Supplementary Material (ESI) for Chemical Communications

Controlling a recognition-mediated reaction using a pH switch

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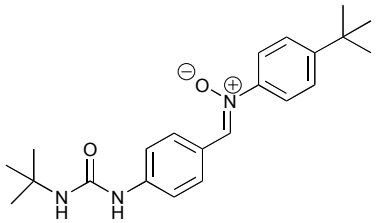
SUPPORTING INFORMATION

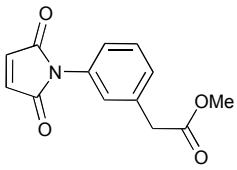
Spectroscopic Data

Compound 1



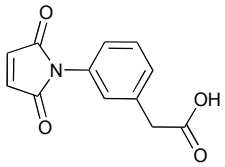
M.p. = 184-193°C decomp., ^{1}H NMR (300.1 MHz, $CDCl_3$) δ_H = 8.46 (1H, s, NH), 8.22 (2H, d, $J_{H,H}$ 8.9, Ar CH), 7.80 (1H, s, CH), 7.63 (2H, d, $J_{H,H}$ 8.8, Ar CH), 7.46-7.41 (4H, m, Ar CH), 5.97 (1H, s, NH), 1.33 (9H, s, CH_3), 1.26 (9H, s, CH_3); ^{13}C NMR (75.5 MHz $CDCl_3$) δ_C = 155.2 (q), 145.7 (q), 144.6 (q), 144.2 (q), 136.6 (CH), 131.3 (Ar CH), 126.6 (Ar CH), 123.5 (q), 121.7 (Ar CH), 118.1 (Ar CH), 50.8 (q), 31.6 (CH_3), 29.6 (CH_3), 18.8 (q); MS (ES-) m/z (%) = 267.2 (10), 366.2 (100) [M-H$^+$]: MS (ES+) m/z (%) = 390.2 (100) [M+Na$^+$]; HRMS (ES+): calcd for $C_{22}H_{29}N_3O_2Na$ (390.2): 390.2157; found 390.2160; FT-IR (thin film) ν_{max}/cm^{-1} = 3308, 2956, 1676, 1587, 1550, 1452, 1416, 1389, 1363, 1317, 1176, 1116, 1053, 835, 767.

Compound **2a**:



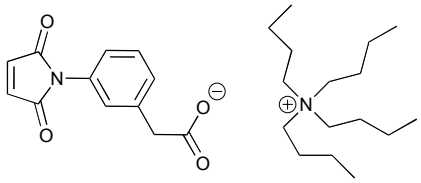
M.p. (waxy yellow solid) = 58.3-59.0°C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ_H = 7.42 (1H, dd, $J_{H,H}$ 8, $J_{H,H}$ 8, Ar CH), 7.27-7.38 (3H, m, Ar CH), 6.82 (2H, s, CH), 3.69 (3H, s, CH_3), 3.68 (2H, s, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 171.8 (q), 169.8 (q), 135.5 (q), 134.6, (Ar CH), 131.8 (q), 129.7 (Ar CH), 129.3 (Ar CH), 127.3 (Ar CH), 125.2 (2CH), 52.6 (CH_3), 41.3 (CH_2); MS (ES+) m/z (%) 268.0 (100) [M+Na$^+$], 300 (75): MS (CI+) m/z (%) 186.1 (100), 214.1 (20), 246.1 (20) [M+H$^+$]; HRMS (CI+): calcd for $C_{13}H_{12}NO_4$ (246.1): 246.0766, found 246.0771; FT_IR (thin film) ν_{max}/cm^{-1} = 3101, 2450, 1716, 1492, 1448, 1385, 1260, 1149, 827, 709.

Compound **2b**



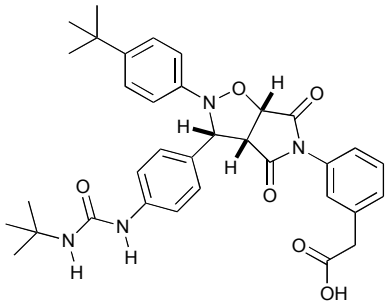
M.p. (yellow solid) = 113.5-114.7°C; ^{1}H NMR (300.1 MHz, $CDCl_3$) δ_H = 7.40-7.33 (1H, m, Ar CH), 7.19-7.28 (3H, m, Ar CH), 6.79 (2H, s, CH) 3.62 (2H, s, CH) ppm; ^{13}C NMR (75.5 MHz CD_3COCD_3) δ_C = 179.5 (q), 170.5 (q), 136.8 (q, 2C), 135.32 (2CH), 133.0 (q), 129.6 (Ar 2CH), 128.3 (Ar CH), 125.9 (Ar CH), 41.0 (CH_2); MS (CI+) m/z (%) = 186.1 (100), 214 (15), 231.1 (15) [M^+]; HRMS (CI+): calcd for $C_{12}H_9NO_4$ (231.1): 232.0532, found: 231.0540; FT-IR (thin film) ν_{max}/cm^{-1} = 3217, 3113, 2914, 1773, 1747, 1694, 1407, 1381, 1146, 697.

Compound 2d



M.p. (waxy solid) = 15 - 20°C; ^{1}H NMR (300.1 MHz, CD_2Cl_2) δ_H = 7.34 (m, 1H), 7.26 (d, 1H), 7.18 (s, 1H), 7.14 (d, 1H), 6.78 (s, 2H), 3.66 (s, 2H), 3.22-3.10 (m, 8H), 1.66-1.48 (m, 8H), 1.40-1.24 (m, 8H), 0.90 (t, 12H) ppm; ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ_C = 172.7 (q), 169.9 (q), 136.8 (q), 134.6 (2CH), 131.8 (q), 129.7 (Ar CH), 129.2 (Ar CH), 127.8 (Ar CH), 125.0 (Ar CH), 59.3 ($4CH_2$), 41.6 ($4CH_2$), 24.3 ($4CH_2$), 20.1 ($4CH_2$) 13.8 ($4CH_3$) ppm; MS (ES+) m/z (%) 242.3 (100) [Bu_4N^+]: (EI+) m/z (%) 187.1 (100), 213.0 (60), 231.1 (70) [M^+]; HRMS (EI+): calcd for $C_{12}H_9NO_4$(231.1): 231.0532, found 231.0533; FT-IR (thin film) ν_{max}/cm^{-1} = 2997, 2871, 1716, 1487 1448. 1379, 1207, 1147, 828, 699.

Compound ***cis*-3**:

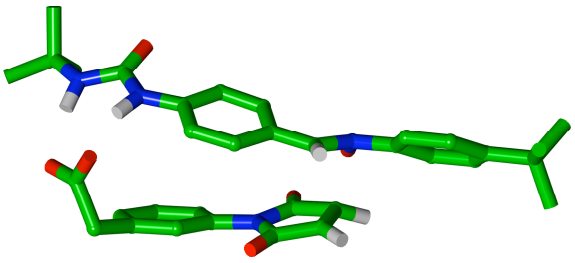


M.p. >130°C decomp.; ^{1}H NMR (500.1 MHz, $CDCl_3$) δ_H 7.31 (2H, d, $J_{H,H}$ 8.6, Ar CH), 7.30 (1H, dd, $J_{H,H}$ 10.2, $J_{H,H}$ 10.2, Ar CH), 7.24-720 (3H, m, Ar CH), 7.05 (1H, d, $J_{H,H}$ 8.1, Ar CH). 7.00 (2H, d, $J_{H,H}$ 8.8, Ar CH), 6.78 (1H, s, ArCH), 6.77 (1H, s, NH), 5.26 (1H, d, $J_{H,H}$ 7.9, CH), 4.94 (1H, d, $J_{H,H}$ 9.1, CH), 4.76 (1H, s, NH), 4.02 (1H, dd, $J_{H,H}$ 7.8, $J_{H,H}$ 9.2, CH), 3.57 (2H, dd, $J_{H,H}$ 14.7, $J_{H,H}$ 39.3, CH), 1.26 (9H, s, CH), 1.22 (9H, s, CH) = ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 173.7 (q), 173.5 (q), 171.9 (q), 155.5 (q), 147.6 (q), 145.0 (q), 139.6 (q), 135.8 (q), 131.2 (q),129.9 (Ar CH), 129.26 (Ar CH), 128.4 (q), 128.1 (Ar CH), 126.2 (Ar CH), 125.8 (Ar CH), 124.4 (Ar CH), 119.5 (Ar CH), 118.0 (Ar CH), 77.3 (CH), 77.2, 70.9 (CH), 54.6 (CH), 50.9 (q), 41.1 (CH_2), 34.3 (q), 31.3 ($3CH_3$), 29.2 ($3CH_3$); MS (ES-) m/z (%) 597.4 (100) [M-H$^+$]: MS (ES+) m/z (%) 179.0 (20), 195 (100), 621.3 (75) (M+Na$^+$]; HRMS (ES+): calcd for $C_{34}H_{38}N_4O_6Na$ (621.3): 621.2689, found 621.2711; FT-IR (thin film) ν_{max}/cm^{-1} = 3372, 2963, 1719, 1595, 1542, 1514, 1451, 1389, 1313, 1253, 1202, 1147, 836, 733.

Electronic Structure Calculations

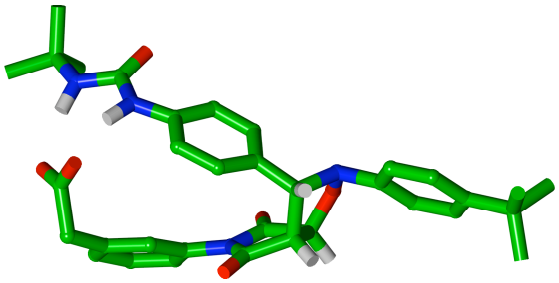
The calculation of the transition state structure leading to ***cis*-3** is a multi-stage process. The process begins with an energy minimization and Monte Carlo conformational search[1] on the model substrate. The conformations detected as local minima in this molecular mechanics calculation are then minimized using the AM1 semi-empirical method as implemented[2] in AMSOL 7.1. A series of grid calculations, describing the dissociation of the *cis*-3 cycloadduct into the corresponding nitrone and maleimide components, are next performed. These grid calculations, performed using AMSOL 7.1 at the AM1 level, scan the carbon-carbon and carbon-oxygen bond lengths in the isoxazolidine ring to locate the point at which the bonds are broken in the retro-1,3-dipolar cycloaddition. A saddle point is located using the grid calculations, and the geometry closest to the saddle point is then used as a starting point for a transition state refinement. From the saddle point geometry, found by the grid calculation, eigenvector following routines are used to find a stationary point. A vibrational analysis of the stationary point geometry reveals a single imaginary frequency describing the transition from reactants to product, and confirming the location of the TS. The AM1 transition state is then used as a basis for higher level *ab initio* calculations – first at the HF/3-21G level and finally, at the HF/6-31G(d) level. Given the size of cis-3, we could not progress the calculation to a higher level of theory with the computing resources available to us. GAMESS-US[3] was used to perform all of these calculations. Transition states were subjected to vibrational analysis to ensure that they were characterised by a single imaginary frequency describing the transition from reactants to product.

***cis*-3 transition state (HF/6-31G(d))**



ν_I = -359.13 cm^{-1}

***cis*-3 (HF/6-31G(d))**



Cartesian Coordinates

cis-3 transition state (HF/6-31G(d))

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.524459
C	1.209028	0.000000	2.205324
C	1.207166	0.072851	3.580541
C	0.024730	0.179780	4.293361
C	-1.190040	0.209551	3.619224
C	-1.186066	0.094131	2.227839
H	-2.110815	0.096610	1.704896
C	-1.212607	3.826422	2.058226
C	-1.314910	4.165457	3.420437
H	-0.472159	4.609098	3.895640
C	-3.584733	3.339976	3.478453
C	-3.492986	3.052403	2.104285
C	-2.339432	3.266012	1.416313
H	-2.226815	2.950183	0.400966
N	-5.030594	3.218473	5.434449
C	-4.817440	3.118645	4.139773
H	-5.690704	3.024995	3.526193
O	-4.004906	2.739567	6.260580
C	-4.671406	0.600692	4.818050
C	-3.995472	0.952170	5.969151
C	-2.518653	0.761120	5.669218
N	-2.417571	0.386250	4.335433
C	-3.735227	0.255570	3.780023
O	-3.969769	-0.101031	2.641092
C	-7.676473	3.010309	7.984354
C	-8.816091	3.434400	7.304130
C	-8.652960	3.809666	5.980112
C	-7.417827	3.755038	5.355679
H	-7.338803	4.097234	4.344564
C	-2.457170	3.885770	4.115351
H	-2.500202	4.070331	5.166413
H	-4.328060	2.602474	1.602959
H	-5.575667	2.639417	7.911805
C	-6.444199	2.944087	7.374527
C	-6.305744	3.298784	6.040294
H	-7.744220	2.725990	9.015090
H	-9.484902	4.164456	5.410070
O	-1.629077	0.892729	6.475702
H	2.119893	-0.000891	1.644147
H	2.135551	0.075627	4.118627
H	-5.711154	0.393446	4.719938
H	-4.312223	0.728999	6.964029
H	0.046327	0.277980	5.351654
N	-0.077501	3.938573	1.315329
H	-0.121508	3.470691	0.400847
H	0.668629	-0.765719	-0.370131
H	-0.998524	-0.149885	-0.379844
C	0.516030	1.382238	-0.439788
O	-0.346008	2.251747	-0.752395
O	1.753268	1.575548	-0.341835
C	1.149260	4.441200	1.729829
O	1.269537	5.177635	2.713520
N	2.161444	4.038236	0.941022
H	2.021086	3.226487	0.339482
C	3.559876	4.434366	1.165130
C	4.365800	3.786127	0.026775
H	4.199809	2.716071	0.013334
C	4.056937	3.906707	2.525807
H	3.964502	2.826677	2.551601
H	5.097772	4.176010	2.678337
H	3.453948	4.329286	3.315944
C	-10.168536	3.484483	8.029095
C	-11.306442	3.975965	7.111597
H	-12.235338	3.985756	7.671318
C	3.701897	5.965319	1.101812
H	3.104278	6.418064	1.878246
H	4.044456	4.186143	-0.928282
H	5.423601	3.989234	0.156878
H	3.358275	6.321993	0.137077
H	4.742338	6.247573	1.230828
C	-10.071658	4.450958	9.232067
H	-11.023775	4.494481	9.751864
C	-10.534508	2.067447	8.527942
H	-11.490640	2.089376	9.041611
H	-11.119068	4.982737	6.755597
H	-11.435437	3.319713	6.258297
H	-9.316167	4.127564	9.937235
H	-9.815735	5.448276	8.893133
H	-9.789797	1.687749	9.216296
H	-10.605889	1.381370	7.691813

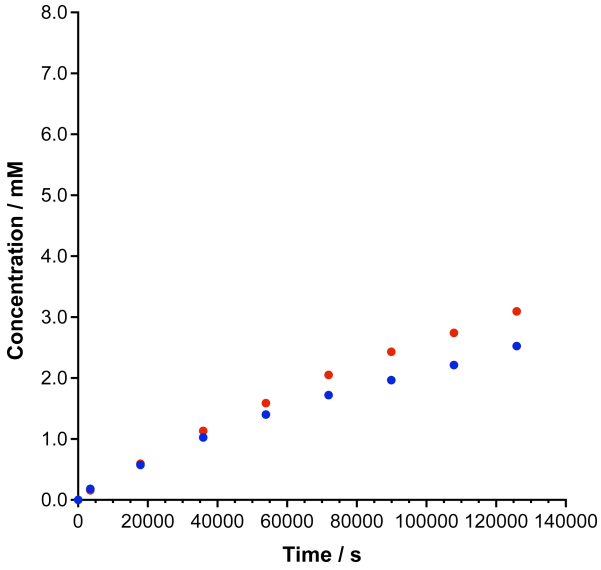
cis-3 (HF/6-31G(d))

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.517577
C	1.190960	0.000000	2.225652
C	1.173792	0.071906	3.603900
C	-0.019374	0.175247	4.295960
C	-1.213688	0.206117	3.592343
C	-1.196373	0.099166	2.208196
H	-2.109704	0.111239	1.662497
C	-2.455378	3.750528	1.547680
C	-2.698277	4.273553	2.815559
H	-2.101557	5.089151	3.152915
C	-4.428010	2.640260	3.201104
C	-4.258618	2.191201	1.896414
C	-3.285815	2.722290	1.086041
H	-3.084976	2.303810	0.122165
N	-5.673986	2.655904	5.347779
C	-5.379926	1.895665	4.104507
H	-6.311795	1.688151	3.604386
O	-4.556519	2.370776	6.241016
C	-4.776006	0.561244	4.676621
C	-4.044085	1.050413	5.903634
C	-2.585199	1.133527	5.464649
N	-2.459854	0.387637	4.291631
C	-3.692033	-0.048662	3.812907
O	-3.873677	-0.796314	2.884894
C	-8.202655	1.846766	7.955962
C	-9.402371	1.987935	7.266666
C	-9.318121	2.373256	5.935961
C	-8.099507	2.592783	5.319296
H	-8.075694	2.927432	4.302131
C	-3.662242	3.709407	3.632016
H	-3.792781	4.083553	4.625402
H	-4.850899	1.374469	1.528371
H	-6.074642	1.966037	7.908749
C	-6.979616	2.054127	7.350912
C	-6.914664	2.413101	6.013559
H	-8.210722	1.569835	8.991416
H	-10.205047	2.520380	5.357088
O	-1.699972	1.670928	6.073506
H	2.118411	-0.022703	1.690850
H	2.095560	0.075013	4.151885
H	-5.555823	-0.156746	4.872570
H	-4.129819	0.406012	6.764625
H	-0.013725	0.287047	5.355346
N	-1.391711	4.106630	0.733292
H	-1.232976	3.466311	-0.047248
H	0.873935	-0.520870	-0.368047
H	-0.900034	-0.453202	-0.385699
C	0.060023	1.476190	-0.464973
O	-1.007272	1.971617	-0.916466
O	1.146745	2.071127	-0.284978
C	-0.415728	5.034277	1.014414
O	-0.573710	5.963104	1.816421
N	0.724607	4.808134	0.322688
H	0.880602	3.869959	-0.042090
C	1.911024	5.666141	0.428373
C	2.948106	5.067876	-0.537269
H	3.129677	4.028673	-0.290976
C	2.467542	5.652489	1.866752
H	2.726326	4.637237	2.146527
H	3.355028	6.274896	1.936033
H	1.710753	6.020906	2.543117
C	-10.736719	1.733136	7.983160
C	-11.948693	1.937716	7.051566
H	-12.860341	1.735651	7.603401
C	1.569982	7.105962	0.005415
H	0.811820	7.504030	0.662644
H	2.574149	5.111288	-1.554021
H	3.878630	5.623142	-0.478796
H	1.192497	7.105221	-1.011242
H	2.457930	7.729521	0.050927
C	-10.878303	2.709876	9.173237
H	-11.820930	2.540288	9.684788
C	-10.771559	0.276305	8.500230
H	-11.710868	0.083057	9.009301
H	-11.996412	2.957262	6.686043
H	-11.912379	1.262762	6.203893
H	-10.076380	2.576946	9.888758
H	-10.853251	3.735051	8.822163
H	-9.964349	0.087582	9.197156
H	-10.676220	-0.418186	7.673268

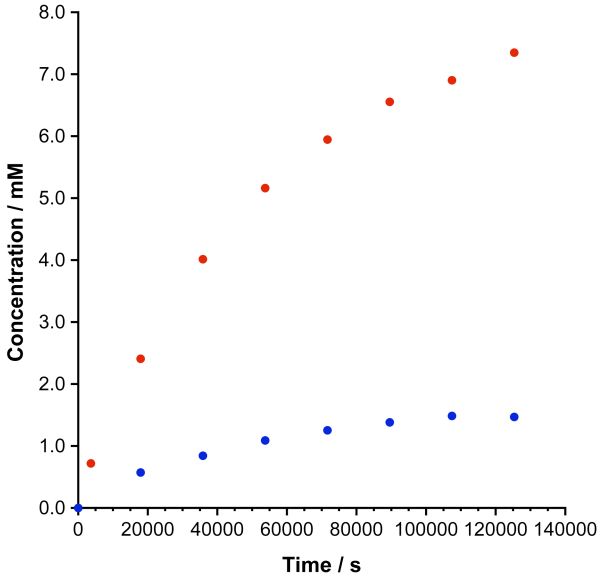
Concentration-Time Profiles

In the graphs below, the concentration of ***cis*-3** is represented by the red circles and the concentration of ***trans*-3** is represented by blue circles. Data were acquired using 500 MHz ^{1}H NMR spectroscopy in d_6-acetone at 10 °C from starting concentrations of either [**1**] = [**2b**] = 12.5 mM or [**1**] = [**2d**] = 12.5mM.

(a) Reaction between 1 and 2b – Recognition 'Off'



(b) Reaction between 1 and 2d – Recognition 'On'



References

1. Molecular mechanics calculations were carried out using the AMBER* force field and the GB/SA solvation model for CHCl3 as implemented in Macromodel (Version 7.1; Schrödinger, Inc.: Portland, OR, **2000**) running on a Linux workstation.
2. AMSOL Version 7.1 by G. D. Hawkins, D. J. Giesen, G. C. Lynch, C. C. Chambers, I. Rossi, J. W. Storer, J. Li, J. D. Thompson, P. Winget, B. J. Lynch, D. Rinaldi, D. A. Liotard, C. J. Cramer, D. G. Truhlar; EF routines by F. Jensen.
3. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.* **1993***, 14*, 1347-1363.