Pergamon

Tetrahedron Letters, Vol. 37, No. 52, pp. 9279-9282, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02201-0

Interactive n→σ* Delocalizations that Control an Aqueous Organic Equilibrium

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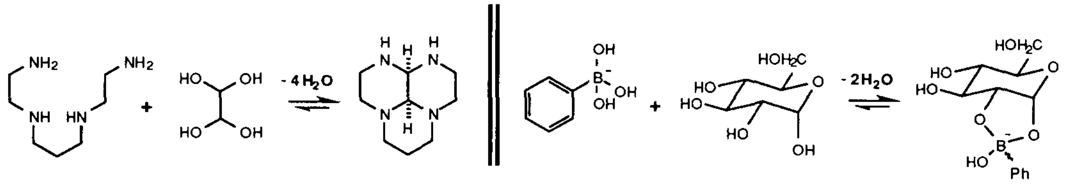
Abstract: Hydrated acetaldehydes were condensed in D_2O with substituted alcohols and thiols to determine ΔG of hemiacetalization by ^1H NMR. Specific n→σ* delocalizations in the alkoxy/alkylthio functionality of the product interact to influence n→σ* delocalization in the hemiacetal functionality. Delocalization in the latter functionality controls ΔG.

Host/guest chemistry in water will become more feasible as we develop relevant binding tactics. Promise has been apparent for some time in systems that operate via reversible covalent interactions. Complexations of glyoxal dihydrate with polyamines and boronates with sugars are conspicuous examples (Figure).[1,2] The products of these condensations are thermodynamically stable in water, probably due to enhanced bonding and/or solvation scenarios relative to their respective reactants. Readily reversible condensations can also be favorable at the level of individual bond formation. For instance, thiols and amines form hemithioacetals and hemiaminals from single hydrated carbonyls in water with free energies falling in the range of -6 to -4 kcal mol^{-1}.[3,4] The hemiacetalization of hydrated carbonyls has received less attention, but it can be a mildly favorable process (ΔG of -2.5 to 0 kcal mol^{-1}).[5]



In thinking about the broader applicability of aqueous covalent condensations to molecular binding, we decided to map some basic structure/favorability relationships in greater detail. The work would suggest ways of modulating individual functional group interactions while improving our understanding of aqueous organic equilibria. Ideally, we would be able to relate observed differences in ΔG of reaction to specific molecular forces. This Letter describes a case in point.

For our first experiments, we studied the influence of substituents on hemiacetalization. We chose hydrated acetaldehydes as a suitable set of electrophiles. They are structurally simple, conveniently available, and very hydrophilic. In their condensations with alcohols and thiols, we found all organic reactants and observed products to be evident as discrete species by ^1H NMR throughout equilibration. Equilibrium concentrations were established from signal integrations, allowing a calculation of the free energy of reaction.

Our results are tabulated below. Some of the energies differ only slightly, but all values were reproducible and the Table presents a consistent pattern of behaviors. Apart from the aforementioned greater favorability of hemithioacetalization relative to hemiacetalization, three effects are apparent. First, condensation becomes less favorable as the steric bulk of the alcohol is increased. Second, condensation is disfavored by the

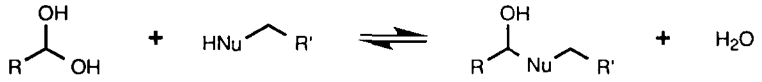


Table Free Energies of Aqueous Reaction (in kcal mol^{-1})[†,§]

	$CH_3CH(OH)_2$	$Cl_3CCH(OH)_2$	$F_3CCH(OH)_2$
Methanol	-1.87 ± .10	-1.14 ± .03	-1.06 ± .16
Ethanol	-1.78 ± .08	-0.82 ± .18	-0.86 ± .03
2-Propanol	-0.97 ± .01	-0.52 ± .02	—
t-Butanol	—	—	—
2-Methoxyethanol	-1.66 ± .04	*	—
2-Chloroethanol	-1.16 ± .08	—	—
2-Fluoroethanol	-1.34 ± .06	—	—
Trichloroethanol	—	—	—
Trifluoroethanol	-0.71 ± .10	—	—
3-Mercapto-1-propanol	-4.92 ± .06	-4.35 ± .04	-4.57 ± .17
2-Mercaptoethanol	-4.78 ± .13	-4.07 ± .13	-4.43 ± .06
Trifluoroethanethiol	-4.36 ± .03	-2.57 ± .06	-2.86 ± .19

[†] All determinations were made using D_2O as solvent and the sodium salt of 3-TMS-propionic acid as an internal reference, analyzing with a 300 MHz Varian spectrometer. Reactants were dissolved and allowed to come to equilibrium at approximately 25°C. The alcohols never composed more than ten percent of the solution volume. Catalytic 4-dimethylaminopyridine was used in some cases.

[§] Given values are the average of at least two trials. Dashes indicate that product was either not observed or its concentration was too small for reliable assignment of peaks.

[*] Inconsistent results were obtained for this pairing.

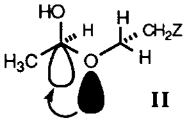
presence of electronegative substituents, especially within the alcohol. Third, there is a synergistic impact when electronegative substituents are present in both the aldehyde and the alcohol or thiol.

The steric effect suggests an increasing number of obligatory gauche interactions in the product. We estimated the relative energies of different reactant and product conformations by quantum chemical calculations. At the AM1 level of the NDDO treatment,[6,7] the most stable conformations were not simply those containing the fewest total gauche interactions. The delocalization of oxygen non-bonding electrons into local $\sigma^*_{C\text{-}O}$ and $\sigma^*_{C\text{-}C}$ bond orbitals was also weighted heavily.[8] Even within this analysis, methanol and ethanol are still expected to act comparably in terms of reaction favorability. Both can also exceed 2-propanol and tert-butanol as observed.

Electronegative substituents influence the thermodynamics of condensation in less obvious ways. AM1-derived estimates of the heats of formation of ethanol, methoxyethanol, chloroethanol, fluoroethanol, trifluoroethanol, and their acetaldehyde hemiacetals suggested a preference of acetaldehyde for ethanol over the other alcohols by 0.34, 0.34, 0.40, and 0.06 kcal mol^{-1}, respectively.[9] These gas-phase values of $\Delta\Delta H$ do not correlate well with the differences in our solution-state free energies (0.12, 0.62, 0.44, and 1.07 kcal mol^{-1}; $\rho = -0.90$), and this is not surprising. However, when we considered only the resonance energy component of the calculated enthalpies, the predicted preferences were 0.24, 0.64, 0.18, and 1.94 kcal mol^{-1}.[10] The consistency with the empirical values of $\Delta\Delta G$ is much better here ($\rho = +0.92$), implying that the substituents perturb the free energy of reaction significantly through their effects on electronic resonances.

An influence on resonance energies is understandable in the following terms. Hemiacetals are stabilized by a delocalization of oxygen non-bonding electrons into the σ^* orbitals of the adjacent C-C and C-O bonds (I and II in Figure).[8a-d,g,11] If substituent Z is electronegative, it will oppose the delocalization of electron density away from itself (i.e., II). We can imagine two modes for this opposition. In one mode, electrons are constrained via a field effect due to Z. In a second, less passive mode, Z enhances the delocalization of oxygen

I



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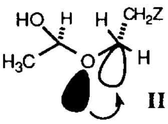

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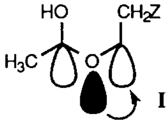

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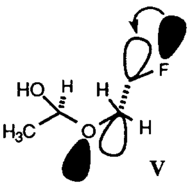

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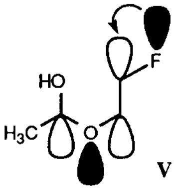

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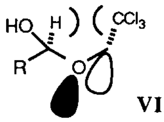

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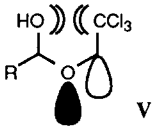

VIII

electrons toward itself, specifically into the σ^*_{C-C} bond orbital (e.g., III and IV). Our calculations suggest this second mode to be the more significant, particularly (but not exclusively) in conformations such as IV where the σ^*_{C-O} and σ^*_{C-C} orbitals overlap a single n orbital on oxygen. This hypothesis explains our data in that all of the substituted ethanols condense less favorably than does ethanol itself. As to why chloro- and trichloroethanol perform poorly compared to fluoro- and trifluoroethanol, further modelling indicated that the capacity of Z for $n \rightarrow \sigma^*_{C-C}$ donation is also important. In the hemiacetals of fluoro- and trifluoroethanol, such donation (e.g., V and VI) disfavors $n \rightarrow \sigma^*_{C-C}$ donation from the hemiacetal ether oxygen.[12] Chlorine, a second-row element, has only a weak ability for $n \rightarrow \sigma^*_{C-C}$ donation,[13] so the ether oxygen's electron density can delocalize well into σ^*_{C-C} of the chloroethyl hemiacetal and be less available to σ^*_{C-O}. A trichloroethyl hemiacetal also has steric problems in maintaining overlap of the n_O and σ^*_{C-C} orbitals (VII/VIII), meaning a net product destabilization.

Electronegative substituents in the aldehyde were also calculated to have an adverse influence on condensation, as observed.[10] AM1 implied that the $n \rightarrow \sigma^*$ delocalization within the hydrates of acetaldehyde, chloral, and trifluoroacetaldehyde is partly sacrificed upon hemiacetalization but particularly so for the last two.

Electronegative substituents in either reactant have only a weak influence on hemithioacetalization. When the substituents are present in the thiol, a weak influence is consistent with the poor delocalizability of sulfur non-bonding electrons into C-O antibonding orbitals.[8b,13] There is less $n \rightarrow \sigma^*_{C-O}$ resonance to constrain in a hemithioacetal vs. a hemiacetal, and the greater length of C-S vs. C-O bonds means that the electronegative substituents are at a greater distance from the electrons that they are constraining. When electronegative substituents are present in the hydrated aldehyde, AM1 interprets hemithioacetalization to involve an especially large cost to resonance (by 5-10 kcal mol^{-1}) that is nearly balanced by an especially low ΔH of electrostatics.

The synergistic action of electronegative substituents when present in both the nucleophile and aldehyde is predicted by AM1. Specifically, the displacement of electron density toward both ends of a hemiacetal or hemithioacetal results in especially reduced electron-nuclear attractions in its center. The AM1 Hamiltonian also proposed that this electrostatic destabilization is partially countered by particularly strong electronic resonance.

To summarize, electronegative substituents oppose aqueous condensation between hydrated acetaldehydes and an alcohol or thiol. The observed differences in reaction favorability are consistent with the calculated differences in the interaction of $n \rightarrow \sigma^*$ resonances plus any special electrostatic product destabilization. Resonance coupling should bear not only on the thermodynamics of hemiacetalization, but on the thermodynamics and kinetics of any molecular system with a relevant constitution (including many biomolecules). The phenomenon is well worth further investigation.

ACKNOWLEDGMENT

Acknowledgment is made to the Donors of the Petroleum Research Fund for support of our research (grant # 29365-AC4). We also thank Professor C. L. Liotta for helpful discussions.

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6. Computational results were obtained using the AM1 quantum mechanical molecular model[7] and the Insight II program, version 3.0.0, from Biosym/MSI (San Diego).
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9. Heats of formation for each compound were taken as a weighted average using the most stable molecular conformation identified with AM1 and all other conformational minima found within 2 kcal mol^{-1}. The weighting factors used were the percent population of each conformation in a Boltzmann distribution.
10. Molecular resonance energies were taken as a weighted average of the conformation-specific resonance energies that are discretely calculated in the NDDO/AM1 treatment (see reference 7, and especially 7b). The weighting factors were the same as those used in arriving at the heat of formation for a given molecule.[9]
11. For an alternative interpretation involving double bond-no bond resonance in hemiacetals and related species, see: (a) Hine, J. *J. Am. Chem. Soc.* **1963**, *85*, 3239-3244, and references therein. (b) Stoddart, J. F. *Stereochemistry of Carbohydrates*, Wiley Interscience: New York, 1971.
12. As with any MO to which multiple sources of non-bonding electrons have access, there is a competition between heteroatoms on a C-C bond for delocalization into σ^*_{C-C}.
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(*Received in USA* 16 *August* 1996; *accepted* 5 *November* 1996)