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Gur, E.H.; de Koning, L.J.; Nibbering, N.M.M.

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JMS Letters

Dear Sir,

Gas-phase Hydrogen–Deuterium Exchange of Protonated Alkyldipeptides with (*S*)- and (*R*)-butan-2-ol

Hydrogen–deuterium (H–D) exchange reactions between protonated alkyldipeptides and either deuterated water,¹ methanol^{1,2} or ammonia¹ have been the subject of studies using Fourier transform ion cyclotron resonance (FTICR) mass spectrometry. Recently, we reported that the H–D exchange behaviour is highly dependent on the proton affinity difference (ΔPA) between the exchange reagent and the dipeptide.¹ In the reactions between the studied alkyldipeptides and deuterated ammonia, for which ΔPA is 40–70 kJ mol^{−1}, exchange is close to collision controlled and non-selective: all three exchangeable sites in the dipeptides incorporate deuterium with equal rate constants. In contrast, for the reactions between the dipeptides and deuterated water, where ΔPA is 200–230 kJ mol^{−1}, only 5–20% of the collisions lead to H–D exchange which is site-selective: the hydrogens of the various functional groups within a given dipeptide exchange with different rate constants. Moreover, the various rate constants have a consistent substituent (side-group) dependence: more basic *N*-terminal amino acids lower the overall rate constants of exchange and less basic *C*-terminal amino acids increase the difference in relative rate constants of site-selective exchange within a given dipeptide. It is considered that the H–D exchange proceeds via competing intermediate complexes characterized by a protonated exchange reagent molecule stabilized by specific multiple hydrogen bonds from the various functional groups in the dipeptide.¹ The reaction complexes of the dipeptides with less basic exchange reagents are more tightly bound since hydrogen bonds need to be geometrically optimal to overcome the larger proton affinity differences. Consequently, reactions with less basic exchange reagents result in a more site-selective H–D exchange behaviour.

If geometrically optimal hydrogen bonds are essential in the competing intermediate complexes, the effects of the alkyl substituents on the H–D exchange behaviour may be related not only to the individual enhancements of the local basicities at

different basic sites, but also to the geometric distortion in the intermediate complexes due to steric hindrance.

The effect of a possible steric hindrance presently has been examined by studying the H–D exchange behaviour of the protonated dipeptides in the reactions with stereoisomeric reagent molecules, knowing that the basicities of the stereoisomeric reagent molecules are identical. To study the stereoselectivity of the H–D exchange, the stereoisomers of butan-2-ol were chosen as exchange reagents. In the experiments performed here, the instrumentation and general procedure were identical with those reported previously,¹ except that instead of studying the exchange reactions between the protonated dipeptides and deuterated exchange reagents the reverse exchange reactions were studied (demonstrated by Gard *et al.*³) where external ion source-generated deuterated dipeptides, $[M-d_4 + D]^+$ (produced by fast atom bombardment ionization of a deuterated peptide–matrix solution), were mass-selected in the FTICR cell, cooled with a pulsed valve addition of argon gas and subsequently reacted with hydrogen-containing exchange reagent molecules in the FTICR cell. This method overcomes the problem of incomplete deuterium content of the exchange reagents and thus allows direct comparison of the studied H–D exchange behaviour of the two stereoisomers of butan-2-ol.

Since the proton affinity of butan-2-ol [816 kJ mol^{−1} (Ref. 4)] falls between those of methanol and ammonia, it is expected that the overall efficiency [k_{exp}/k_{AAD0} (Ref. 5)] of H–D exchange should be intermediate between those of methanol and ammonia. This is confirmed by the results given in Table 1, which show that the efficiency ranges from 42 to 58% within the series of studied dipeptides, compared with the previously reported 30–70% and about 100% for the exchanges of the same series of dipeptides with methanol and ammonia, respectively.

Furthermore, the substituent effect, as reflected in the relative rates of exchanges ($H_{1,2,3}$, H_4 and H_5 in Table 1) at the amino, amide and carboxylic groups, is found to be qualitatively similar to that reported previously¹ for water and methanol. The magnitude of the substituent effect in the exchange with butan-2-ol is reduced as expected for a more

Table 1. Hydrogen–deuterium exchange in the reaction between $[M-d_4 + D]^+$ and (*S*)- and (*R*)-butan-2-ol^a

M	k_{exp} (10^{-10} cm ³ mol ^{−1} s ^{−1}) ^b	k_{exp}/k_{AAD0} ^c	Relative rate of H incorporation (%) ^d		
			$H_{1,2,3}$	H_4	H_5
GlyAla	10.2	0.56	100	81	63
GlyVal	9.4	0.53	100	100	80
AlaGly	9.0	0.50	100	71	43
AlaAla	9.3	0.52	100	68	49
AlaVal	10.2	0.58	100	84	84
ValGly	7.4	0.42	100	40	26
ValVal	8.3	0.50	100	70	56

^a The pressures of the (*S*)- and (*R*)-butan-2-ol in the FTICR cell were determined to be 3.7×10^{-8} mbar after correction for relative gauge sensitivity according to Ref. 7. Results for the reactions with (*S*)- and (*R*)-butan-2-ol are the same, within experimental error (see Fig. 1). The values given are averages of the results for the reaction with the *S* and *R*-enantiomers.

^b Rate constant for the decay of $[M-d_4 + D]^+$ ions.

^c Overall reaction efficiency. k_{AAD0} was calculated according to Ref. 5.

^d Qualitative changes in the rate of H incorporation in the $[M-d_4 + D]^+$ ions during the progression of H–D exchange as determined from the kinetic data in Fig. 1 (see Ref. 1).

Figure 1. Macroscopic degree of H incorporation in the deuterated dipeptides, $[M-d_4 + D]^+$, in the reactions with (*R*)-(full lines) and (*S*)-(dashed lines) butan-2-ol as a function of reaction time at a butanol pressure of 3.7×10^{-8} mbar. (a) $M = \text{AlaAla}, \text{AlaVal}, \text{ValVal}$; (b) $M = \text{GlyVal}, \text{GlyAla}, \text{AlaGly}, \text{ValGly}$.

loosely bound intermediate complex, relative to those involved in the reactions with the less basic water and methanol.

None of the studied deuterated dipeptides was observed to exhibit a significantly different exchange behaviour in the reactions with the *S*- and *R*-stereoisomers of butan-2-ol, either with respect to the overall exchange rate constant or with respect to the relative rates associated with exchange at the three functional groups of a given dipeptide. It is clearly demonstrated that no stereoselectivity is detected by comparing the hydrogen incorporation in the $[M-d_4 + D]^+$ ions in the reactions with the two stereoisomers of the butan-2-ol as a function of reaction time (Fig. 1). This may be due to the relatively small proton affinity difference ΔPA between butan-2-ol and the series of dipeptides which can be estimated^{4,6} to range from 80 to 110 kJ mol⁻¹. (An estimated range of ΔPA s is indicated based on the PA values obtained from Ref. 6. Since these PA values suffer from relatively large errors and do not yet seem to be consistent, indication of the ΔPA s for the specific reactions of butan-2-ol with the different dipeptides is still

too speculative and may tentatively lead to misinterpretation of the results.) As a result of this relatively small proton affinity difference, H-D exchange can occur via relatively loosely bound intermediate reaction complexes. Consequently, the difference between the stability of the diastereomeric intermediate reaction complexes in the reactions of (*S*)- and (*R*)-butan-2-ol may become negligible.

Yours

EREZ H. GUR, LEO J. DE KONING and NICO M. M. NIBBERING*
Institute of Mass Spectrometry,
University of Amsterdam,
1018 WS Amsterdam,
The Netherlands

* Author to whom correspondence should be addressed.

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