

was removed by filtration and washed with EtOH (2 × 25 mL). The combined filtrates were evaporated to furnish 0.44 g (91%) of **27a** as a white foam. In a similar way compounds **18**, **20**, and **26** were hydrogenated to furnish **19**, **21**, and **26a**, respectively (Table I).

Method F (E.g., 23 → 28, 24 → 29, 25 → 30, 26a → 31) (27a → 32: A Representative Example). To a suspension of **27a** (0.24 g, 0.5 mmol) in dry MeOH (25 mL) was added freshly prepared NaOMe in MeOH (1 N) until a pH of 9 was reached. After 2 h, TLC of the reaction mixture indicated no further reaction. To the clear solution, Dowex 50 (H⁺) resin was added to adjust the pH to pH ~6. The resin was removed by filtration, washed with MeOH (25 mL) and the filtrate evaporated to dryness. Crystallization of the residue from EtOH furnished 0.10 g (87%) of **32**. Detoluoylation of **23-25** and **26a** by this method furnished **28-31**, respectively (Table I).

Method G (35 → 40). To a solution of **35** (1.66 g, 3 mmol) in dry dichloromethane (50 mL) at -78 °C was added BCl₃ (25 mL, 1 M in dichloromethane). The reaction mixture was stirred at this temperature for 2 h and then at -40 °C for an additional 2 h. To the reaction mixture was added MeOH (50 mL) at -40 °C and stirring was continued at room temperature for 30 min. The mixture was then neutralized with NH₄OH and filtered to remove inorganic salts. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography using CHCl₃/MeOH (6:1, v/v) to yield **40** (0.8 g, 93%) after crystallization from acetone.

Method H (E.g., 34 → 39, 36 → 41, 37 → 42) (38 → 43: A Representative Example). To a solution of **38** (0.56 g, 1 mmol)

in absolute EtOH (30 mL) were added cyclohexene (30 mL) and Pd(OH)₂ (0.2 g of 20%), and the mixture was refluxed for 48 h. After filtration of the reaction mixture through a Celite pad, the filtrate was evaporated to dryness and the residue was purified by flash silica gel column chromatography using CHCl₃/MeOH (6:1, v/v) to give 0.18 g (70%) of **43**. Following this method nucleosides **34**, **36**, and **37** were converted to **39**, **41**, and **42**, respectively (Table I).

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The Binding of Benzenesulfonamides to Carbonic Anhydrase Enzyme. A Molecular Mechanics Study and Quantitative Structure-Activity Relationships

Maria Cristina Menziani,^{*,†,§} Pier G. De Benedetti,[‡] Federico Gago,^{†,||} and W. Graham Richards[†]

Physical Chemistry Department, Oxford University, Oxford OX1 3QZ, U.K., and Dipartimento di Chimica, Università di Modena, 41100 Modena, Italy. Received July 6, 1988

Molecular mechanics methods have been applied to study the interaction between a series of 20 deprotonated benzenesulfonamides and the enzyme carbonic anhydrase. The different contributions to the binding energy have been evaluated and correlated with experimental inhibition data and molecular orbital indices of the sulfonamides in their bound conformation. The results suggest that the discrimination shown by the enzyme toward these inhibitors is dominated by the short-range van der Waals forces.

Calculating binding energies between inhibitors and macromolecular targets is not enough. If the results are to be usable in molecular design, we need to be able to partition the energies into the various contributing aspects. Here this is done for sulfonamides binding to carbonic anhydrase.

The zinc metalloenzyme carbonic anhydrase (EC 4.2.1.1) catalyzes the reversible hydration of carbon dioxide. Aromatic and heterocyclic sulfonamides with an unsubstituted sulfonamido group constitute a class of highly active inhibitors possessing unusual selectivity toward different carbonic anhydrase isozymes.¹ The structure-activity relationships of sulfonamides have been analyzed both qualitatively^{2,3} and quantitatively.⁴⁻¹⁴ In earlier studies^{12,14} we showed that certain calculated properties of these molecules, such as charge distribution and frontier

molecular orbital indices, are good predictors of the inhibitory activities of sulfonamides on carbonic anhydrase.

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[†] Oxford University.

[‡] Università di Modena.

[§] Permanent address: Dipartimento di Chimica, Università di Modena, 4100 Modena, Italy.

^{||} Permanent address: Departamento de Farmacología, Universidad de Alcalá de Henares, Madrid, Spain.