1 Hamiltonian predict the structure of **1** to have the flanking phenyl groups and the best plane of the carboxyl group perpendicular to the central phenyl ring.
(6) This reduces the interference from solvent effects speculated to cause problems in systems like 2-phenylbenzoic acid.
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error, there is no difference between the pK_a values of meta- and para-substituted compounds; therefore, when evaluated at their σ_{meta} values, these data deviate greatly from the fitted line.

There are four transmission mechanisms normally observed for aromatic ring substituents: resonance, π-steric, polarization (through bond or space), and field.[14] Because conjugation between the central ring and both the substituted phenyl and the carboxyl groups is conformationally prohibited, resonance is excluded. When invoked, the π-steric effect is independent of the electronic character of the substituent, and is therefore not applicable here because of the direct and significant relationship between pK_a and σ. The result that para- and meta-substituted acids give the same pK_a also eliminates this possibility. The data are most consistent with the polar–π effect being transmitted through space with strong field and π-polarization components.[15]

In the case of para-substituted benzoic acids, pK_a correlates linearly with K_b for 9-EA.[16] The 9-EA/DPBA complex shows a similar relationship between $\sum\sigma$ and K_b. For the three compounds studied, **1**, **6**, and **7**, K_b increased from **1** to **7** as pK_a decreased, but with a larger slope than for the benzoic acids (1430 vs 520 M^{-1} σ^{-1}). In addition, although the pK_a for 2-PBA (6.47) is comparable to **1**, the K_b (270 M^{-1}) of 2-PBA[11a] is roughly $^1/_3$ that for **1**. Thus, there is something more than hydrogen bonding governing the strength of complexation.

Shifts in the ^1H NMR spectra during titration provide some insight into the geometry of complexation.[17] The amino protons of 9-EA shift downfield, consistent with participation in a hydrogen bond. The ortho aryl protons on the flanking rings and H-2 and H-8 of 9-EA move upfield, indicating that 9-EA sits between the flanking rings in a range close enough to feel the ring current. Two possible arrangements still exist for the complex, one with Watson–Crick and one with Hoogsteen type geometries, however, the magnitude of the shift at H-2 vs H-8 (ca. 250 vs 50 Hz) favors the Watson–Crick option.[18] Thus, a tight complex with close aryl–heterocycle interactions is the proposed picture (Figure 2).

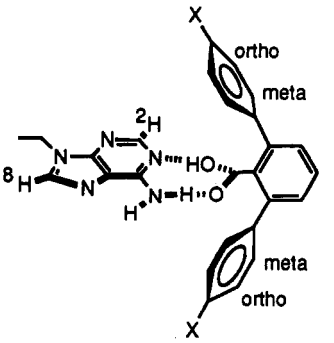

Figure 2. Proposed general complex of 9-EA with a generic DPBA.

The interaction energy between stacked phenyls has been shown to vary as a function of the electronic demand of the substituent. Therefore it seems to be a reasonable extension to assume that a secondary interaction of this type is leading to the enhanced sensitivity of K_b to substitution.[19]

From our intuitive understanding of the distance dependence of chemical forces it is natural to assume that through-bond effects should fall off rapidly with distance compared to simple electrostatic effects.[20] Nonetheless, discussion still remains as to the nature of how substituent effects are transmitted.[21] The terphenyl acids studied here offer a simple and interpretable model. The trends revealed by complexation and acidity experiments lead to the conclusion that chemical intuition is quite accurate here and that through-space effects should become an integral part of our repertoire in the design of molecular receptors and catalysts and in the rationalization of their mode of action.[22]

Acknowledgment. This work was supported by the National Science Foundation (CHE-9307582), the NATO Collaborative Research Programme, and the Alfred P. Sloan Foundation.

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(17) Separate titrations were done using either component as titrant (guest). Shift data are interpreted from shifts of the species acting as host.

(18) This is a best guess based on chemical shifts; a more rigorous analysis including NOE and 2-D NMR would be more conclusive.

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