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# THE DEPENDENCE OF ASYMMETRIC INDUCTION ON SOLVENT POLARITY AND TEMPERATURE IN PEPTIDE SYNTHESIS

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Abstract: When a racemic 2,4-dialkyl-5(4H)-oxazolone reacts with an L-amino acid ester, the D-L epimer is formed in excess in apolar solvents and the L-L epimer is formed in excess in polar solvents, the proportion of L-L isomer increasing with decreasing temperature.

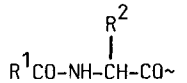
In peptide synthesis, when an activated amino acid residue (1) ($R^1 \neq RO$) couples with an amine nucleophile (2), racemization often occurs as a result of the competing intramolecular cyclization reaction which gives rise to the 2,4-dialkyl-5(4H)-oxazolone (3).[1] The oxazolone undergoes nucleophilic attack just as does the activated acid (1), however, because of its chiral instability under these conditions, it racemizes probably completely[2] before coupling. The peptide product (4) arising from the amination of the racemic oxazolone is nevertheless not a 1:1 mixture because asymmetric induction occurs during attack by the chiral amine (2) at the carbonyl carbon atoms of the oxazolone enantiomers.[3] Little attention has been devoted to studying the influence of this phenomenon on the amount of diastereomeric product which is formed in a coupling. Weygand et al.[3] showed that when the oxazolone (3a) from benzoyl-DL-valine was aminated by an L-residue (2) in tetrahydrofuran, an excess [20-60%] of D-L isomer was formed, the amount depending on the nature of the side-chain of 2 [$R^3$: Me < s-Bu < $PhCH_2$ < iPr]. For the same nucleophile (2), the diastereomeric excess [d.e.] varied with the nature of the N-substituent $R^1CO$ [$R^1$: Ph > Z-$NHCH_2$ > Me]. The results were explained[3] on the basis that the amine reacts at different rates with the two oxazolone enantiomers.

We have identified two new parameters, independent of the nature of the reactants, which exert a major influence on the asymmetric induction in peptide synthesis, namely solvent and temperature. The effect is so profound that one can obtain the L-L or D-L isomer in excess by appropriate choice of solvent, i.e. polar or apolar. Similarly, one can get either isomer in excess in dichloromethane by appropriate choice of the temperature.

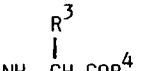
Chemically pure racemic oxazolones[4] 3b and 3c from Bz-Leu and Z-Gly-Leu were reacted with L-Lys(Z)-OMe (2b) and L-Lys(Z)-OBzl (2c) respectively, and the diastereomeric products were determined by $^1$H-nmr[5] spectroscopy [MeO singlet] in the first case, and with an amino acid analyser[6] after deprotection in the second case.

Data on the effect of solvent are given in Table 1 in order of increasing L-L epimer from the peptide oxazolone (3c). Apolar solvents gave an excess of D-L isomer from both oxazolones; polar solvents, an excess of L-L isomer. Except in acetonitrile and aqueous dimethylformamide, the 2-phenyl-oxazolone gave rise to more induction than the 2-benzyloxycarbamidomethyl-oxazolone. The least induction occurred for the peptide oxazolone

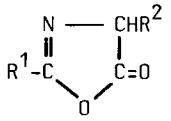
in dichloromethane [d.e. 2% D-L]. No change in the degree of induction was caused by the addition of dimethylformamide to dichloromethane to a concentration of 33%.



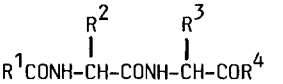
1 [L]



2 [L]



3 [DL]



4 [L-L + D-L]

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| a | Ph | $CHMe_2$ | | |
| b | Ph | $CH_2CHMe_2$ | $Z\text{-}NH(CH_2)_4$ | MeO |
| c | $Z\text{-}NHCH_2$ | $CH_2CHMe_2$ | $Z\text{-}NH(CH_2)_4$ | $PhCH_2O$ |

Z = $PhCH_2OCO$

Data on the effect of temperature appear in Table 2. Lower temperature favored the L-L epimer in both solvents. The L-L epimer predominated in dimethylformamide at all temperatures [5° to 35°], but a different isomer predominated in dichloromethane depending on the temperature. The temperatures of transition from an excess of one isomer to the other were quite different, at less than 0°C for the 2-phenyl-oxazolone and at about 18°C for the peptide oxazolone. This difference in transition temperatures produced the apparently incongruous phenomenon that between 0° and 15°, the epimer in excess was not the same for the two oxazolones. It follows from this that conclusions on asymmetric induction and consequently racemization in general based on data obtained solely from benzoylamino acids or 2-phenyl-oxazolones might not aways be applicable to the general case of peptide synthesis [see ref. 7 for other examples].≠

It emerges from this and previous[3,8] work that when a stereomutation occurs during the coupling of -W-Xxx + Yyy-, the amount of epimeric peptide formed is determined partly by the extent of asymmetric induction which depends on at least five factors, the nature of W, Xxx and Yyy, the solvent and the temperature.

It is well known that the degree of racemization in a coupling is diminished by lowering the temperature.[1] It follows from our work that one of the reasons for this is the fact that the lower temperature reduces the amount of D-L isomer which is generated by reaction of the amine with the racemized oxazolone.

≠ Also accompanying paper

Table 1. Effect of solvent on asymmetric induction during amination of 2,4-dialkyl-5(4H)-oxazolones**

| Solvent | 3b† | | 3c≠ | |
|---|---|---|---|---|
| | L-L | D-L | L-L | D-L |
| Acetonitrile | | 10 | | 22 |
| Tetrahydrofuran | | 30 | | 12 |
| Toluene | | 26 | | 3 |
| DCM | | 24 | | 2 |
| DCM-DMF (2:1) | | 24 | | |
| DCM-DMF (1:1) | 10 | | | |
| DCM-DMF (1:2) | 15 | | | |
| DMF | 36 | | 16 | |
| Dimethyl sulfoxide | 32 | | 20 | |
| DMF-$H_2O$ (2:1) | 22 | | 53 | |

** Percent diastereomeric excess [d.e.] after addition of oxazolone to a solution of the ester hydrochloride [1.0 equiv.] and N-methylmorpholine [0.90 equiv.] at 23°C. DCM = dichloromethane; DMF = dimethylformamide. d.e. L-L = [L-L - D-L]/[L-L + D-L]; d.e. D-L = [D-L - L-L]/[L-L + D-L].

† Oxazolone from Bz-DL-Leu reacting with L-Lys(Z)-OMe.

≠ Oxazolone from Z-Gly-DL-Leu reacting with L-Lys(Z)-OBzl.

Table 2. Effect of temperature on asymmetric induction during amination of 2,4,dialkyl-5(4H)-oxazolones**

| Solvent | Temperature (°C) | 3b | | 3c | |
|---|---|---|---|---|---|
| | | L-L | D-L | L-L | D-L |
| DCM | 35 | | 28 | | |
| DCM | 23 | | 24 | | 2 |
| DCM | 5 | | 18 | 6 | |
| DCM | -10 | 12 | | | |
| DMF | 35 | 22 | | 10 | |
| DMF | 23 | 36 | | 16 | |
| DMF | 5 | 54 | | 28 | |

** Percent diastereomeric excess, as in Table 1.

Most data are results from single experiments. Because of the uncertainty associated with the ninhydrin color constants which were obtained from the diastereomeric mixture,[7] the results for 3c are less accurate than those for 3b.

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