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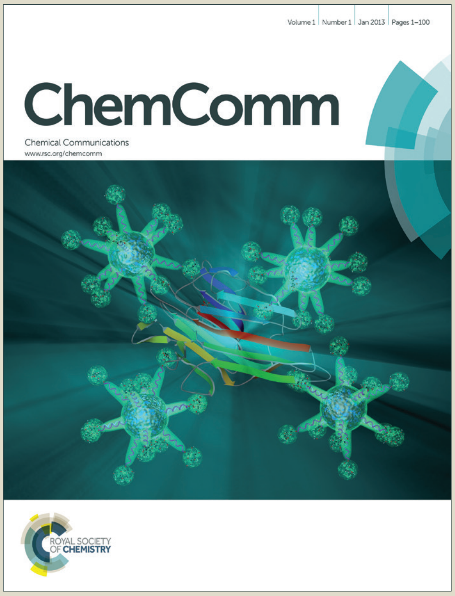

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Communication

Hydrogen Bonds Distinction and Activation on Catalytic Etherification of Hydroxyl Compounds

Penghua Che,[a,b] Fang Lu,*[a] Xin Nie,[a] Yizheng Huang,[a] Yanliang Yang,[a] Feng Wang[a] and Jie Xu*[a]

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An excellent linear correlation between lnδ (OH chemical shift) and 1/T (temperature) is first discovered for hydroxyl compounds. The derived slope (A) provides information as an index not only for distinguishing different types of H-bonds, but also for predicting their reactivities. This finding can be extended to other H-bonds containing molecules.

The renewable biomass as raw materials attracts increasing attention for production of chemicals and fuels, particularly the widely distributed and naturally abundant cellulose, hemicellulose, and lignin.[1] This essentially involves selective cleavage of C-O-C and C-C bonds in order to decrease the ratio of O/C.[2] However, these molecules usually contain strong hydrogen bonding networks formed by hydroxyl groups (–OH), which make the highly ordered and crystallized structures and thus can significantly modify their chemical reactivities.[3] Therefore, it is essential to explore a method which can distinguish intra- and intermolecular hydrogen bonds (H-bonds) and investigate their fundamental roles in catalytic reactions.

Several spectroscopic techniques have been developed to characterize the H-bonds.[4] Among them, nuclear magnetic resonance (NMR) spectroscopy is a versatile methodology for studying H-bonding since the chemical shifts are sensitive to the electronic and chemical environment of the investigated nuclei.[5] The magnetic resonance of H-bonded proton moves in general downfield compared to non-H-bonded proton.[6] In addition, the chemical shifts (δ) of the H-bonding protons have pronounced dependence on the temperature (T), for both intra- and intermolecular H-bonds.[7] The temperature-dependent changes in chemical shift are generally linear in dimethyl sulfoxide-d_6 (DMSO-d_6), and are nicely applied to proteins and peptides in conformational analysis.[8] However, OH groups may form strong intermolecular H-bonds through interaction with DMSO, which will cause confusion with their own intermolecular H-bonds.[9] In poor H-bond accepting solvent like $CDCl_3$, however, it has been reported that the OH chemical shift depends nonlinearly upon the temperature within 223 to 323 K.[10] It indicates that the linear functional relationship between δ and T is not representing the intrinsic principle of H-bonds. Therefore, it is desirable to develop a new correlation between the OH chemical shift and temperature to distinguish the intra- and intermolecular H-bonds and provide the inherent characteristic information of the H-bonds.

We showed here that the natural logarithm of hydroxyl proton NMR chemical shift (lnδ) of a series of sugar-derived alcohols correlates linearly with the inverse of temperature (1/T) from 263 to 328 K in $CDCl_3$. The slope, suggesting the energy difference of the O–H···O hydrogen bonds, clearly indicates the different strengths for the intra- and intermolecular H-bonds. It also can be used directly to predict the chemical reactivities, which is validated by a probe reaction of the nucleophilic etherification of different OH groups in isohexides.

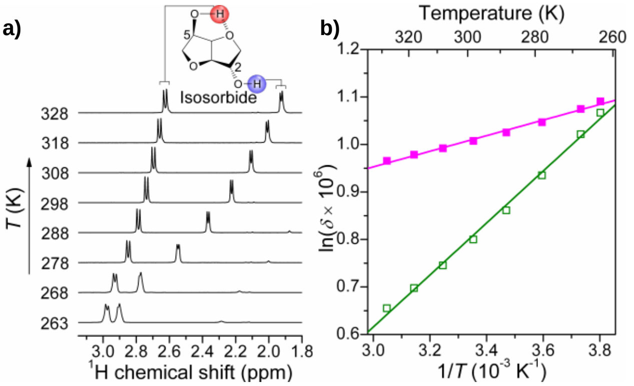

Fig. 1 Temperature dependences of OH proton chemical shifts of isosorbide in $CDCl_3$, concentration 0.13 mol L^{-1}. a) Variable-temperature ^1H NMR spectra of OH protons of isosorbide. b) Plots of lnδ of OH protons versus 1/T for isosorbide. The solid square corresponds to C5-OH with intramolecular H-bond, while the open square is C2-OH with intermolecular H-bond. The solid lines represent linear fits ($R^2 > 0.99$) (Table S2, ESI†).

The variable-temperature ^1H NMR experiments were carried out in $CDCl_3$ in the range of 263 to 328 K on a 400 MHz instrument with tetramethylsilane (TMS) as internal standard. Isosorbide which has both the intra- and intermolecular H-bonds was taken as model compounds.[11] Fig. 1a shows the temperature dependence of the OH proton chemical shifts of isosorbide. The chemical shift of C5-OH proton (2.98 ppm) moves slightly downfield compared to that of C2-OH proton (2.91 ppm) at 263 K, indicating that the two OH protons are electronically nonequivalent. Furthermore, C2-OH proton, involved in an intermolecular H-bond, shows a significant temperature dependence and its chemical shift changes dramatically towards a lower frequency with increasing temperature, whereas C5-OH shows a much weaker dependence. Thus, the chemical shift of C2-OH remains more shielded. Although previous studies showed that the temperature coefficient $\Delta\delta/\Delta T$ values of OH proton for intramolecular H-bonds were smaller in absolute terms than those for intermolecular H-bonds,[12] our attempt did not work out because the plot of δ versus T deviates obviously from linearity in the temperature range of 263 to 328 K (Fig. S1 and S2, ESI†).

Fig. 1b shows that the natural logarithm of OH chemical shift ($\ln\delta$) is well correlated linearly with the inverse of temperature ($1/T$) for both C2-OH and C5-OH protons within the range of 263 to 328 K. This Arrhenius-like behavior is given by eq. 1 with a slope of A. This leads to a slope of 164.2 for the plot of C5-OH (intramolecular H-bond) and 547.2 for that of C2-OH proton (intermolecular H-bond).

$$\ln\delta = A/T + B \qquad (1)$$

In order to verify whether it is a general feature, we investigated a series sugar-derived molecule. Firstly, molecules with a structure similar to isosorbide were chosen including isomannide and 2-*O*-monoethyl isosorbide, containing exclusively intramolecular H-bonds, and isoidide and 5-*O*-monoethyl isosorbide with intermolecular H-bonds. The nonlinear dependences on temperature of OH chemical shifts are observed (Fig. S3–S7, ESI†). All molecules give a nice linear correlationship between $\ln\delta$ and $1/T$ (Fig. S8, ESI†). The slope values for OH protons of isomannide and 2-*O*-monoethyl isosorbide are 137.8 and 90.6, corresponding to intramolecular H-bonds. They are 493.1 and 655.4 for the intermolecular H-bonds in 5-*O*-monoethyl isosorbide and isoidide, respectively. Further studies on other sugar-derived alcohols, containing intermolecular H-bonds with different structures including 5-hydroxylmethylfurfural, furfuryl alcohol, tetrahydrofurfuryl alcohol, (*S*)-3-hydroxytetrahydrofuran and ethanol (Table S1 and Fig. S9–S14, ESI†), validate the different temperature dependence behaviors (Fig. S15, ESI†). The slopes (A) of the intramolecular H-bonds for all studied molecules are smaller than those of the intermolecular H-bonds, as demonstrated in Fig. 2. The intramolecular H-bonds generally give a slope in the range of 90.4 to 164.2, while the intermolecular H-bonds show a slope of 289.3 to 655.4. Therefore, one may distinguish well the intra- and intermolecular H-bonds from the slope of the plot for $\ln\delta$ versus $1/T$.

Since NMR at a given temperature measures the proton chemical shift as a Boltzmann average of the chemical shifts associated with each vibrational level, the chemical shift is the resonant frequency of a nucleus relative to a standard, which is energy related.[13] *Kumar et al.* reported a linear correlation between computed binding energies of H-bonds and proton NMR chemical shift.[14] Garcia-Viloca *et al.* also reported that the dependence on the temperature of the proton NMR chemical shift could be used to identify the nature of low barrier H-bonds via theoretical potential energy calculation.[15] Therefore, the slopes for the plots of $\ln\delta$ versus $1/T$ (Fig. 1b, Fig. S8 and S15 in ESI†) may reflect the energy changes ΔE of the H-bonds from 263 to 328 K. Thus, the corresponding energy changes ΔE can be estimated from the slope A of eq. 1 times the universal gas constant (R) (eq. S1, ESI†), and the results are listed along in Fig. 2. One sees that the ΔE of the intramolecular H-bonds ranges from 0.2 to 0.3 kcal mol^{-1}, and for the intermolecular H-bonds it falls in a range of 0.6 to 1.3 kcal mol^{-1}. Because of the nuclear magnetic resonance absorption phenomenon, the absorption energy differences of OH proton nuclei from 263 to 328 K are calculated based on eq. S2–S4 (ESI†) and listed in Fig. S16 (ESI†). Interestingly, we found that the order of proton nuclei absorption energy difference is consistent with the apparent energy difference ΔE for sugar-derived molecules. We wonder if this energy changes can be used as an index for chemical reactivity. Therefore, we chose etherification as a probe reaction, in which the reactivity of OH group is strongly dependent on different H-bonds.

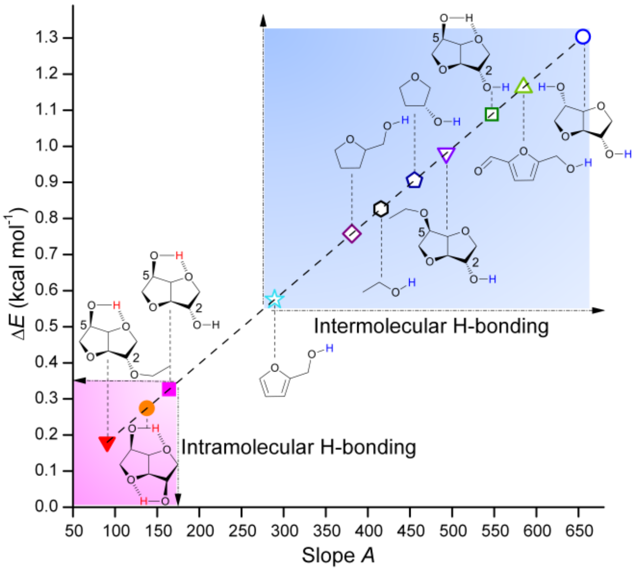

Fig. 2 The correlation between energy change (ΔE) of intra- and intermolecular H-bonds and slope A of the plots of $\ln\delta$ versus $1/T$ for sugar-derived alcohols.

Two types of molecules were mixed in the reactor, *i.e.* isomannide which contains exclusively the intramolecular H-bonds and isoidide only the intermolecular H-bonds. This would allow us to study the competitive etherification reactions between intra- and intermolecular H-bonds. The reaction was carried out using tungstosilicic acid as the catalyst. The main etherification products are monoethyl isomannide and monoethyl isoidide (Fig. S17a, ESI†). The results show that the conversion of isomannide is higher than that of isoidide over the same time scale (Fig. 3a). The turnover frequency (TOF) is 40.3 h^{-1} for the isomannide conversion, in comparison to 26.4 h^{-1} from isoidide, suggesting a higher reactivity of isomannide with the intramolecular H-bonds.

To further understand the reactivities of different OH groups, we looked into the etherification reaction of isosorbide, which contains both intra- and intermolecular H-bonds. With the time on stream, isosorbide was consumed gradually forming 5-*O*-monoethyl isosorbide and 2-*O*-monoethyl isosorbide (Fig. 3b and Fig. S17b, ESI†). The yield is 5.2% for 5-*O*-monoethyl isosorbide formation, in comparison to 3.6% for 2-*O*-monoethyl isosorbide in the initial 10 min. The preferential formation of 5-*O*-monoethyl isosorbide indicates that the intramolecular H-bond at C5-OH is more reactive than the intermolecular H-bond at C2-OH. This result is consistent with the report by Lemieux *et al.*, who observed that the intramolecular H-bond enhances the reactivity of C5-OH for the esterification of isosorbide.[16] The different reactivities of the intra- and intermolecular H-bonds are

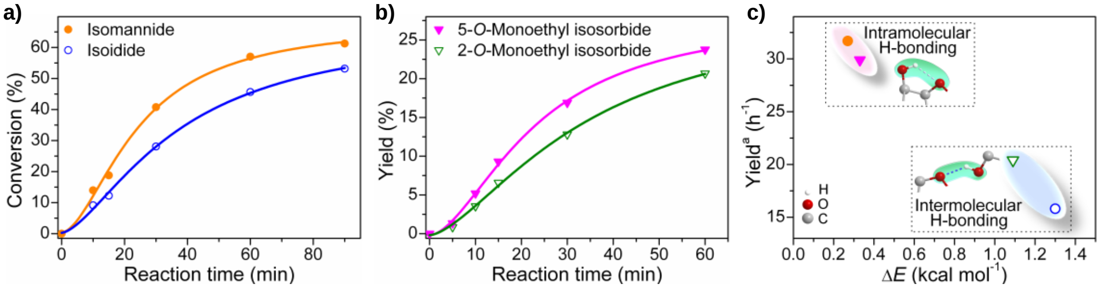

Fig. 3 The reactivity comparison of different types of H-bonds in the tungstosilicic acid-catalyzed etherification as a model reaction. a) Competition etherification of isomannide and isoidide with ethanol. b) Etherification of isosorbide which contains both intra- and intermolecular H-bonds with ethanol. c) The correlation between the reactivities of different types of H-bonds and their energy changes Δ*E* for isohexides. The yield^{a} of isohexides monoether is calculated as moles of isohexides monoether product formed per mole of acid per hour in the initial 10 min. Solid circle represents monoethyl isomannide, open circle for monoethyl isoidide, solid triangle for 5-*O*-monoethyl isosorbide, and open triangle for 2-*O*-monoethyl isosorbide. Reaction conditions: a) isomannide (2.40 mmol) and isoidide (2.40 mmol) or b) isosorbide (4.80 mmol), tungstosilicic acid (0.05 mmol), ethanol (2.80 mL) and toluene (2.70 mL) were stirred in an autoclave at 453 K.

likely related to their absorption energy differences, as reflected by the NMR chemical shifts of different OH protons. The shielding constant change of the C5-OH proton ($\Delta\sigma$) is smaller than that of C2-OH proton based on eq. S5 in ESI†, which suggests that electron density around the proton in C5-OH is lower than that of the C2-OH proton. This indicates a higher electron density on neighboring oxygen in C5-OH, resulting in a higher nucleophilic reactivity at C5-OH than at C2-OH. In order to further understand the correlation of the etherification activities of different types of H-bonds and their energy changes, we plotted the yield^{a} of isohexides monoether versus their corresponding Δ*E* of different H-bonds in Fig. 3c. The results suggest that the molecules with the intramolecular H-bonds exhibit a lower energy change and consequently show a higher nucleophilic reactivity, whereas those with the intermolecular H-bonds show a lower nucleophilic reactivity, as it is validated by etherification as a model reaction.

Conclusions

In summary, we have established an experimental index for predicting the chemical reactivities of different types of hydrogen bonds, *i.e.* the intra- and intermolecular H-bonds. The natural logarithm of OH proton NMR chemical shift ($\ln\delta$) is linearly correlated with $1/T$. Its slope may reflect directly the energy changes of the H-bonds for a wide range of alcohols. The molecules with the intramolecular H-bonds exhibit a lower energy change and consequently show a higher nucleophilic reactivity. This finding is not only fundamentally important because H-bonding is a general feature for a wide range of biomass-derived molecules, but also may be extended to other H-bonds containing molecules such as cellulose in different reactions.

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Notes and references

[a] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian National Laboratory for Clean Energy, Dalian 116023, P. R. China. Fax: +86-411-8437-9245; Tel: +86-411-8437-9245; E-mail: xujie@dicp.ac.cn; lufang@dicp.ac.cn*
[b] *University of Chinese Academy of Sciences, Beijing 100049, P. R. China.*

† Electronic Supplementary Information (ESI) available: Experimental procedures; variable-temperature ^{1}H NMR spectra; additional figures, tables and equations; and NMR as well as GC-MS traces. See DOI: 10.1039/b000000x/

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