Neighboring group interactions in dynamic covalent networks

J. del Barrio[1], E. Guerreiro[1], J. Ruiz,[1,2] M.P. Romero[1], L. Oriol[1]

[1] Instituto de Nanociencia y Materiales de Aragón (INMA), CSIC - Universidad de Zaragoza.
Dpto. de Química Orgánica, C/ Pedro Cerbuna, 12. 50009, Zaragoza (Spain).
[2] Current address: CerTest Biotec S.L. Dpto. I+D+i de Inmunoensayos por Quimioluminiscencia (CLIA),
Polígono Industrial Río Gallego II Calle J, 1, 50840 Zaragoza (Spain).
E-mail: jdb529@unizar.es

Introduction

Anchimeric assistance or neighboring group participation is of fundamental importance to a number of chemical transformations and self-assembling systems. In this regard, a promising interaction is the reversible condensation of ortho-substituted aryl aldehyde or ketone boronic acids with amines and other nucleophiles (Figure 1a).[1] Quantitative condensation takes place in aqueous media at mM concentrations and neutral pH when a boronic acid group is in close proximity to the carbonyl group of the electrophile. The remarkable stability of the adducts is associated with neighboring-group interactions between the electron-rich imine nitrogen and the electron deficient boron. It has been suggested that Lewis acid–base interactions dominate in the case of adducts of **1** (Figure 1b) whereas hydrogen bonding and Coulombic interactions operate in concert to stabilize the adducts of **2** (Figure 1b).[2] Additionally, the presence of a boronic acid group in **1** and **2** provides an opportunity to form, in the presence of a cis-diol derivative, the corresponding boronic ester.

We report, here, the formation of a series of dynamic covalent adducts derived from a family of ortho-substituted aryl aldehydes and ketone boronic acids. An overview on the binding mode (i.e. stoichiometry), thermodynamics and kinetics associated with the formation of the adducts, both in organic and aqueous media, is provided. We also delineate our synthetic strategies leading to dynamic polymeric materials, which exploit neighboring-group interactions.

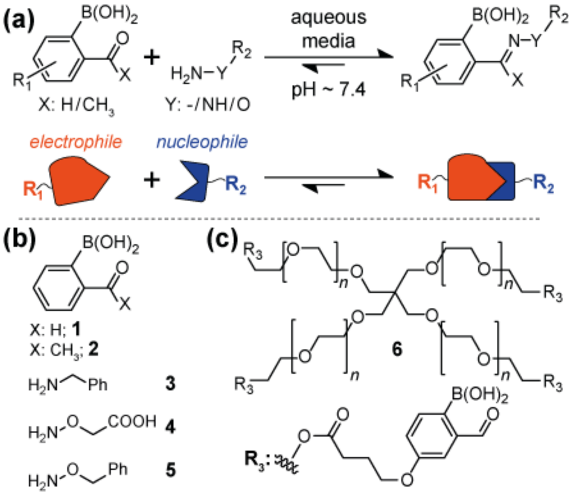

Figure 1. Schematic representation of adduct formation (a), and selected low molecular weight (b), and polymeric building blocks (c).

Experimental

All low molecular weight compounds (**1** to **5**, Figure 1a) were purchased from Merck KGaA (Germany), and used without further purification. Polymer **6** (Figure 1c) was synthetized following well-established procedures. Isothermal titration calorimetry (ITC) experiments were carried out in an AutoITC200 (MicroCal) that was thermostated at 25 °C. Typically, 10.0 mM nucleophile and cis-diol solutions were used to titrate the electrophile (ca. 500 µM) in a 200-µL cell. Titrations were performed by injecting the titrating the nucleophile or cis-diol compound in a step-wise fashion. Up to 19 injections of 2 µL each were added to the calorimetric sample cell and mixed at a stirring speed of 1000 r.p.m. ITC data was analyzed with Origin 7.0 and Affinimeter-ITC-Advanced software. Rheological measurements were performed on a HAAKE™ MARS™ 40 rheometer with a parallel plate measuring system.

Results and Discussion

The thermodynamics associated with the formation of imines, hydrazones, oximes and boronic esters from a set of small molecule building blocks have been investigated by ITC and nuclear magnetic resonance in aqueous buffer. Such techniques allow for the determination of the binding stoichiometry and affinity as well as the kinetics of adduct formation and exchange. Stable binary complexes (K_{eq} in the range of 10^2 - 10^6 M^{-1}), and also tetramers, result from the binding of **1** and **2** to selected nucleophiles. Some of the adducts form in neutral aqueous buffer with rate constants of ca. 10^3 M^{-1} s^{-1}. We have also investigated the stability of heteroternary adducts and the cooperativity associated with the reaction of nucleophiles and cis-diol compounds with **1** leading to termolecular complexes. These results contribute to our fundamental understanding of the formation of dynamic covalent adducts and the role of specific intramolecular neighboring-group effects, which unveils new opportunities for the design of dynamic materials.

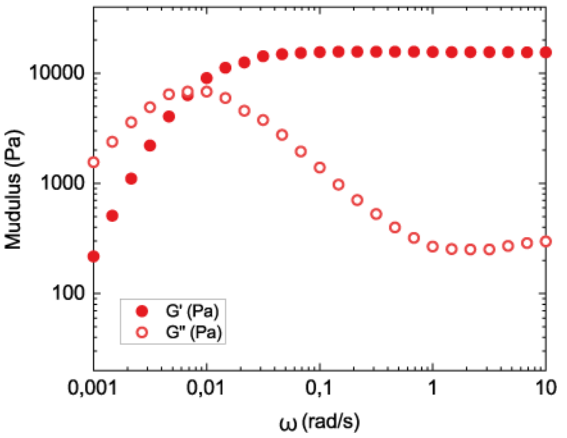

Figure 2. Frequency-sweep plot of G' and G'' for a selected dynamic covalent polymer network

Based on these principles, we have prepared a series of dynamic covalent polymer gels with fine-tuned rheological properties and stimuli responsive behavior. Some of the new polymer networks exhibit canonical Maxwell model viscoelasticity (Figure 2), and offer opportunities to link molecular to macroscale behavior.

Acknowledgements

J.D.B acknowledges grant RYC-2015-18471, funded by MCIN / AEI / 10.13039/501100011033 and by “ESF Investing in your future;” and grant CTQ2017-84087-R funded by MCIN / AEI / 10.13039/501100011033, and by “ERDF a way of making Europe”, by the European Union. E.G.G. acknowledges Gobierno de Aragón for a PhD grant. J.R. acknowledges AEI for an industrial PhD grant.

References

1. Cal, P. M.; Vicente, J. B.; Pires, E.; Coelho, A. V.; Veiros, L. F.; Cordeiro, C.; Gois, P. M. P. J. Am. Chem. Soc. 2012, 134, 10299−10305
2. Gillingham, D. Org. Biomol. Chem. 2016, 14, 7606−7609